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Review Article

# Glycobiology-targeted therapies in hematologic oncology: ushering in a new era of cancer diagnostics and therapeutics

**Ashraf Abdullah Saad***

*Department of Pediatric Hematologic Oncology and BMT, Sultan Qaboos University Hospital, Muscat, Oman*

## ABSTRACT

Despite that immunotherapy has revolutionized cancer treatment, a considerable proportion of patients do not respond. While scientists continued to make perpetuating efforts in order to bridge this gap, glycans (carbohydrates) have come under scrutiny as the next frontier in pharmaceutical research. Immunologically speaking, tumor-specific glycan signatures that mediate tumor cell recognition by the immune system offer novel immunotherapy targets for developing both specific and powerful therapeutic strategies against cancer. Notwithstanding that we are lately witnessing breakthrough discoveries in glycan-targeting therapies for solid tumors being reported in a substantial number of studies, the utilization of these therapies in liquid tumors (i.e., leukemia, lymphoma and myeloma) continued to lag far behind. On the other hand, humoral and cellular immunotherapeutic agents were quite successful in selected hematologic malignancies, albeit patients with Relapsed/Refractory (R/R) disease and those crippled by financial and/or drug toxicities remain extremely disadvantaged. Between the currently employed immunotherapeutic modalities and the Overall Survival (OS) rate, the full potential of glyco-oncology creates a divide that must be continuously researched and bridged. Therefore, this review aims to contextualize the glycosylation landscape of liquid tumors within the field of hematologic oncology in order to establish 'Glycobiology in Hematology' as a new emerging paradigm in cancer research and therapeutics.

**Keywords:** leukemia, lymphoma, multiple myeloma, cancer-associated glycans, selectins, galectins, Siglecs, hematologic oncology, glycobiology, cancer immunotherapy.

## INTRODUCTION

Anti-tumor immunity is the basis for durable disease-free treatment-free survival in cancer patients [1]. Historically, the idea of harnessing the immune system to fight cancer had been actively investigated since the early 1900s when William Cooley attempted to cure advanced sarcoma with heat-inactivated bacterial toxins [2,3]. After a century of intense efforts, immunotherapy is currently established as the fifth pillar of cancer therapeutics, joining surgery, cytotoxic chemotherapy, molecularly targeted therapy, and radiation therapy [4].

Currently, the main cancer immunotherapy constructs include Antibody–Drug Conjugates (ADCs), bispecific Antibodies (bsAbs) such as Bispecific T cell engagers (BiTEs), Dual Affinity Retargeting antibodies (DARTs), and Bispecific Killer Cell Engagers (BiKEs) [5], and Chimeric Antigen Receptor (CAR)-T cells. Cancer immunotherapy, named 'breakthrough of the year 2013' [6,7] and 'the cancer advance of the year 2016' [8], has led to unprecedented and durable response rates in several cancers [9,10]. Nonetheless, the majority of patients do not benefit from cancer immunotherapies and some responders relapse after a period of response [11]. Sharma et al., [12] classified immune resistance into three main categories: primary (a clinical scenario where a cancer does not respond to an immunotherapy strategy), adaptive (appearance of resistance mechanisms as a Darwinian mechanism of adaptation), and acquired/secondary (a clinical scenario in which a cancer initially responded to immunotherapy but after a period of time it relapsed and progressed).

Remarkably, tumor cell-extrinsic mechanisms that lead to primary and/or adaptive resistance involve components within the Tumor MicroEnvironment (TME) (other than tumor cells) which contribute to inhibition of anti-tumor immune responses. The immunosuppressive TME had long been incriminated in chemoresistance as well as now considered the root cause of resistance to the majority of cancer immunotherapies leading to their failure [13,14,15,16]. Notably, T-cell exhaustion (including

**Correspondence to:** Ashraf Abdullah Saad, Department of Pediatric Hematologic Oncology and BMT, Sultan Qaboos University Hospital, Muscat, Oman, E-mail: dr.ashraf123321@gmail.com

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CAR T-cell exhaustion) [17,18], is a cardinal feature of the TME that eventually result in tumor escape [19,20,21]. The hallmark of exhausted T-cells is their expression of multiple co-inhibitory receptors that operate the immune escape of target tumor cells [22,23]. These co-inhibitory receptors (also referred to as inhibitory immune checkpoints or T-cell exhaustion markers) are the intrinsic brakes of the immune system that protect against autoimmunity under homeostatic conditions. Mechanistically, these T-cell exhaustion markers (Table-1) limit the strength and duration of immune responses by negatively regulating T-cell responses, thereby curbing immune-mediated tissue damage, regulating resolution of inflammation, and maintaining tolerance to prevent autoimmunity [33,34]. Interestingly, tumors hijack the mechanisms of these immune checkpoints as protection against anti-tumor immune responses elicited by $CD4^+$ and $CD8^+$ T-cells in order to establish an immunosuppressive TME, hindering their eradication [35]. Consequently, restroring T-cell effector fuctions *via* Immune Checkpoint Blockade (ICB) had become an established modality of immunotherapy [36]. ICB employs Immune-Checkpoint Inhibitors (ICIs) such as ipilimumab, nivolumab, and pembrolizumab to block these co-inhibitory receptors on T-cells in order to release the potential of the anti-tumor immune response. Although reversing immune checkpoint inhibitor pathways have generated much excitement, these approaches still lack absolute success [37]. As a matter of fact, ICB was only effective in a minority of patients with heavily mutated tumors [38]. Additionally, managing immunotherapy-related severe adverse effects remains a challenge [39]. In fact, these immunotherpautic agents brought a new wave of unique toxicity profiles that are distinct from the toxicities of other cancer therapies (because they activate a broad range of immune cells) [40]. In particular, ICB induced novel toxicities that were labelled as immune-related Adverse Events (irAEs) including colitis, hepatitis, myositis, pneumonitis, endocrinopathies, kidney injury, and skin toxicities [41]. Moreover, a growing body of basic science, translational, and clinical evidence now suggests that myocarditis may be the tip of the iceberg in terms of cardiac irAEs, with ICI-induced acceleration of AtheroSclerotic CardioVascular Disease (ASCVD) contributing significantly to vascular toxicity in the long term [42]. Furthermore, CAR T-cell therapy induce potentially severe or even life-threatening immune-related toxicities including Cytokine Release Syndrome (CRS), Hemophagocytic LymphoHistiocytosis (HLH) and/or Macrophage Activation Syndrome (MAS) which often manifests following resolution of CRS (recently termed immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, IEC-HS), and the life-threatening albeit commonly occurring Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) [43]. CAR-T-associated neurotoxicity also include recent reports of encephalitis caused by reactivation of Human HerpesVirus 6 (HHV-6) in patients receiving CAR T-cells [44,45,46]. Moreover, prolonged and persistent cytopenias, recently termed Immune Effector Cell-Associated Hematological Toxicity (ICAHT), leading to increased risk of infections, life-threatening bleeding, and long-term transfusion support have become a major therapeutic challenge added to the bill of CAR T-cell therapy [47,48,49]. One major limitation for broader applicability of CAR T-cell therapies is that more than 50% of patients who respond to CAR T-cell therapies eventually relapse [50]. For instance, more than half of patients with high-grade lymphomas will progress and require additional therapy after CAR T-cell therapy. Failure after CAR T-cell therapy is caused by a variety of factors that can be divided into 3 broad categories: tumor intrinsic factors, other host factors, and inadequacies of the CAR T-cells [51]. To sum up, paucity of therapeutic targets, toxicities related to CAR T-cell therapy, and resistance to CAR T-cell therapy are the main challenges that hinder widespread commercialization of CAR T-cell therapy [52]. In a similar vein, although BiTEs- the concept of which dates to the 1960s when Alfred Nisonoff envisioned the potential of replacing one of the two identical antigen binding arms with a different antigen binding specificity [53] -have been proved to be efficient in many R/R hematologic malignancies, a subset of patients still have no response to BiTEs [54]. Often overlooked, the financial toxicities of these agents can negatively affect patient outcomes and quality of life. In particular, CAR-engineered immune cells continue to remain a complex and extremely expensive technology hindering affordability and access to CAR T-cell therapy [55,56].

**Table 1:** The main T cell exhaustion markers and their ligands

| T cell exhaustion marker | Also known as | Ligand | Also known as | Reference (s) |
|---|---|---|---|---|
| PD-1 | CD279 | PD-L1 | CD274 (B7-H1) | [24] |
| | | PD-L2 | CD273 (B7-DC) | |
| CTLA-4 | CD152 | CD80 | B7.1 | [25] |
| | | CD86 | B7.2 | |
| | | Galectin-3[1] | Mac-2 antigen, CBP-35, and LBP | [26] |
| TIM-3 | CD366, HAVCR2 | Galectin-9 | Ecalectin and UAT | [27] |
| LAG-3 | CD223 | MHC class II[2] | | [28] |
| | | Galectin-3 | | |
| | | LSECtin | | |
| | | FGL-1 | | |
| | | α-syn | | |

| | | | | |
|---|---|---|---|---|
| TIGIT[3] | WUCAM | CD155 | PVR, Necl-5[4] | [29-31] |
| | VSTM3 | CD112 | PVRL2, Nectin-2 | [32] |

PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; Mac, macrophage; CBP35, carbohydrate binding protein 35; LBP, a non-integrin laminin binding protein in macrophages; TIM-3, T cell immunoglobulin mucin-3; UAT, urate transporter; LAG-3, lymphocyte-activation gene 3; LSECtin, liver sinusoidal endothelial cell lectin; FGL-1, Fibrinogen-like protein 1; α-syn, α-synuclein fibrils; TIGIT, T cell immunoreceptor with Ig and ITIM domains; WUCAM, Washington University Cell Adhesion Molecule; VSTM3, V-set and transmembrane domain-containing protein 3; PVR, the poliovirus receptor; Necl, nectin-like molecule; PVRL2, Poliovirus receptor-related 2.

**Note:** [1]Galectin-3 was found to interact with two clinically-relevant immune checkpoint molecules: CTLA-4 and LAG3. In the first case, galectin-3 associated to complex branched N-glycans, increasing CTLA-4 retention on the cell surface and downregulating TCR signal strength. On the other hand, galectin-3 has been found to promote $CD8^+$ T cell dysfunction by engaging LAG-3.

[2]Major histocompatibility complex (MHC) class II on antigen-presenting cells (APCs) is the canonical LAG-3 ligand.

[3]TIGIT is a co-inhibitory molecule and a novel member of the CD28 family (was first identified in 2009). Similar to LAG3 and TIM3, belongs to the immunoglobulin superfamily.

[4]Nectins and nectin-like (Necl) molecules are a family of 9 adhesion molecules that belong to the immunoglobulin superfamily. They play a key role in different biological processes such as cell polarity, proliferation, differentiation and migration in epithelial, endothelial, immune and nervous systems. Some of these molecules also function as receptors for poliovirus and herpes simplex viruses.

Despite that B-cell Acute Lymphoblastic Leukemia (B-ALL) has an excellent prognosis in children with long-term survival of 80%–90% [57], the event-free survival for pediatric B-ALL has plateaued over the past decade leaving approximately 25% of patients with R/R disease [58]. Patients with R/R B-ALL especially in the post-transplant setting continue to have a dismal prognosis [59]. On the other hand, there is no light at the end of the tunnel where multiple myeloma (MM) exists. MM - a B-cell malignancy and the second most frequently diagnosed hematologic cancer- remains incurable despite significant advances in treatment due to the lack of appropriate antigen(s) for targeted-cell killing [60]. Despite many new approved drugs and numerous combinations of these agents, including the use of proteasome inhibitors, immunomodulatory drugs, and mAbs, resistance eventually ensues and most patients will die from their disease [61]. Currently, CD19 and the B-Cell Maturation Antigen (BCMA) are the most common targets for CAR T-cell therapy in B-cell malignancies. Although initial CAR T-cell activity shows promising response rates, especially in Diffuse Large B-Cell Lymphoma (DLBCL) and B-ALL, only a minority of patients attain long-term disease remission [62]. For instance, resistance or relapse after CD19-directed CAR T-cell therapy occurs in the majority of patients within 1–2 years [63]. Approximately, 30%–60% of patients relapse after CD19-directed CAR T-cell therapy, and 10 to 20% of relapsed patients experience CD19-negative relapse [64]. Although CAR T-cell therapy is considered the game-changer for B-cell malignancies, their use for other malignancies is still challenging [65]. For instance, CAR T-cell therapy does not work for Acute Myeloid Leukemia (AML), mainly due to high incidence of CRS and relatively poor clinical efficacy [66]. In addition, generating autologous CAR T-cells from patients with T-cell malignancies has been particularly problematic and quite challenging [67,68]. So far, none of the immunotherapeutic modalitis can completely replace allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) in spite of the remarkable advances in immunotherapy for blood cancers over the past decades [69]. It is worth noting that allo-HSCT is one of the oldest forms of cancer immunotherapy for hematologic malignancies. However, this approach was prohibitive as the first choice in any treatment strategy due to its inherent risks of Transplantation-Related Mortality (TRM) and morbidity including the development of Graft-versus-Host Disease (GvHD) [70]. On the other hand, achieving and maintaining CR before allo-HSCT is paramount, but it remains a significant hurdle. Moreover, viral pathogens are a significant source of morbidity and mortality after allo-HSCT [71]. Indeed, many post-HSCT patients eventually enter a deadly vicious cycle of GvHD and viral infections. In addition, invasive fungal infections are a major cause of morbidity and mortality among HSCT recipients [72]. Strikingly, HSCT still often fails due to the relapse of the malignancy [73]. Please note that details on hematologic malignancies (Figure-1) are beyond the scope of this article but are summarized elsewhere [74].

Despite that glycans (carbohydrates) have been overlooked in drug discovery strategies for many centuries, glycobiology has recently come to the forefront of biomolecular and biomedical research. Every cell in our body is virtually surrounded by a dense coating of complex and diverse glycans (the "glycocalyx") which have essential role in the interaction between cells and the microenvironment [75]. Glycosylation, the process by which sugars are post-translationally added to proteins or lipids with the aid of certain enzymes, is an integral part of cellular function governing innumerable biological processes. Glycans bind several Pattern Recognition Receptors (PRRs) on immune cells, the so-called lectins.

Lectins are a diverse group of non-antibody Glycan-Binding Proteins (GBPs) that are found abundantly in nature (the other group of GBPs, sulfated Glycosaminoglycan (GAG)-binding proteins is not addressed here) [76]. Through binding to lectins, glycans regulate key biological processes including protein folding, cell adhesion, molecular trafficking and clearance, receptor activation, signal transduction, and endocytosis [77]. As glycosylation is universal in living organisms, aberrant glycosylation as a result of changes in glycan synthetic pathways is also a universal feature of tumor cells with fundamental role in oncogenesis and metastasis [78].

In fact, aberrant glycosylation is causally associated with the acquisition of all hallmarks of cancer [79]. "Hallmarks of Cancer"– a phrase originally coined by Doug Hanahan and Bob Weinberg –define a set of cell biological processes frequently dysregulated in tumors, contributing to their progression [80]. In particular, changes in sialic acid glycosylation allow cancers to participate in 'immune evasion' by engaging inhibitory sialic-acid-binding immunoglobulin-like lectins (Siglecs) on the surface of immune cells [81,82].

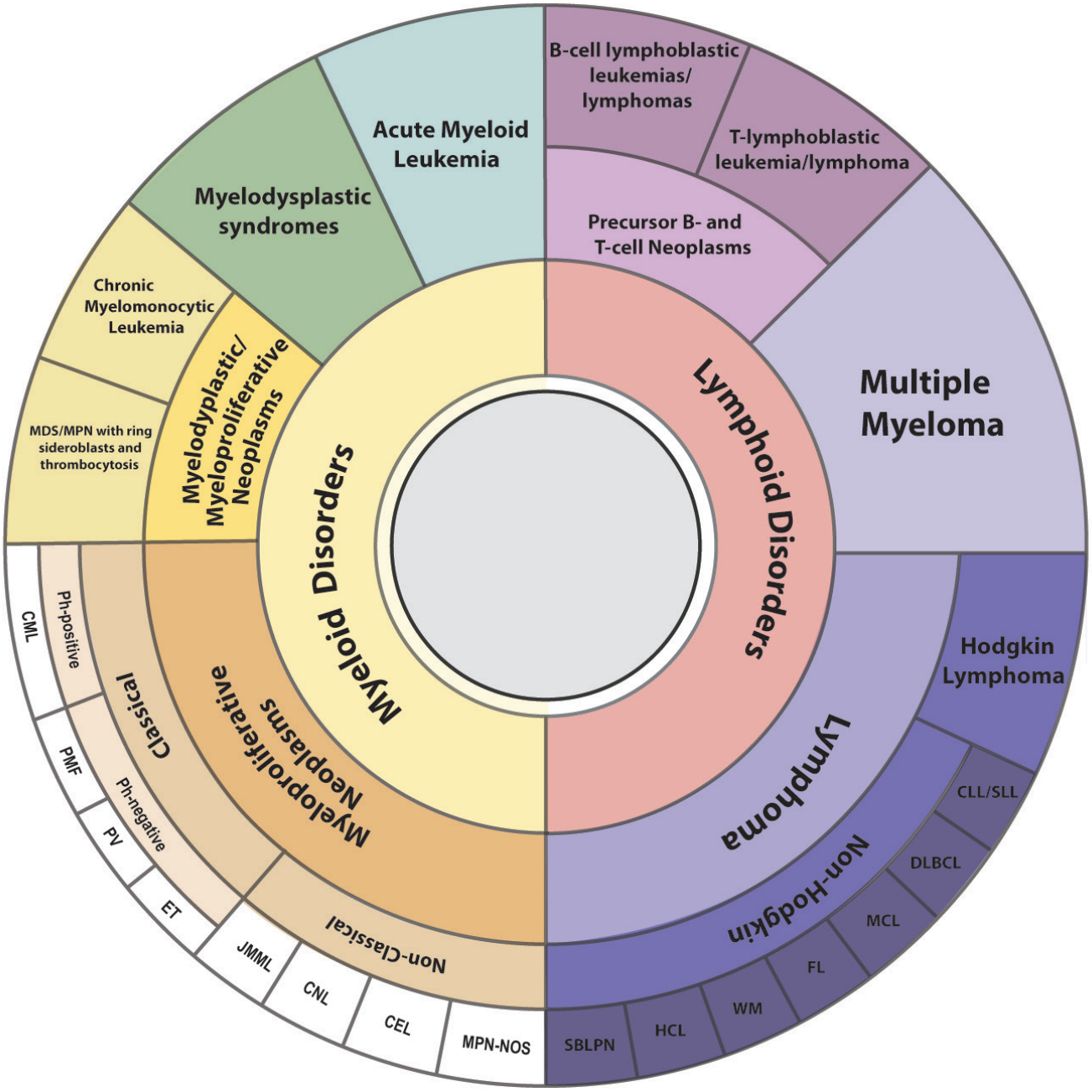


**Figure 1:** Overview of hematologic malignancies.
CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; WM, Waldenström macroglobulinemia; HCL, hairy cell leukemia; SBLPN, splenic B-cell lymphoma/leukemia with prominent nucleoli; Ph, Philadelphia chromosome; CML, chronic myeloid leukemia; PMF, primary myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia; JMML, juvenile myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; CEL, chronic eosinophilic leukemia; MPN-NOS, myeloproliferative neoplasm, not otherwise specified; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm.
NB. JMML is categorized under myeloproliferative neoplasms according to 5th edition of the WHO classification of Haematolymphoid Tumours.

Noteworthily, sialic acid residues terminate cell-surface glycans and serve as Self-Associated Molecular Patterns (SAMPs). Similar to the Cytotoxic T-Lymphocyte–Associated Antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) checkpoint proteins, Siglecs contain signaling domains capable of preventing immune activation which render overexpressing tumor-associated sialoglycans (sialic acid-containing glycans) a strategy employed by tumors to evade the immune system. Hence, there is compelling evidence supporting that the sialoglycan-Siglec axis have become a powerful and appealing target for cancer immunotherapy [83,84].

Moreover, glycans expressed in malignant cells, known as Tumor-Associated Carbohydrate Antigens (TACAs), are abundantly and uniquely expressed on tumor cells. TACAs are strongly implicated in malignant transformation and tumor progression. As cancer-specific antigens, TACAs serve as ideal targets for the development of novel modalities in cancer diagnostics and therapeutics [85,86].

During the past decade, remarkable progress has been achieved in the application of glycan-targeting therapies for solid tumors. Glycan-targeting approaches include monoclonal antibodies

(mAbs) [87], Antibody-Drug Conjugates (ADCs) [88,89], bispecific antibodies [90,91,92,93], vaccination [94,95,96,97,98,99], and recently lectibodies [100,101]. Lectibody is a chimeric protein composed of lectin and crystallizable fragment (Fc) of IgG antibody that can act as a carbohydrate-targeting antibody (102). Two anti-glycan mAbs have been approved by the United States Food and Drug Administration (FDA or US FDA) for high-risk neuroblastoma (dinutuximab/Unituxin and naxitamab/nyelza) [103]. Despite that CAR T-cell therapy has enjoyed success in the clinic for liquid tumors (blood cancers), the broad effectiveness of CAR T-cell therapy for treating solid tumors remains disappointing [104,105]. In fact, the discrepancy in success of CAR T-cell therapy between liquid and solid tumors is attributable to the CAR T-cell's ability to physically enter and penetrate deeply into the TME [106]. Surprisingly, however, targeting glycopeptides by CAR T-cells in solid tumors have yielded promising results [107,108], providing compelling evidence for the enormous potential of glycan-targeting therapies to rejuvenate the field of tumor immunology. For example, GD2 CAR-T phase I trial showed feasibility and safety in osteosarcoma and neuroblastoma [109]. In spite of the irrefutable potential of glycan-targeting therapies in solid tumors, this field remains underexplored in liquid tumors. Undoubtedly, the expression of TACAs occurs in most hematological malignancies and their roles were reviewed in the literature [110,111]. Recent research has shown that changes in the glycosylation profile of T-cells and B-cells have been related to the development of leukemias including B-ALL, B-Cell Chronic Lymphocytic leukemia (B-CLL), T-cell Acute Lymphoblastic Leukemia (T-ALL)] [112]. Unfortunately, glycobiology remains a very little commented subject in the classrooms of different biomedical courses as it is an emerging field within immunology [113]. This case is even worse when it comes to clinicians. Most hematologists are generally unaware of glycobiology. Therefore, the aim of this review is to make hematologists familiar with TACAs and immune lectins within the context of hematologic oncology while focusing on mechanistic pathways that link lectin pattern recognition and potential tumor targeting strategies.

## UNTANGLING THE SWEET MECHANICS OF LIQUID TUMORS

### Aberrant glycosylation: the sugar sculpting art of cancer

Glycobiology is the study of glycans and their recognition by motif-specific glycan-binding proteins or lectins [114]. Carbohydrates (glycans) are among the four major classes of biomolecules (besides nucleic acids, proteins, and lipids). Glycans are ubiquitous on the surface of all living cells and also found on most secreted proteins. Glycans are essential structures that play remarkable roles in the immune system, cellular signaling, and host-microbe interactions. Glycans usually exist as glycoconjugates (glycoproteins, proteoglycans and glycolipids), rather than existing in a free state [115]. Nearly all initial interactions of a cell with neighbouring cell(s), cell matrix, other proteins, or with a pathogen are mediated mainly by glycans [116]. Glycans are sensed by glycan binding receptors expressed on immune cells, such as C-type Lectin Receptors (CLRs) and Siglecs that respond to specific glycan signatures by triggering tolerogenic or immunogenic signaling pathways [117]. Noteworthily, the term "glycomics" refers to studies that profile the glycome, while the term "glycome" describes the complete repertoire of glycans and glycoconjugates that cells produce under specified conditions of time, space, and environment [118]. On the other hand, the term "glycoproteomics" describes this glycome as it appears on the cellular proteome. Correspondingly, glycoproteomics determines which sites on each glycoprotein of a cell are glycosylated and ideally includes the identification and quantitation of the heterogeneous glycan structures at each site [119]. Strikingly, the cell-surface glycome, termed glycocalyx, is a dense layer combining glycoproteins and sugar moieties on cell surfaces, can extend more than 30 nm from the plasma membrane. It is worth noting that all cells in the bone marrow (BM) are surrounded by a glycocalyx which regulates such cell-cell and cell-matrix interactions [120]. The process by which oligosaccharides are added to the proteins or lipids to form glycoconjugates in the Endoplasmic Reticulum (ER) and Golgi apparatus is called glycosylation. Noteworthily, the Golgi apparatus is home to a multitude of glycosyltransferases, glycosidases, and nucleotide sugar transporters that function together to complete the synthesis of glycans from founding sugars covalently attached to protein or lipid in the ER [121]. Mechanistically, the primary mechanisms by which glycans can be linked to proteins or lipids are *N*-glycosylation and *O*-glycosylation, where glycans are added sequentially to the amide group of an Asparagine (Asn) residue and the hydroxyl oxygen of Serine/Threonine (Ser/Thr) residues respectively. Although *N*-and *O*-glycans are often found on the same proteins, they differ strongly in their compositions and biosynthesis [122]. It is important to note that in most of the cases both *N*-and *O*-linked glycans are capped at the terminal position with sialic acids, Lewis blood group related antigens or ABO (H) blood group determinants. Furthermore, glycosylation of proteins and lipids in mammals is essential for embryogenesis and the development of all tissues [123]. Not surprisingly, glycosylation is the most common Post-Translational Modification (PTM), dynamically shaping the glycans on proteins and lipids traveling through the secretory pathway, and comprising an extensive glycocalyx on the cell surface [124]. The three major classes of cell surface glycoconjugates execute numerous functions, including fine-tuning of molecular interactions, intra- and intercellular communications, and immune modulation [125,126]. Mechanistically, glycosylation modification of proteins or lipids provides a vital stabilizing force for proteins within their microenvironment, thereby modulating their biological functions [127]. For instance, glycans added to proteins play a pivotal role in protein folding, oligomerization, quality control, sorting, and transport [128]. These glycoproteins represent the majority of the key molecules involved in the innate and adaptive immune response [129]. Dysregulated (aberrant) glycosylation plays a crucial role in disease processes, including oncology. The aberrant glycosylation occurs because of cellular and metabolic variations leading to variant expressions of integrated glycans [130]. Aberrant glycosylation results in various functional changes of glycoproteins which confer the unique characteristic phenotypes associated with cancer cells. In a similar vein, glycolipids play critical roles in various aspects of tumorigenesis as well as considered promising immunotherapeutic targets for cancer therapy [131]. Strikingly, cancer cells have adapted to the selection pressure exerted by the immune system through harnessing their glycome to create an immunosuppressive environment that results ultimately in immune evasion. This is called aberrant glycosylation, a universal feature of cancer cells found in essentially all tumor cells [132]. Not surprisingly, emerging evidence highlighted that altered glycans play key roles in tumorigenesis and tumor progression.

Moreover, glycosylation is currently a subject of much interest for its potential role in metastasis, which is responsible for 90% of cancer-related deaths [133].

Noteworthily, the glycocalyx drives the interplay between cancer cells and the TME, a complex scaffold of Extracellular Matrix (ECM) and various cell types. Stiffening of the ECM, likely due directly to specific changes in glycan content/composition of the tumors, is common in cancer. Cancer cells sense and transduce mechanical stiffness of the ECM into intracellular responses by a process called mechanotransduction, which promotes aberrant cell functions and contributes to cancer progression. A wide range of glycans are also involved in cancer cell mechanotransduction [134]. Cumulative evidence shows that cell surface glycosylation expression pattern is altered on cancer cells, leading to aberrant expression of cancer-associated glycans - also called Tumor-Associated Carbohydrate Antigens (TACAs)-serving as biomarkers of cancer progression as well as ideal targets for novel anti-tumor immunotherapy approaches [135]. TACAs are created by the collaborative activities of glycosyltransferases, glycosidases, nucleotide-sugar transporters, sulfotransferases, and glycan-bearing protein/lipid scaffolds [136]. In addition, TACAs contribute to shape unique glyco-codes with distinct mechanisms of immunosuppression through their interactions with endogenous lectin receptors expressed by immune cells such as the C-type selectins and the S-type galectins; and therefore, defining the glyco-code of each tumor is essential for understanding its immune evasion potential [137]. In this context, the best characterized TACAs in hematologic malignancies are shown in Figure-2.

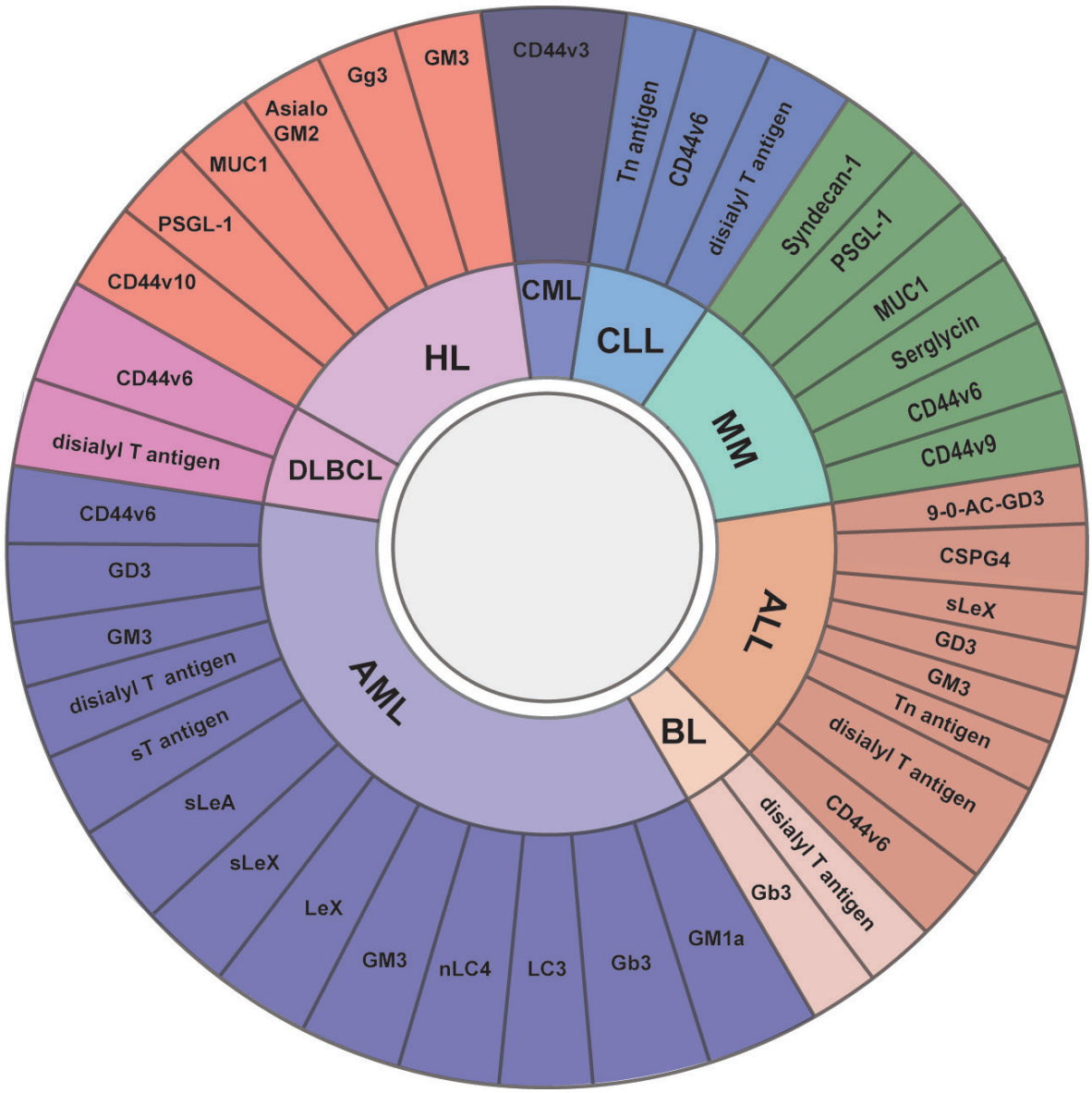


**Figure 2:** The expression of cancer-associated glycans and glycoproteins in hematologic malignancies

Glycoproteins require specific glycopeptide epitope (such as sLeX on a core 2 residue with nearby sulfated tyrosine on PSGL-1 and TF on MUC1) to bind their partner lectins. Therefore, these glycoproteins and their glycopeptide epitopes represent target antigens that can be harnessed to treat hematologic malignancies.

CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; ALL, acute lymphoblastic leukemia; BL, Burkitt's lymphoma; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; CSPG4, chondroitin sulfate proteoglycan 4.

## Cancer-associated changes in glycosylation

Genetic and epigenetic modifications of glycan biosynthesis result in the characteristic pattern of cancer-associated glycosylation. The most-widely occurring cancer-associated changes in glycosylation are sialylation, fucosylation, O glycan truncation, and *N*-and O linked glycan branching [138,139]. Mechanistically, TACAs arise either from [140] incomplete synthesis (originating from truncated structures - more common in early carcinogenesis) [141,142] or neo-synthesis processes (de novo synthesis of neoantigens is more frequent in advanced stages of several cancers) [143]. Noteworthily, these changes affect how the immune system responds to malignant cell transformations [144]. Strikingly, aberrant glycosylation is under the regulation of glycosylation enzymes- glycosyltransferases and glycosidases. After *N*-glycosylation or *O*-glycosylation, a series of fucosylation and sialylation are required to complete the assembly. The addition of sialic acid or fucose moieties to the *N*-linked or *O*-linked glycoproteins, the so-called glycan capping [145,146], is one of the most frequently occurring modifications in cancer [147]. It worth noting that these terminal variations have produced highly antigenic epitopes with species-specific functions. Aberrant sialylation and fucosylation are closely associated with the development and progression of cancer [148]. In particular, aberrant sialylation is one of the most common changes in glycosylation occurring in cancer that have been shown to correlate with tumor progression and metastasis [149]. In this vein, the most widely occurring changes in glycosylation linked to cancer progression include an enhancement of *N*-glycan branching due to increased activity of the glycosyltransferase β1,6-*N*-acetylglucosaminyltransferase-5 (GnT-5 or *MGAT5*), and alterations to α2-6 sialylated *N*-glycans - a modification driven by the sialyltransferase enzyme β-galactoside α-2,6-sialyltransferase 1 (ST6GAL1) [150]. Despite that alterations in glycosylation have emerged as a significant player in malignant transformation and tumor progression [151], cancer-associated glycans and glycosyltransferases remain largely unexplored as potential biomarkers or therapeutic targets [152].

### *N*-linked glycosylation

*N*-glycosylation allows tumor cells to resist cell death induced by chemotherapy [153]. Biochemically, *N*-Glycans consist of *N*-Acetylglucosamine (GlcNAc) attached by a β1-glycosidic linkage to the nitrogen atom of the amino group of Asn (N) at the consensus glycosylation motif Asn-X-Ser/Thr (in which X denotes any amino acid except for proline). These Asn-linked glycoconjugates contain a GlcNAc 2 mannose (Man) 3 core, to which a variable number of other monosaccha-rides can be added or removed. Additions determine whether the final structure is classed as a high-mannose *N*-glycan (in which only mannose residues are attached to the core), a hybrid *N*-glycan (addition of galactose or fucose residues along with mannose in the Golgi complex) or a complex *N*-glycan (addition of GlcNAc further extends the chain in the Golgi complex) [154]. Noteworthily, one of the major factors conferring structural variation of *N*-glycans is the variable number of GlcNAc branches [155]. Branching of the nascent N-linked glycan chain is initiated in the medial Golgi through a family of enzymes known as N-acetylglucosaminyltranferases (GnTs), which are encoded by MGAT genes. Strikingly, the degree of branching of N-linked glycans is dictated by the collective action of GnTs and ranges from hybrid glycans with a single antenna to complex N-glycans with bi-, tri-, or tetra-antennary structures [156]. In this context, GnT-5/*MGAT5* (encoded by the *GnT-5/MGAT5* gene) is a mammalian glycosyltransferase involved in complex *N*-glycan formation [157]. Mechanistically, GnT-5/*MGAT5* was found to be critical for the formation of tri- and tetra- antennary complex *N*-linked glycans by catalyzing the attachment of β1,6-GlcNac to an α1,6-linked mannose residue of the nascent *N*-glycan core as it passes through medial Golgi [158]. Strikingly, GnT-5/*MGAT5* is one of the most characterized cancer-associated glycosyltransferases that has long been implicated in tumor progression and metastasis [159,160]. A growing body of evidence suggests that malignant transformation is associated with increased expression of β1,6GlcNAc-branched *N*-glycans, resulting from enhanced expression of GnT-5/*MGAT5*, which is regulated by the RAS/RAF/MAPK signaling pathway in cancer [161]. Strikingly, GnT-5-dependent *N*-glycans play important roles in cell-cell and cell-matrix adhesion. Mechanistically, GnT-5 functionally modifies cell adhesion molecules, including the Epithelial cadherin (E-cadherin), and growth factor receptors, thereby promoting cancer cell migration and proliferation [162]. Within this context, the degree of *N*-glycan branching of several Receptor Tyrosine Kinases (RTKs) contributes to its capability to induce or arrest cellular proliferation [163,164]. Not surprisingly, a wide variety of malignant tumors exhibits a high expression of *MGAT5*, and this characteristic has also been related to the acquisition of malignant potential [165]. In this vein, the increased expression of the β1,6-GlcNAc–branched *N*-glycans has been linked to tumor aggressiveness and poor prognosis in several cancers involving the breast, colon, oesophagus, stomach, liver, brain (gliomas) and endometrium [166,167,168]. Reciprocally, loss of *MGAT5* has been associated with decreased tumor growth in multiple cancers both *in vitro* and *in vivo*, including Colorectal cancer (CRC) [169,170], breast cancer [171,172], nasopharyngeal carcinoma [173], lung adenocarcinoma [174], Hepatocellular Carcinoma (HCC) [175,176,177], and gastric cancer [178]. Recently, Hollander et al., demonstrated that loss of *MGAT5* results in tumor clearance that is dependent on T-cells and Dendritic Cells (DCs), with Natural Killer (NK) cells playing an early role. Using a panel of murine Pancreatic Ductal Adenocarcinoma (PDAC) clonal cell lines that recapitulate the immune heterogeneity of PDAC, they found that *MGAT5* is required for tumor growth *in vivo* but not *in vitro* which provides support for *MGAT5* as a target for clinical translation [179].

Furthermore, the β1-6-GlcNAc branch initiated by GnT-5/*MGAT5* can be further elongated by the addition of galactose to the initiating GlcNAc to produce the ubiquitous building block Galβ1-4GlcNAc, referred to as a type-2 *N*-acetyllactosamine or "LacNAc" sequence. The sequential addition of LacNAc disaccharides gives tandem repeats known as poly-*N*-acetyl-lactosamine (poly-LacNAc). This poly-LacNAc structure is a ligand for galectins (a family of conserved carbohydrate-binding proteins involved in a plethora of cellular activities), which bind to the carbohydrate structures of the receptors forming a lattice, which regulates their turnover on the plasma membrane, usually potentiating the signaling downstream [180,181]. Mechanistically, the ability of receptors to bind galectins is critically dependent on the degree of branching of their *N*-linked chains, in particular on the presence of the β1,6-branch synthesized by GnT-5/*MGAT5*. The functional role of branched *N*-glycosylation in cancer was later shown to be dependent on galectin binding and thereby altering the phenotype of the cell [182]. For instance, evidence

revealed that the galectin lattice formation due to interaction with the β1,6 attached poly-LacNAc *N*-linked glycans on the T-Cell Receptor (TCR) forms a spatial barrier that restricts spontaneous clustering of TCR in the absence of T cell-specific antigen [183,184]. In addition to regulating TCR clustering and signaling, further studies revealed that GnT-5/*MGAT5* is also critical to maintaining surface expression/retention of the inhibitory receptor CTLA-4/CD152 (cytotoxic T-lymphocyte–associated antigen 4) on T-cells due to enhanced CTLA-4-galectin lattice formation [185]. Not surprisingly, GnT-5/*MGAT5* is a therapeutic target for cancer and immune-related diseases [186]. Notably, complex and hybrid *N*-glycans may also carry a "bisecting" GlcNAc residue that is attached to the β-Man of the core by MGAT3 or GnT-3 (encoded by the *MGAT3* gene) [187]. Despite being involved in the suppression of cancer metastasis (contrary to GnT-5/*MGAT5*), bisecting GlcNAc are the commonest *N*-glycan alterations described in hematological malignancies. Mechanistically, it was suggested that this reduced metastasis was caused by functional alterations of E-cadherin by bisecting GlcNAc modification and suppression of Epithelial–Mesenchymal Transition (EMT) by MGAT3 [188,189]. Intriguingly, MGAT3, the enzyme responsible for the addition of bisecting GlcNAc residues, has been reported to be elevated in MM and chronic myeloid leukemia (CML) patients in blast crisis [190]. The experimental upregulation of MGAT3 in K562 leukemia cells enhanced resistance to NK cell's cytotoxicity and spleen colonization [191], *via* regulation of cell recognition by bisecting GlcNAc moieties [192].

**Receptor Tyrosine Kinases (RTKs)**

Importantly, glycosylation adds a second level of proliferation regulation by mediating growth factor receptor activation and structural alterations [193]. Within this context, one of the major cell surface protein groups implicated in the cellular signal transduction include glycoprotein Receptors with Tyrosine Kinase activity (RTKs) which control essential cellular processes like cell division, metabolism, differentiation, motility and death, ensuring homeostasis of the cell and the human body [194]. RTKs are important *N*-linked glycosylated proteins expressed by both immune cells as well as cancer cells which get activated by receptor modification and impact key features of metastasis like migration, invasion etc. Intriguingly, many RTKs linked to proliferation and survival are governed through glycosylation, including the Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor Receptor (FGFR), Epidermal Growth Factor Receptor (EGFR), v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ErbB2, also known as human epidermal growth factor receptor 2 (HER2) and neu), mesenchymal-epithelial transition factor (Met or c-Met), or insuli*N*-like growth factor receptor (IGFR, also known as CD221; IGFIR;IGF1R) [195]. These RTKs are all known to be regulated by cancer-associated glycans [196], glycosyltransferases [197], and proteoglycans (major constituents of the extracellular matrices as well as the cell surfaces and basement membranes) [198,199]. Not surprisingly, aberrant RTKs are associated with nearly all human cancers and RTKs constitute molecular targets for numerous selective therapies [200,201]. Typical RTK is composed of a highly glycosylated *N*-terminal extracellular ligand binding domain (ectodomain) which initiates receptor signaling upon binding to either soluble or membrane-embedded ligands, a single helical transmembrane domain and an intracellular tyrosine kinase domain [202]. Nevertheless, there is a large diversity found within their extracellular domains, which enables the recognition of structurally different ligands [203,204,205]. The diversity of extracellular domain structures allows for coupling of many unique signaling inputs to intracellular tyrosine phosphorylation but, importantly, this diversity is further increased by the fact that multiple ligands can typically interact with the same receptor [206]. On the other hand, the transmembrane domain plays a key role in the formation and stabilisation of the dimer of the receptor chains [207]. Notably, one of the factors that contribute to the diversity of RTK activities are post-translational modifications, including glycosylation of RTKs and their ligands. This post-translational modification may directly modulate RTK stability, ligand binding and cellular trafficking, deciding about strength, specificity and duration of the signals [208]. Not surprisingly, the glycosylation pattern of RTKs' extracellular ligand binding domains may largely differ between normal and cancer cells. Strikingly, a highly abundant RTK-attached glycans constitute multiple binding sites for galectins. Mechanistically, interaction of receptors with galectins and their consequent entrapment in a lattice promotes retention of receptors at the cell surface [209]. Intriguingly, most of RTKs are subjected to extensive site-specific *N*-and *O*-glycosylation. Depending on the receptor type and structure of the extracellular domain there is a great diversity in the number and type of glycan structures attached to RTKs. For instance, N Fujitani et al., found that the extracellular domain of ErbB2 possesses eight sequons, suggesting that ErbB2 is highly *N*-glycosylated. In addition to *N*-glycans, this study proposed a specific structure for the *O*-glycans that ErbB2 may possess, although the exact site was not definitively determined [210]. In a similar vein, A. Gędaj et al., showed that all FGFRs are heavily *N*-glycosylated in numerous positions within their extracellular domains; while 15 out of 22 members of their ligands (FGFs) are *N*-glycosylated and few FGFs are *O*- glycosylated [211]. Strikingly, *N*-linked glycosylation is a critical step in the maturation of transmembrane RTKs and plays a central role in RTK ligand binding, trafficking, and stability. For instance, the extracellular domain of the Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) is highly *N*-glycosylated and these *N*-linked glycans play a significant role in stabilizing the VEGFR-2 extracellular domain and may also influence ligand and drug binding to VEGFR2 [212]. In addition, the degree of *N*-glycan branching of several RTKs contributes to its capability to induce or arrest cellular proliferation. In this vein, it has been shown that growth-promoting receptors such as EGFR, IGFR and FGFR exhibit a higher number of *N*-linked chains than inhibitory receptors like Transforming Growth Factor Beta (TGF-β) Receptor (TGFBR) and CTLA-4 [213,214]. Noteworthily, EGFR is the most studied RTK and one of the four members of the Human Epidermal Growth Factor Receptor (HER) family receptors (EGFR/HER1/erbB1, HER2/erbB2, HER3/erbB3, and HER4/erbB4) [215]. Using the EGFR as a prototypical RTK, studies have shown that *N*-glycosylation is required for EGFR trafficking, efficient ligand binding, and receptor activation [216,217,218,219,220]. Mechanistically, *N*-glycosylation critically determines membrane interactions and structural arrangement of the ligand-binding EGFR ectodomain [221]. However, both fucosylation and sialylation of EGFR *N*-linked glycans has been shown to impact ligand binding and signaling [222]. As a result, it has been proposed that disruption of *N*-linked glycosylation could lead to a decreased expression level of mature RTKs and thus interfere with the RTK signaling cascades in cancers [223]. Showcasing

this, Contessa et al., found that nanomolar concentrations of the *N*-linked glycosylation inhibitor, tunicamycin (Tm), reduced the tumor cell protein levels of four RTKs (EGFR, ErbB2, ErbB3 and IGF1R) that contribute to tumor cell proliferation and survival. Mechanistically, disrupting this synthetic process impairs RTK signaling in tumor cells through retention of the receptors in the ER/Golgi compartments resulting in a reduction in RTK expression levels [224]. Not surprisingly, there is growing interest in exploring glycans found on RTKs as promising therapeutic targets, aiming to overcome drug resistance and advance cancer treatment strategies [225].

**The N-glycan-dependent quality control mechanism of glycoprotein folding**

Newly made membrane and secreted proteins undergo quality control as they enter the ER lume to ensure proper protein folding and function. Proper protein folding and localization depend on efficient glycosylation, without which cells may respond to the presence of unfolded protein by pathways that lead to apoptosis. Mechanistically, *N*-glycosylation directly affects the folding of glycoproteins by altering their biophysical properties [226]. As part of a quality control system for protein folding, *N*-glycans are recognized by two homologous molecular chaperones in the ER: Calnexin (CNX) and Calreticulin (CALR) [227]. Both CALR and CNX are $Ca^{++}$-binding L-type lectins that bind to monoglucosylated, high-mannose-type glycans. This binding keeps misfolded glycoproteins in the ER until they are correctly folded [228]. Interestingly, mutations in *CALR* were added to the 2016 version of the World Health Organization (WHO) classification for myeloproliferative neoplasms (MPNs) [229]. *CALR* mutations are the second most frequent mutation after *JAK2* in essential thrombocythemia (ET) (25% of patients) and primary myelofibrosis (PMF) (35% of patients). Surprisingly, *CALR*-mutant patients often have a more benign clinical course than those patients Janus kinase 2 (*JAK2*) V617F-mutated disease [230]. Trials using INCA033989 (a fully human monoclonal IgG1 antibody that selectively binds to mutated *CALR*) in *CALR*-mutated ET and/or patients with MF are expected soon [231]. Mechanistically, mutant *CALR* stabilizes the transmembranous MPL (myeloproliferative leukemia protein, also known as the Thrombopoietin Receptor or TPO-R), resulting in ligand-independent activation of MPL and downstream JAK–STAT signaling pathway activation [232,233,234,235,236,237]. Strikingly, mutations in *CALR* drive overstimulation of MPL signaling in a glycosylation-dependent manner. Specifically, mutant *CALR* binds the immature *N*-glycan form of the MPL in the ER. Subsequently, the complex is transported to the cell membrane, where MPL is constitutively activated by mutant *CALR*, leading to cytokine-independent proliferation and development of MPNs [238]. Interestingly, elucidating the mechanisms by which mutant CALR causes MPN paved the path for immunological targeting of this cell surface neoantigen (e.g., by mAbs) resulting in the abrogation of JAK–STAT signaling indicating successful inhibition of MPL activation [239]. It is worth noting that accumulation of UN- or mis I folded proteins in the ER lumen induce ER stress that triggers the Unfolded Protein Response (UPR) which either restores the balance of protein homeostasis or induces apoptosis of the damaged cell if it is deemed unrepairable [240]. Strikingly, UPR signaling is often dysregulated in leukemias and represents a novel therapeutic target [241]. Normally, the wild-type *FLT3* (*FLT3*-WT) is synthesized as a 130 kDa underglycosylated species but then is folded in the ER and exported to the Golgi apparatus, where it is glycosylated to form a 150 kDa protein prior to translocation to the cell surface [242,243]. By contrast, the FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD), which confers a strong negative prognosis in AML patients, is mostly retained in the ER as the underglycosylated 130 kDa species due to impaired glycosylation and folding [244]. Mechanistically, Marcotegui et al., showed for the first time that the protein SET (I2PP2A/TAF-Iβ) is involved in the transport of *FLT3*-WT to the membrane; however, *FLT3*-ITD mutation impairs the SET/*FLT3* binding, leading to its retention in the ER. Interestingly, results also showed that the *FLT3* inhibitor midostaurin promotes *FLT3* transport to the cytoplasmic membrane in part by facilitating *FLT3* binding to SET [245]. In this vein, the therapeutic induction of ER stress/UPR-mediated apoptosis has emerged as a promising avenue for the treatment of *FLT3*-ITD positive AML. In particular, 2-Deoxy-D-glucose (2-DG), tunicamycin and fluvastatin have has anti-proliferative and pro-apoptotic effects on *FLT3*-ITD positive AML by inhibiting *FLT3*-ITD *N*-glycosylation which keep *FLT3*-ITD in the ER [246,247,248]. Intriguingly, 2-DG displays a significant anti-leukemic activity in AML with *FLT3*-ITD or *KIT* D816V mutations, opening a new therapeutic window in a subset of AML with mutated RTKs [249]. Furthermore, 2-DG and Tm have also produced ER stress/UPR-mediated apoptosis in patients with T-ALL and B-ALL [250,251]. Noteworthily, 2-DG, because of its structural similarity to mannose, inhibits *N*-glycosylation *via* competition with endogenous D-mannose and misincorporation into the precursors of *N*-glycosylation [252]. Interestingly, Li et al., revealed that the combining 2-DG with imatinib resulted in a synergistic inhibition against CML cells, including those with T315I mutation that were otherwise resistant to imatinib alone [253]. Recently, Toshihiko et al., demonstrated that 2-DG-treated CAR T-cells augmented the efficacy of CAR T-cell therapy. Mechanistically, 2-DG causes CAR T-cells to resist immunosuppression in the TME *via* decreasing *N*-glycosylation of the heavily glycosylated immune-inhibitory receptors (PD-1 and CTLA-4) on T-cells and thereby decreasing their affinities to their ligands released from tumor cells (PD-L1 and CD80/CD86 respectively) [254]. In a similar vein, treatment with 2-DG prevented T-cells from binding to galectin-3 (a potent tumor antigen associated with T-cell anergy), resulting in suppression of galectin-3-induced T-cell apoptosis. Notably, human T-cells treated with 2-DG upregulated the NK-specific transcription factors TOX2 and EOMES, thereby acquiring NK cell properties, including surface marker expression and high levels of cytotoxic molecules, such as perforin/granzyme leading to enhanced cytotoxicity to tumor cells. Mechanistically, 2-DG-treated T-cells expressed higher levels of surface interleukin-2 receptor (IL-2R) with increased sensitivity to IL-2, resulting in greater secretion of perforin and granzyme. Moreover, cancer cells expressing Natural Killer Group 2D (NKG2D) ligands were killed more effectively by 2DG-treated T- cells than by control T-cells [255]. Furthermore, it is important to note that *N*-glycosylation also directly regulates T-cell function by altering the threshold of TCR activation [256]. The TCR, in association with CD8, recognizes a complex formed by antigenic peptides and class I MHC [257,258]. The association between the TCR and CD8 depends on reduced TCR glycosylation. Conversely, interaction of galectin-3 with *N*-glycan impairs TCR clustering and decreases T-cell activation by restraining lateral TCR movement [259]. Therefore, by disruption of this interaction, 2-DG promotes TCR clustering

with CD8 while decreasing the threshold for activation, resulting in a hyperimmune response.

**O-linked glycosylation**

Mucin-type O-glycans (O-GalNAc glycans) are a class of glycans initiated with *N*-acetylgalactosamine (GalNAc) α-linked primarily to Ser/Thr residues within glycoproteins and often extended or branched by sugars or saccharides. Mucin-type O-glycans were first observed on mucins. Mucins, the biomolecular components of mucus, are large and heavily glycosylated proteins (glycoproteins) that form a thick physical barrier at all tissue-air interfaces, forming a first line of defense against pathogens [260]. As they are carrying the greatest number of O-GalNAc glycans, mucins constitue an important source of glycopeptides in cancer. However, most secretory and membrane-bound proteins also receive O-GalNAc glycans, which are important in regulating many biological processes. Notably, mucin-type O-glycosylation is present at the interface between cells where it has important roles in cellular communication [261]. Cancers express altered mucin-type O-glycans. Physiologically, these tumor O-glycans comprise (1) oncofetal antigens, which are rare in normal adult tissue but expressed embryonically; (2) neoantigens, which are novel structures not appreciably expressed either embryonically or in normal tissues; and (3) altered levels of normal antigens. Normal adult tissues do not express oncofetal or neoantigens which makes them ideal for targeted diagnostics and therapeutics. Chemically, tumor O-glycans consist of both relatively small-sized, truncated O-glycans including the truncated glycans Tn, sialyl Tn, and T as well as the extended glycans ABO(H) and sialylated Lewis antigens on poly-LacNAc. Truncated O-glycans tend to be tumor-specific, or only found in tumors but not in normal cells, while altered terminal structures tend to be tumor-associated, with distinct changes noted in tumors but the structures themselves present in some normal tissues. Importantly, alterations in O-glycan terminal structures are also observed on *N*-glycans and glycolipids, in contrast to truncated O-glycans found only on O-glycans.

**Biochemistry**

Mucin-type O-glycosylation initiates with transfer of *N*-acetylgalactosamine (GalNAc) from UDP-GalNAc to Ser/Thr in a glycoprotein *via* an α-linkage to form GalNAcα1- Ser/Thr, which is also recognized as the Tn antigen [262]. This reaction is catalyzed by a family of enzymes called polypeptide GalNAc-transferases (ppGalNAcTs or GalNAc-Ts), consisting of 20 members in humans. Importantly, alterations in GalNAc-Ts expression patterns are associated with malignant transformation. In addition, some GalNAc-Ts have been have been characterized as diagnostic and prognostic markers [263,264,265,266,267,268 ,269,270,271,272,273]. Tn is a truncated form of the elongated cell surface O-glycan. The hypoglycosylation leading to Tn may occur when the enzyme responsible for O-glycan Elongation-T-synthase-or its associated chaperone-Cosmc-becomes functionally inhibited [274]. Expression the Tn antigen may itself be involved in driving oncogenesis as its expression directly induces oncogenic features, including dysplastic morphology, increased invasive properties, and decreased cell-cell and cell-matrix adhesion [275,276,277,278,279]. The Tn antigen has been shown to modulate immune cell interactions through interactions with the macrophage galactose C-type lectin (MGL) [280,281,282,283]. Intriguingly, G. Libisch et al., found a Tn antigen expression in most of the CLL patients studied when the VVB4 lectin was used. Gene expression analysis showed for the first time that GALNT11, which encodes the polypeptide *N*-acetylgalactosaminyltransferase 11 (GalNAc-T11), is overexpressed in 96% of B-CLL cells when compared to normal B- cells. GalNAc-T11mRNA was also present in Jurkat (leukemic T-cell lines) and T-cells, but was not detected in Daudi cells (leukemic B-cell lines). Because GalNAc-T11 is present in B–CLL cells and in T-cells from healthy donors, while its expression is very low in normal B-cells, it seems that GalNAc-T11 could be included with ZAP-70 among markers normally expressed by T-cells, which are aberrantly expressed by B–CLL cells. These results suggest that *GALNT11* constitutes a new molecular marker for CLL capable to act as surrogate marker for unmutated IGHV genes with poor prognosis, and is associated with the progression status of the disease and LPL expression. In this vein, since there is not a perfect concordance between ZAP-70, LPL and the *IGHV* mutational status, further work is needed to better define whether the addition of *GALNT11* expression could improve prognosis assessment in CLL patients [284]. Synthesis of Tn antigen is typically followed by transfer of galactose (Gal), GlcNAc, or GalNAc to the Tn antigen to form core O-glycan structures 1–8. Cores 5–8 are rare structures, whereas cores 1–4 are common. Alternatively, the Tn antigen can be sialylated by *N*-acetylgalactosamine α2,6 sialyltransferase 1 (ST6GALNAC1), which generates sialyl Tn antigen on O-glycans and prevents LacNAc formation on O-glycans (which inhibits galectin-3 binding; see below). Core 1 (Galβ1–3-GalNAcα-Ser/Thr) is synthesized by the T-synthase (Core 1 β3-galactosyltransferase, C1GalT1), which transfers Gal from UDP-Gal to Tn in the cis- and medial-Golgi. Core 1 is the most common O-GalNAc glycan that forms the core of many longer, more complex structures. It is antigenic and is also named the Thomsen-Friedenreich (TF or T) antigen. The oncofetal TF antigen can also be expressed in various pathologies, such as cancer, as well as on activated B-cells during a germinal center reaction. Indeed, the TF carbohydrate antigen is a pan-carcinoma antigen highly expressed by about 90% of all human carcinomas (normally covered by more expanded glycosylation and sialylation in normal epithelium) [285]. Notably, MUC1 is amongst the few proteins known to express unsubstituted TF antigen [286,287]. Interestingly, core 1 is classically defined as a type 3 chain (Galβ1–3GalNAc-R) and can serve as a platform for blood group antigens, such as H, A, and B antigens, as well as for O-glycan-specific modifications such as the Cad (Sda) antigen, which is also found on extended core 2, 3, and 4 structures. Core 1–4 structures are often extended to form various structures. Core 1- and core 2-based structures are ubiquitously expressed. On the other hand, core 3 is restricted to the GI tract in humans (most often found on mucins in the colon) and core 4 is formed from core 3 by the addition of GlcNAc to GalNAc with a β1,6-linkage. Strikingly, cores 3, 4, and their extended structures are generally not observed in cancer cell lines [288,289]. In fact, the expression of the core 3 is down-regulated in colon cancer tissues and colon cancer cell lines, while the expression of core 1 and core 2 is up-regulated [290,291].

**Extended core 1:** Core 1 can be further converted to core 2 O-glycan by one of three β1,6-*N*-acetylglucosaminyltransferases (Core 2 GlcNAc Transferases, C2GnT1–3) that add GlcNAc to the core 1 O-glycan [292]. Core 2 GlcNAc Transferases have recently been shown to be necessary for proper function of the innate immune system, since core 2 O-glycans are essential for selectin ligand biosynthesis [293]. C2GnT1 (GCNT1) and C2GnT3 (GCNT4) only modify core 1 to form core 2 structures,

whereas C2GnT2 (GCNT3) can also modify core 3 to form core 4 structure. Noteworthy, the expression of C2GnT1 (GCNT1) is associated with the progression of several cancers [294]. Notably, core 1 is most often sialylated by ST3GAL1 (responsible for adding α2,3-linked sialic acids to substrates to generate α-2,3 sialylated core 1 O-glycans) and/or ST6GALNAC 1-4 to form mono or disialyl core 1. In addition, core 1 can be elongated or extended by Core 1 β3-*N*-acetylglucoaminyltransferase (Core 1 GnT) by transferring GlcNAc from UDP-GlcNAc to form extended core 1, GlcNAcβ1–3Galβ1–3GalNAcα1-Ser/Thr. This can be further modified by other glycosyltransferases to form sulfated sLeX structures on extended core 1. Noteworthily, extended core 1 O-glycans are expressed by specialized endothelial cells within the high endothelial venules (HEVs) and these also contain sulfated GlcNAc residues within the sLeX motif (6-sulfo- sLeX) [295].

**Extended core 2:** Extended core 2 are quite common and mediated by alternating activity of β4GalTs and β3GnTs, which form polyLacNAc chains based on type 2, repeats (3Galβ1–4GlcNAcβ1-)n. These structures can be expressed as linear (nonbranched) chains, branched by I-branching β-1,6-*N*-acetylglucosaminyltransferase (Gcnt2, also known as β1–6GnT-I or IGnT) to form branched structures, and/or modified by fucosyltransferases, ST3Gal- and ST6Gal-sialyltransferases, sulfotransferases, etc., to form various blood group antigens as well as Lewis, sialyl Lewis, and sulfo sialyl Lewis structures. Intriguingly, these linear and branched polyLacNAc chains represent the fetal i antigen and the adult "I-branches" (I-blood group antigen) respectively. The blood group I antigen is present on adult human erythrocytes and many mucins, whereas the i antigen is expressed on fetal human erythrocytes. Interestingly, the blood group I antigen is found in *N*-glycans and glycolipids, in addition to *O*-glycans [296].

### Mucins

Mucins-barrier glycoproteins that form mucus and other gel-like secretions -are densely *O*-glycosylated glycoproteins that play critical roles in a host of healthy and disease-driven biological functions [297]. Glycoproteomics and prediction algorithms identified mucin-type *O*-glycans on ~83% of proteins entering the ER–Golgi secretory apparatus, including many non-mucin proteins [298]. This indicated that mucin-type *O*-glycans are ubiquitous [299]. In particular, mucins are dominant carriers of cancer-associated carbohydrates and they are able to amplify changes at the surface of the cancer cells [300]. Mechanistically, cancer-associated mucins form nanoscale material barriers that resist attack by immune cells, including NK cells and CAR T-cells. Interestingly, glycocalyx editing with mucin degrading enzymes including sialidases (enzymes that cleave terminal sialic acids from glycoproteins and glycolipids) and mucinases (enzymes capable of degrading mucins) can overcome the glycocalyx armour of cancer cells [301]. Not surprisingly, mucins have long been a target of interest in oncology [302]. Within this context, the mucins MUC1, MUC2, MUC4, and MUC16 are mucins associated with cancer progression, whereas [303], whereas MUC1 (also known as CA 15-3, the most widely used serum marker in breast cancer), MUC4, and MUC16 (also known as Ovarian cancer-related tumor marker CA125) serve as circulating biomarkers of different types of cancer [304]. MUC1/ CD227 (also known as episialin, EMA, PEM, CA15–3 and DF3) is a a large and heavily glycosylated transmembrane mucin protein expressed at the apical surface of epithelial cells at mucosal surfaces including the breast tissue, airways, and gastrointestinal tract where it has a barrier function against bacterial invasion [305]. MUC1 is is the most intensively studied transmembrane protein of the mucin family [306]. Interestingly, MUC1 was the first identified transmembrane mucin in many solid tumors and hematopoietic cancers, which is often upregulated and aberrantly glycosylated, making it a potential therapeutic target for cancer immunotherapy [307]. MUC1 consists of a large extracellular domain, a transmembrane region and a short cytoplasmic domain/tail. The MUC1 extracellular domain contains variable numbers of 20-amino acid tandem repeat peptides (VNTR) that are heavily glycosylated (up to 50% of the MUC1 molecular weight) with complex *O*-linked mucin type glycans [308]. Physiologically, MUC1 forms a protective barrier through the mucosal surface and protects the cells from extreme environmental conditions. Pathologically, MUC1 loses polarity upon malignant transformation and becomes overexpressed and aberrantly glycosylated, revealing an immunogenic region of tandem repeats of 20 residues. The novel MUC1 glycoforms that arise carry shortened glycan moieties: Tn (GalNAc), T (Galβ1, 3GalNAc), sT (NeuAcα2, 3Galβ1, and 3GalNAc), and sTn (NeuAcα2, 6GalNAc) [309,310]. In this vein, numerous studies have shown that interactions of sialylated glycans of tumor-associated MUC1 with Siglecs promote tumor immune escape, ultimately affecting the body's antitumor immunity [311,312]. Not surprisingly, MUC1 is commonly overexpressed (up to 10-fold ) in various epithelial adenocarcinomas including lung, liver, colon, breast, pancreatic, and ovarian cancer where it has intracellular signaling functions and plays a significant role in cancer development [313]. Strikingly, MUC1 interacts with various cellular proteins involved in regulating proliferation, adhesion and immunomodulation of epithelial cancers. One such interaction is with EGFR, an important regulator of epithelial cell growth and survival in normal and cancerous tissues [314]. In this context, MUC1 is associated with EGFR in epithelial cancers such as breast, pancreatic, endometrial and lung. Of particular interest, EGFR mutations are the most common oncogenic drivers in Non-Small-Cell Lung Cancer (NSCLC) [315]. EGFR exists normally in an inactive conformation but its activity is increased in neoplasia. Interestingly, Engel et al., showed for the first time that MUC1 increases expression and signaling of EGFR which indicates that MUC1-EGFR co-expression is associated with increased cellular proliferation in human tumors, highlighting the importance of MUC1-driven EGFR expression and signaling [316]. Not surprisingly, EGFR has become a principal therapeutic target for cancer treatment. Examples of established EGFR inhibitors include the reversible inhibitors (gefitinib and erlotinib) and the irreversible inhibitors (dacomitinib, osimertinib, and poziotinib) which have become prominent and effective treatments for EGFR-driven NSCLC [317]. Furthermore, MUC1 promotes the migration and invasion of a variety of cancers and can lead to the emergence of drug resistance during cancer therapy [318]. MUC1 appears in many hematological malignancies, including T-cell and B-cell lymphomas and myelomas [319], and is a potential prognostic marker and therapeutic target for several types of Non-Hodgkin Lymphomas (NHLs) [320,321].

### Fucosylation

The process of transferring fucose from GDP-fucose to their substrates catalyzed by fucosyltransferases is referred to as fucosylation. Fucosylation is a nonextendable modification and generally sub divided into terminal fucosylation (giving rise to specific Lewis blood-group antigens) and core fucosylation.

Pathologically, abnormal fucosylation is associated with various cancers. The process of fucosylation relies on a series of Fucosyltransferases (FUT1-11). Fucosyltransferase 8 (FUT8) is the most important FUT in mammalian cells, which catalyzes the transfer of GDP-β-L-fucose to the *N*-sugar chain of Asn in the adjacent GlcNAc residues to form core fucose (Fuc) [322]. Interestingly, FUT8 is the only enzyme responsible for core fucosylation of *N*-glycans during glycoprotein biosynthesis [323]. Core fucosylation directly modulates the biological activity of glycoproteins, such as the bioactivities of several tyrosine kinase receptors [324,325], and the Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) of IgG antibodies [326]. For instance, the expression of FUT8 is important for the biological functions of TGF-β receptors, keeping in mind that TGF-β is a major inducer of EMT in different cell types, and TGF-β-mediated EMT is thought to contribute to tumour cell spread and metastasis [327]. As a matter of fact, over 90% of *N*-glycans from human serum IgG are core fucosylated [328]. Intriguingly, removal of core Fuc from therapeutic IgG was found to raise its ADCC by about 100-fold [329], and this approach is now used clinically. In addition, FUT8 has been reported as a responsible factor for the synthesis of cancer-associated *N*-glycan structures [330,331]. Not surprisingly, enhanced core fucosylation is often associated with cancer progression [332]. Showcasing this, the upregulated expression of FUT8 has been reported in several cancers, including lung cancer [333], prostate cancer [334], HCC (a major form of liver cancer) [335,336,337], and CRC, for which FUT8 was discovered as a prognostic marker in patients with stage II and III CRC, demonstrating that FUT8 is involved in biological tumor characteristics and patient outcomes [338]. Besides, the upregulated expression of FUT8 increased the fucosylation of the TGFBR and its downstream signaling, promoting the breast cancer tissue invasion and metastasis [339]. It is worth noting that core fucosylation of alpha-fetoprotein (AFP-L3 fraction) due to the upregulation of FUT8 in HCC cells is a FDA-approved serum tumor marker for the specific diagnosis of HCC [340,341]. Among the family of FUTs, there are six α-1,3-FUTs that specifically modify terminal lactosaminyl glycans, the last step in biosynthesis of Lewis X antigens (i.e. "Lewis X" (Le X ; CD15) and "sialyl Lewis X" (sLeX ; CD15s) [342]. Notably, upregulated α-1,3-FUTs activity, resulting in the overexpression of LeX and sLeX determinants, is etiologic in several human diseases including cancer and autoimmune conditions [343,344,345,346,347,348]. The principal α -1,3-FUTs that mediate sLeX creation (the canonical binding determinant for selectins) are FUT6 and FUT7 [349], with FUT9 dominating LeX synthesis [350]. FUT7, which makes only sLeX, was significantly upregulated in AML M5. FUT7 fucosylation has also been reported to play a crucial role in the generation of PSGL-1 (also called CD162), expressed on the surface of most leukocytes, is a counter-receptor for P-selectin [351]. Interestingly, adult T-cell leukemia/lymphoma (ATLL) cell lines strongly express sLeX which is dependent on FUT7 [352,353,354,355]. Mechanistically, HTLV-1, the etiologic agent of ATLL, encodes a transcriptional activator protein (TAX) which regulates the *FUT7* gene [356].

### *O*-GlcNAcylation

*O*-GlcNAcylation was discovered in the 1980s, overturning the previously accepted dogma that protein glycosylation did not occur in the nucleus and cytoplasm. Indeed, it has been shown that *O*-GlcNAcylation plays an important role in a broad range of cellular functions by modifying nuclear, cytosolic, and mitochondrial proteins. Chemically, *O*-GlcNAcylation is a ubiquitous form of intracellular glycosylation [357], that results when the amino-sugar GlcNAc made in the hexosamine biosynthetic pathway (HBP) is covalently attached to Ser/Thr residues in thousands of proteins in the nucleus, cytoplasm and mitochondria by the glycosyltransferase *O*-linked GlcNAc transferase (OGT). *O*-GlcNAcylation is an abundant protein post-translational modification. There are known to be at least 8000 human proteins modified and regulated by this dynamic sugar modification of proteins [358].

Furthermore, *O*-GlcNAcylation has extensive crosstalk with phosphorylation both at the site level on polypeptides and by modifying many kinases. *O*-GlcNAcylation also cross-talks to regulate ubiquitination, methylation, acetylation, and other post-translational modifications [359]. Like phosphorylation and ubquitination, *O*-GlcNAcylation regulates many different cellular processes [360]. Intriguingly, *O*-GlcNAcylation appears to be particularly abundant on proteins involved in signaling, stress responses, and energy metabolism [361]. Not surprisingly, *O*-GlcNAcylation is highly sensitive to nutrient availability and stress, and levels of protein *O*-GlcNAcylation change in response to nutrient availability and metabolic, oxidative, and proteotoxic stress [362]. In addition, *O*-GlcNAcylation plays a role in a broad range of biological processes, such as transcription, translation, enzyme activity, cell division, protein localization and degradation [363]. Intriguingly, the dynamic and reversible modification of nuclear and cytoplasmic proteins by *O*-GlcNAcylation has the potential to significantly alter immune responses. For instance, *O*-GlcNAcylation is essential in the process of lymphocyte activation in both B- and T-lymphocytes [364]. Therefore, understanding the precise molecular mechanisms involving *O*-GlcNAcylation in the immune system is critical for developing new therapeutics for immune and inflammatory diseases, as well as for lymphoid and myeloid cancers [365]. The donor sugar for *O*-GlcNAcylation, uridine-diphosphate *N*-acetylglucosamine (UDP-GlcNAc), is synthesized from glucose through the HBP. The recycling of *O*-GlcNAc on proteins is mediated by two highly conserved and ubiquitous nucleocytoplasmic enzymes that carry out its addition and removal. OGT is the only enzyme capable of adding *O*-GlcNAc to proteins, and *O*-GlcNAcase (OGA) removes it [366]. By the way, the UDP-GlcNAc metabolite is a common substrate for *O*-GlcNAcylation and for *N*-glycan branching. Furthermore, despite being a type of protein glycosylation, *O*-GlcNAc is very different from other *N*-linked and O-linked glycans [367]. Firstly, *O*-GlcNAcylation occurs mostly on intracellular proteins (confined to nucleocytoplasmic and mitochondrial compartments). Secondly, *O*-GlcNAc moiety remains as a monosaccharide (i.e., not generally elongated or modified). Thirdly, in contrast to the dynamic nuclear/cytoplasmic *O*-GlcNAcylation, *O*-glycans in the secretory pathway are stable throughout the life of the glycoprotein (unless acted upon by glycosidases, such as sialidases/neuraminidases derived from pathogens during infection). Cancer cells, including lymphoid and myeloid malignancies, display enhanced levels of *O*-GlcNAcylation, likely due to their relatively higher levels of glucose flux and altered growth kinetics [368]. Within this context, evidence indicates that the HBP, specifically through *O*-GlcNAcylation, helps fuel cancer cell metabolism, growth, survival, and spread [369]. Cancer cells also show increased OGT expression, which increases *O*-GlcNAcylation and promotes cancer cell proliferation and resistance to chemotherapy

[370]. Consequently, elevated *O*-GlcNAcylation (hyper-*O*-GlcNAcylation) is a signature of cancer-specific metabolism and linked to various hallmarks of cancer, including cancer cell proliferation, survival, invasion, and metastasis; energy metabolism; and epigenetics [371]. Not surprisingly, hyper-*O*-GlcNAcylation has emerged as a new hallmark of cancer [372]. Hyper-*O*-GlcNAcylation is a general feature of several cancers including breast, prostate, pancreas, lung and colon [373] but also occur in hematologic malignancies. In this context, MM cells resistant to bortezomib were found to have higher concentration of UDP-GlcNAc and OGT levels as compared to bortezomib-sensitive cells [374]. Y. Jin et al., showed for the first time an increased GlcNAcylation in the BM of MM patients, and by using AANL6, a mutant Agrocybe aegerita GlcNAc-specific lectin, found that the combined expression of two secreted glycoproteins (FBLN1and DKK1) can be used as a novel clinical biomarker for the diagnosis of MM [375]. These findings suggest that increased GlcNAcylation is associated with the pathogenesis of MM, which could potentially have therapeutic implications. Converesly, CLL cells express high levels of *O*-GlcNAcylated proteins, such as p53, c-Myc, and Akt but are surprisingly associated with with an indolent clinical behaviour [376]. This observation is somewhat paradoxical as important signaling pathways in CLL including the NFκB, MEK/ERK, PI3K/AKT/mTOR, JAK, and Notch pathways can all be affected by *O*-GlcNAcylation. Reasons for the inverse correlation between total *O*-GlcNAcylated protein levels and clinical course in CLL are still unclear [377].

**Aberrant sialylation**

In 1957, a 9-carbon acidic (based around an alpha-keto acid core) monosaccharide was designated "sialic acid" and is one of the ten monosaccharides used in the enzymatic process of glycosylation in mammals [378]. Sialic acids are predominantly found at the non-reducing end of *N*-linked and O-linked glycans attached to glycoproteins or glycolipids. Fundamentally, all jawed vertebrates have cell-surface glycans that terminate with sialic acid residues [379]. Intriguingly, these sialic acids have a pivotal role in infection (viruses, bacteria, protozoa) [380]. The sialic acid family consists of nearly 50 members that are derivatives of *N*-acetylneuraminic acid (Neu5Ac), *N*-glycolylneuraminic acid (Neu5Gc), and 3-deoxy-d-*glycero*-d-*galacto*-non-2-ulopyranosonic acid (deaminoneuraminic acid; 2-keto-3-deoxy-d-*glycero*-d-*galacto*-nononic acid; Kdn). However, Neu5Ac is the most abundant sialic acid in humans [381] and serves as a key marker of self in glycan-coding sequences [382]. Sialylation is defined as the terminal addition of sialic acid to the oligosaccharide and glycoconjugates. This enzymatic process is tightly regulated by Sialyltransferases (STs) and sialidases/Neuraminidases (NEUs) in normal cells. There are twenty Golgi localised sialyltransferases with different substrate and linkage specificity in charge of protein and lipid sialylation in humans [383]. On the other hand, only 4 mammalian sialidases (NEU1, NEU2, NEU3 and NEU4) release sialic acids from sialylated glycoconjugates [384]. However, the accumulation of sialylation in tumors is due to the high expression of sialyltransferases and the altered expression of sialidases [385]. Not surprisingly, both sialyltransferase inhibitors [386,387] and sialidases have emerged as novel anticancer therapeutic interventions in cancer [388]. Based on the category of glycosidic linkage, sialylation can be classified into three types: α2-3-, α2-6-, and α2-8-sialylation [389]. As sialic acids decorate the majority of mammalian glycans at the cell surface and in the extracellular space, they are considered as SAMPs [390,391]. Physiologically, sialic acids confer a negative charge to the sialylated glycoproteins and glycolipids that contribute to glycoconjugates' biophysical and physiological functions. Pathologically, sialylation modifies the conformation of essential proteins to promote cancer cell proliferation, invasion, and migration. Recently, Tharp et al., found that the physical properties of the microenvironment influence immune surveillance *via* compositional and topological dynamics of the sialic acid-containing glycocalyx [392]. Aberrant sialylation is the most critical change in glycosylation occurring in cancer. It is not only a consequence of tumor transformation but is a driver of the malignant phenotype. Therefore, aberrant sialylation is an established hallmark of several types of cancer. The alterations of sialic acid processing have two main implications:

1. Hypersialylation: a general upregulation of sialoglycans (sialylated glycans) on cell surfaces of tumors. Sialoglycans including sialyl-Tn (sTn), sialyl-T (sT) and sialyl-Lewis antigens, polysialic acid, and gangliosides are often exploited as tumor-associated antigens (i.e., as markers for cancer detection and monitoring) [393,394]. By interaction with sialoglycan-binding lectins, including Siglecs and selectins, hypersialylation has been linked to immune evasion, drug resistance, tumor invasiveness, and metastasis. In fact, the ability of tumor cells to metastasise correlates with total sialic acid levels [395].

2. An increased introduction of the non-human sialic acid Neu5Gc instead of Neu5Ac into cell surface glycans.

**Sialyltransferases**

Hypersialylation is the result of dysregulated expression of sialyltransferases. Sialyltransferases are categorized under inverting glycosyltransferases, i.e., enzymes which invert the stereochemistry of the donor's anomeric bond (α → β). In the Golgi apparatus, these enzymes catalyze the transfer of sialic acid moiety from an activated sugar nucleotide donor, that is, CMP-Neu5Ac (Cytosine 5′-monophosphate *N*-acetylneuraminic acid) to non-reducing positions of acceptors such as galactose, *N*-Acetyl galactosamine, and other sialic acid residues [396]. Altered sialyltransferase expression leads to the formation of specific sialylated structures [397]. Notably, an increase in α2,6 sialylation on *N*-glycans (the addition of α2,6-linked sialic acids onto subterminal galactose residues of lactosaminic chains of N-glycans), a modification driven by ST6GAL1 is a common change in tumor cell glycosylation [398]. In this vein, Munkley et al., have recently revealed the mechanisms underlying how ST6GAL1-mediated aberrant sialylation of *N*-glycans promotes prostate cancer bone metastasis and provided proof-of-concept data to show that sialic acid blockade can inhibit bone metastasis which is a common, debilitating and incurable consequence of advanced prostate cancer [399]. In addition, the α2-3 sialyltransferases (ST3GAL) family transfer sialic acid residue in an α2,3-linkage to terminal Gal residues present on glycolipids or glycoproteins resulting in the synthesis of gangliosides (ST3GAL2 and 5), the tumor-associated sialyl-T (sT) (ST3GAL1) and the sialylated derivatives of Lewis antigens (sialyl-Lewis X [sLeX]), sialyl-Lewis A [sLeA]). Within this context, ST3GAL3, ST3GAL4 and ST3GAL6 are involved in the synthesis of sLeX, while sLeA (also known as carbohydrate antigen 19-9 [CA19-9] which serves as a tumor marker) is predominantly generated by ST3GAL3 [400]. Sialyltransferases are implicated in cancer and immune suppression by synthesizing sialoglycans, which act as ligands for Siglec receptors [401]. Moreover, the tumor markers sLeA and sLeX are ligands for selectins [402]. Since selectins are one of the

main mediators of leukocytes trafficking, it is conceivable that sLeA and sLeX are potentially involved in the malignant behavior of cancer cells as they both promote tumor metastasis [403,404]. In a similar vein, the dysregulated expression of the sialyltransferase ST3GAL6, a key regulator of selectin ligand synthesis, is implicated in disease progression and survival in MM [405]. Mechanistically, the upregulation of sialyltransferases promotes tumor metastasis *via* several routes, including stimulating tumor invasion and migration through integrin-mediated processes, inhibiting Fas-mediated apoptosis and evading immunosurveillance [406]. For instance, ST6GAL1–mediated sialylation of EGFR influences integrin-dependent adhesion and cell mechanics across different cancer cell lines [407]. Interestingly, studies have shown that inhibition of sialyltransferases reduces cancer metastasis [408,409]. Furthermore, sialyltransferases can promote resistance to chemotherapy and radiotherapy [410,411,412,413]. Within this context, the expression of sialylated antigens on the cell surface is emerging as an important feature of cancer cell Multidrug resistance (MDR). MDR is a well-established cause of chemotherapy failure and disease progression in patients with leukemia [414]. The efflux of cytotoxic drugs mediated by transporter proteins belonging to the ATP binding cassette (ABC) family is the "classical MDR" pathway [415]. In fact, MDR is conventionally regarded as the consequence of overexpression of ABC transporters in tumor cells which lead to lower intracellular drug accumulation and hence reduce cellular toxicity of chemotherapeutic agents [416]. While there is strong evidence that activation of the phosphoinositide 3 kinase (PI3K)/Akt signaling network plays a significant role in rendering AML blasts drug resistant, data confirmed the correlation of the ST6GAL1-mediated PI3K/Akt signaling pathway with multidrug resistance [417,418]. It has been reported that the PI3K/Akt signaling enhances drug efflux by transporter proteins belonging to the ATP binding cassette (ABC) family in order to maintain MDR of tumor cells [419]. In fact, MDR is conventionally regarded as the consequence of overexpression of ABC transporters which lead to lower intracellular drug accumulation and hence reduce cellular toxicity of chemotherapeutic agents. The two main members of ABC transporters frequently used as markers to screen MDR patients clinically are P-glycoprotein (P-gp) and MDR-associated protein 1 (MRP1). While the membrane glycoprotein P-gp actively pumps cytotoxic agents out of cells and decreases their intracellular concentration [420], MRP1 plays an active role in protecting cells by its ability to efflux a vast array of drugs to sub-lethal levels [421]. Interestingly, ST6GAL1 was found to increase the expression of P-gp and MRP1 through PI3K/Akt pathway, thereby mediating MDR of leukemia cells [422]. Table-2 delineates the role of several sialyltransferases in hematologic malignancies.

**Table 2:** The role of selected sialyltransferases in hematologic malignancies

| Enzyme elevated | Antigen | Significance | Reference (s) |
|---|---|---|---|
| ST6GALNAC4[1] | disialyl-T[2] | As disialyl-T antigen protects CLL B-cells from NK cell cytotoxicity, disialyl-T antigen is a potential prognostic marker of CLL | [423] |
| ST6GAL1 | α2–6 sialylated N-glycans | Overexpression of this glycotope is detected in patients with MDR AML and CML | [424] |
| ST3GAL1 [3] | Sialylated TF antigen | Increased expression of ST3GAL1 (either alone or combined with increased expression of ST3GAL6) identified a subgroup of MM patients with particularly poor outcome | [425] |
| ST3GAL4 | sLeX [4] | Elevated expression was found in CML cells with imatinib resistance | [426] |
| | | Upregulated in M5 AML [5]<br>Associated with poor survival in AML patients<br>Significantly upregulated in patients displaying MDR phenotype | [427] |
| ST8SIA4 | Polysialic acid | Cellular MDR phenotype in CML positively correlated with ST8SIA4 and ST8SIA6 levels [7] | [428, 429] |
| ST8SIA6 | disialic acids (specifically on O-linked glycoproteins)[6] | | |
| ST3GAL5 and ST8SIA4 | sialylated N-glycans | Overexpressed in association with MDR of AML cells | [430] |
| ST6GALNAC4 | disialyl-T | Associated with chemoresistance in AML cell lines and AML patients<br>ST6GALNAC4 showed a significant upregulation in M6 AML | |
| ST3GAL6 [8] | sLeX | ST3GAL6 expression is positively correlated with homing and engraftment of MM cells<br>High expression of ST3GAL6 in MM cell lines and patient samples is associated with inferior outcomes | [431] |
| ST6GalNAc IV | sialyl-T antigen | The major enzyme controlling the expression of sialyl-T antigen in leukemia cell lines | [432] |
| ST8Sia I (GD3 synthase) | GD3 | Upregulated in HTLV-I -positive adult T-cell leukemia cell lines | [433] |

| | | | |
|---|---|---|---|
| ST3GAL5 (GM3 synthase) | GM3 | Upregulated ST3GAL5 (and ST6GAL1) positively correlated with the high risk of pediatric ALL | [434] |
| ST8Sia II and ST8Sia IV | Polysialic acid | Found on the unidentified proteins in basophilic leukemia cell lines | [435] |
| ST3GAL3 | sLeA and sLeX | Several cases of lymphoma displayed strong cytoplasmic staining | [436] |
| | | *ST3GAL3* is one of the genes that showed an increase in methylation in MDS/secondary AML compared with de novo AML specimens | [437] |

**Note:** [1]Patients with high MYC expression are also likely to have high ST6GALNAC4 expression. High ST6GALNAC4 expression, among all sialyltransferases, is the strongest predictor of adverse patient outcomes in BL, DLBCL, CLL, and T-ALL, which notably all have high MYC activity
[2]This glycotope is recognized by Siglec-7. CD162/PSGL-1 and CD45 are the major carriers of disialyl-T antigen on CLL B-cells.
[3]The primary role of ST3GAL1 is to catalyze the attachment of Neu5Ac and Thomsen-Friedenreich (TF) antigens (Gal-β1,3-GalNAc), resulting in the production of sialylated TF antigens.
[4]ST3GAL4 contributes to the synthesis of either Siglec-9 or selectin ligands. ST3GAL4 is one of three sialyltransferases attaching sialic acid to N-glycans *via* α2,3 linkage in mammals (along ST3GAL3 and ST3GAL6), with ST3GAL4 likely to play a major role.
[5]Based on ST3GAL4/FUT7 expression, M3 cells may also be a subtype with elevated sLeX levels.
[6] This is the first report of a mammalian α2,8-sialyltransferase that preferentially sialylates O-glycans.
[7] This study indicated that α-2,8-sialyltransferases involved in the development of MDR of CML cells probably through ST8SIA4 regulating the activity of phosphoinositide-3 kinase (PI3K)/Akt signaling and the expression of P-gp.
[8] ST3GAL6 contributes to formation of Siglec and Selectin ligands.
BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; HTLV-1, the human lymphotropic virus type 1; MDR, multidrug resistance.

### Hypersialylation

Hypersialylation is an established hallmark of several cancers where it is directly proportional to their metastatic phenotype and poor prognosis [438,439]. Tumor cells commonly mask themselves by hypersialylating their surface glycans leading to the enhanced expression of sialoglycans, which through the interaction with Siglec receptors, leads to immune evasion by shutting down anti-tumor responses. Mechanistically, sialoglycans on the hypersialylated cancer cell surface bind to Siglecs on immune cells to mediate immunosuppression, inhibiting the cytotoxicity of NK cells and the activation of T-cells, and inducing a Tumor-Associated Macrophage (TAM) phenotype, to promote continued tumour growth. Hypersialylation can also induce immune evasion by interference with the complement system *via* a "molecular cloaking" mechanism mediated by Factor H sequestration and dampening of the complement-mediated cell lysis and opsonisation [440]. Conversely, sialic acid deficient tumors showed a favorable T-cell landscape characterized by enhanced $CD8^+$ T-cells and decreased $CD4^+$ regulatory T-cells (Tregs). Noteworthily, $CD8^+$ T-cells are end effectors of cancer immunity; and hence, most forms of effective cancer immunotherapy involve $CD8^+$ T-cell effector function [441]. Not surprisingly, targeting sialic acids synergizes with immunotherapy and can improve survival [442]. Additionally, sialic acids represent critical determinants of selectin ligands, which contribute to extravasation of immune cells to target organs and sites [443]. The expression of selectin ligands (SleA/X) on cancer cells seems to correlate with metastatic phenotype [444,445,446,447,448]. For instance, E-selectin ligands expressed on MM cells played a role in BM homing and possibly retention of the malignant cells in the BM [449,450]. In addition to the generation of selectin ligands, sialylation plays other roles in MM. In 2020, Natoni et al., reported that desialylation (removal of sialoglycans from cancer cells) by using a global sialyltransferase inhibitor (3Fax-Neu5Ac) impaired maturation of the α4 integrin which affected its affinity for its counter-receptor as well as greatly reduced the ability of MM cells to interact with E-selectins, Vascular Cell Adhesion Molecule 1 (VCAM-1) and Mucosal vascular Addressin Cell Adhesion Molecule 1 (MADCAM-1), which altered adhesion and rolling mediated by α4β1 and α4β7 integrins respectively. Intriguingly, 3Fax-Neu5Ac reduced the tumor burden, increased survival and showed a synergistic therapeutic effect in combination with bortezomib [451]. Noteworthily, both α4β7 and α4β1 integrins are highly expressed on MM cells [452,453], and the expression levels of β7 integrin (2 known members: α4β7 and αEβ7) on MM cells correlates with poor survival in MM patients [454]. Therefore, inhibiting sialylation may represent a new therapeutic strategy to overcome BM-mediated chemoresistance [455].

### O-Acetylation of sialic acids

Sialic acids found in mammalian organisms vary in their substituent at C5, which in Neu5Ac is an acetylated amino group, in Neu5Gc a glycolylated amino group, and in Kdn a hydroxyl group [456]. The 5-amino group can also exist in nature in non-N-acylated form, giving rise to neuraminic acid (Neu). Neu5Ac, Neu5Gc, Kdn, and Neu collectively comprise the four 'core' Sia molecules. The four 'core' Sia molecules can also undergo various natural modifications that impart a second level of diversity as they sometimes carry one or more additional substitutions on the hydroxyl groups at C-4, C-7, C-8, and C-9 (O-acetyl, O-methyl, O-sulfate, or O-lactyl groups). The most common modification of sialic acids is O-acetylation preferentially occurring at the C-4, C-7, C-8, and C-9 hydroxyl groups of the nonulosonic acid and sialic acid backbone. However, because O-acetyl esters from C-7 and C-8 positions are known to spontaneously migrate to C-9 even under physiological conditions, O-acetylation at C-9 is considered the most common biologically occurring modification.

For example, N-acetyl-9-O-acetylneuraminic acid (Neu5Ac9Ac) is the most frequent postsynthetic change in humans [457].

**Neu5Gc**

The two most common forms of sialic acid found in mammalian cells are Neu5Ac and its hydroxylated derivative, Neu5Gc. The enzyme cytidine monophospho-Neu5Ac hydroxylase (Cmah, encoded by the CMAH gene) catalyzes the convertion of Neu5Ac to Neu5Gc. However, in humans this enzyme is inactive [458]. In spite of this, Neu5Gc-sialoconjugates have been detected in human tissues, particularly in tumors with dietary incorporation of Neu5Gc being currently the most accepted hypothesis [459,460]. The higher proliferation of malignant cells would explain the preferential expression of these antigens in tumors [461], also favored by the increased uptake under hypoxic conditions [462,463]. Neu5Gc expression in human tissues enhances inflammation due to an anti-Neu5Gc immune response, which can potentially influence inflammation-induced cancer and cancer-associated inflammation [464]. Since expression of Neu5Gc in humans being associated with malignant transformation, therefore, Neu5Gc is an attractive target for cancer immunotherapy [465].

**O-linked modifications in epidermal growth factor repeats on Notch**

Two unusual forms of O-linked glycans, namely, O-fucose and O-glucose, were initially described on the Epidermal Growth Factor (EGF) repeats of mouse Notch1 [466]. Later, evidence unraveled that the signaling pathway best known to be regulated by *O*-glycans on EGF repeats is the Notch signaling pathway. Intriguingly, Notch is an evolutionary-conserved signaling system that regulates cell fate decisions through local cell–cell interactions [467]. In this context, the available evidence indicates that Notch signaling has important roles in many cellular processes, including differentiation, proliferation, apoptosis, and stem cell maintenance [468]. Not surprisingly, dysregulation of Notch signaling leads to various human diseases, including cancer [469]. Interestingly, investigations into Notch predate the identification of almost all signal transduction systems [470]. The principal understanding of the interaction between Notch and its ligands was obtained through studies on Drosophila, flies with Notch-ed wing phenotype as originally observed by John S. Dexter in 1914 [471]. However, the discovery of human-specific Notch genes has led to a better understanding of Notch signaling in development and diseases and will continue to stimulate further research in the future [472]. Notch is a large (>300 kDa) cell-surface receptor that contains 36 tandem EGF repeats comprising the majority of its extracellular domain (ECD). However, the Notch pathway core components include Notch receptors, Delta/Serrate/LAG-2 (DSL) family of ligands, the Notch receptor proteases Adam and γ-secretase, and the nuclear effector CSL (CBF1/RBPjκ/Su(H)/Lag-1) [473,474]. Both Notch receptors and the DSL Notch ligands are Type-I transmembrane glycoproteins with a single transmembrane domain. Mammals have four Notch receptors (Notch1–4), all consist of an ECD or NECD (Notch extracellular domain) and an intracellular domain (ICD) or NICD (Notch intracellular domain); and two types of canonical DSL (Delta/Serrate/LAG-2 family) ligands: three Delta-like ligands (DLL1, DLL3, and DLL4), and two Serrate-like (Jagged) ligands (JAG1 and JAG2). The ECD of DSL ligands contain a conserved N-terminal DSL domain and several EGF-like repeats, whereas NECD consists of a series of EGF repeats and a Negative Regulatory Region (NRR). Remarkably, Notch signaling pathway mediates cell to cell communication by transducing short-range signals *via* interactions between cell-surface receptors (Notch 1-4) with transmembrane ligands [475]. For signaling to occur, the transmembrane ligands from one cell bind the transmembrane Notch receptor in a neighboring cell, inducing the cleavage of Notch and the release of the Notch ICD into the cytoplasm, where it can translocate to the nucleus and promote the expression of its target genes [476]. Notch1-ICD comprises an RBPJ-associated molecule (RAM) domain, seven ankyrin (ANK) repeats, flanked by Nuclear Localization Signals (NLS), a Transactivation Domain (TAD) required for target gene activation, and a C-terminal PEST domain, a region rich in proline (P), glutamic acid (E), serine (S), and threonine (T), which regulates stability and proteasomal degradation of active Notch1-ICD [477,478,479]. While Notch1 contains a strong TAD capable of autonomous transcriptional activation [480,481,482], Notch2 has a weak TAD, while Notch3 and Notch4 have no TAD in the endodomain [483]. The EGF repeats, which are defined by the presence of six conserved cysteine residues forming three disulfide bonds modified with *O*-glycans at distinct sites, participate in receptor-ligand interactions [484]. The ECD of both Notch receptors and Notch ligands contains numerous EGF-like repeats which are post-translationally modified by a variety of glycans. Inactivation of a subset of genes that encode glycosyltransferases which initiate and elongate these glycans inhibits Notch signaling and cause Notch signaling defects of varying severity [485]. Importantly, strong evidence indicates that deregulation of the components involved in glycosylating Notch proteins are implicated in human developmental disorders and Notch-induced tumorigenesis [486,487,488,489]. Specifically, the EGF repeats of NECD are modified by O-fucose, O-glucose, *O*-GlcNAc, and O-xylose [490]. To a larger extent, the ligand-dependent Notch signaling pathway requires glycosylation of the NECD for signaling activation [491]. In particular, O-fucose glycans appear to function both directly and indirectly in the recognition of receptors by ligands. For instance, O-fucose glycans directly participate in the binding of Notch1-DLL4 and Notch1-JAG1 [492,493,494]. In 2000, an entirely new field opened up with the discovery that the Fringe molecule is a glycosyltransferase that catalyzes the addition of GlcNAc to O-fucose and this discovery demonstrated an association of the Notch signaling pathway with glycobiology [495,496,497]. Before Fringe can act, EGF repeats must first be glycosylated with an O-fucose and this O-fucosylation is mediated by O-fucosyltransferase 1 (O-FucT-1) (encoded by Pofut1 in mammals), which then are elongated by Fringe, an N-acetylglucosaminyl transferase [498,499]. As fucosylation is one of the prevalent glycosylation types on Notch proteins, O-Fucosylation by POFUT1 is essential for Notch activation in mammals [500,501]. The O-Fucose monosaccharides can then be elongated with GlcNAc residues using Fringe which is essential to promote Notch/Delta-binding, in preference to Notch/Serrate, whose interaction is inhibited by this modification [502,503]. Similarly, O-glycosylation of the EGF repeats is mediated by O-glucosyltransferase, Rumi in Drosophila or POGLUT1 (also known as hCLP46) in mammals [504, 505,506], and elongated by Shams, a xylosyltransferase. In humans, xylosyltransferase (GXYLT)1 and (GXYLT)2, that add first and second xylose residues to Notch EGF repeats, have been identified [507,508]. The O-glucose modification on Notch is essential for Notch signaling and embryonic development [509,510].

Strikingly, POGLUT1 is overexpressed in primary AML, T-ALL, and other leukemia cell lines [511,512]. In addition, EGF-specific *O*-GlcNAc-transferase (EOGT in Drosophila and Eogt1 in mammals) adds GlcNAc to EGF repeats. This unique non-nucleocytoplasmic *O*-GlcNAc modification mediate the ECM interactions of Notch [513,514]. Intriguingly, aberrant Notch activity has either tumor-promoting (oncogenic) or tumor-suppressive roles or both in a context-specific manner [515]. In the hematopoietic system, while an oncogenic role of Notch has been described in several hematologic malignancies including T-ALL, CLL, B-cell leukemias, and lymphomas [516,517,518], a tumor-suppressive role has been proposed in Chronic Myelomonocytic Leukemia (CMML) [519] and also suggested in AML [520]. Such dualism has been linked to the function of Notch in the regulation of cell fate choices during immune cell development [521]. Interestingly, aberrant Notch signaling also triggers anti-apoptotic program and drug resistance in T-ALL [522], B-ALL [523], CLL [524], AML [525], Hodgkin and Anaplastic Large Cell Lymphoma (ALCL) [526], and MM [527,528]. In this vein, overwhelming evidence indicate that Notch signaling is instrumental in the pathological communication between tumor cells and BM leading to the reprogramming of surrounding microenvironment and the development of pharmacological resistance [529]. Remarkably, the Notch family of receptors and ligands has gained growing interest in the recent years due to their early dysregulation in MM and their ability to affect multiple features of the disease, including tumor cell growth, drug resistance, angiogenesis and bone lesions [530]. For instance, the dysregulation of Notch1 and JAG1 has been associated with progression from a pre-malignant stage termed Monoclonal Gammopathy of Undetermined Significance (MGUS) to MM [531]. Mechanistically, Notch signaling mediates the pathological communications between Bone Marrow Stromal Cells (BMSCs) and MM cells which favors MM progression by increasing MM proliferation [532], promotes chemotherapy resistance, and stimulates angiogenesis [533]. Intriguingly, Notch communication increases osteoclast differentiation and function and induces apoptosis of osteocytes to further promote bone resorption and destruction [534,535]. In addition, Notch signaling also takes part in the migration of MM cells through the expression of the CXCR4/SDF-1 axis system [536]. Unlike other Notch-related malignancies, where the majority of patients carry gain-of-function mutations in Notch pathway members, Notch signaling is aberrantly activated in MM cell due to an increased expression of Notch receptors and ligands [537]. The first outcome of Notch receptors and ligands dysregulation in MM is the activation of Notch signaling within tumor cell due to homotypic interaction among nearby myeloma cells or to the engagement of Notch receptors by ligands expressed on the surrounding BMSCs (heterotypic interaction). The latter contributes to myeloma cell proliferation, survival and migration, as well as to bone disease and intrinsic and acquired pharmacological resistance [538]. To elucidate further, Notch activation in malignant plasma cells may occur in two distinct ways: MM cells simultaneously express Notch-1, -2, -3 and their ligands (JAG1 and JAG2) resulting in an autonomous pathway activation (homotypic; among MM cells), or Notch activation can be triggered by BMSCs expressing DLL1 or Jagged ligands (heterotypic; between MM cells and host cells). Indeed, *in vitro* and animal studies show that this dual mechanism of Notch signaling activation increases MM cell proliferation and decreases apoptosis in both human and murine MM cell lines and primary cells from patients [539,540,541,542,543]. In a similar vein, Xu et al., demonstrated that BMSC-derived DLL1 can activate Notch signaling mostly through Notch2 receptor and can contribute to drug resistance to bortezomib, both in murine and human MM cells, through the upregulation of CYP1A1(a member of the cytochrome P450 family involved in drug metabolism). In line with these data, the combined treatment of Notch inhibition with bortezomib resulted in increased bortezomib sensitivity and OS in the 5T33MM mouse model [544]. Within this context, it was shown that DLL1/Notch interaction promotes MM-cell proliferation predominantly in $CD138^{+}$ MM cells [545]. As a conclusion, the multifunctional role of Notch communication in MM provides a strong rationale to block Notch signaling in the MM tumor niche [546]. In this context, it was shown that Notch inhibition with γ-secretase inhibitors (GSIs) decreases MM tumor growth. Mechanistically, the inhibition of Notch pathway causes decreased MM cell proliferation, induces MM cell apoptosis, and inhibits osteoclastogenesis [547]. In addition, Notch inhibition in MM cells increases their sensitivity to pro-apoptotic compounds such as Bcl-2/Bcl-xL inhibitors. In fact, the pro-survival effect of Notch in MM is due to upregulation of anti-apoptotic proteins like Bcl-2 and Bcl-xL, and downregulation of Bax and Bak, pro-apoptotic proteins [548]. Intriguingly, Notch blockade causes an increase of MM cells sensitivity to standard chemotherapies such as doxorubicin and melphalan both *in vitro* and *in vivo*, which ultimately prevents the development of BM-derived drug resistance [549]. Notably, an oncogenic role of Notch has been described in both T-ALL and CLL.

Historically, T-ALL is the hematological neoplasia most closely related to Notch signaling pathway. As a matter of fact, T-ALL is primarily a Notch1-driven disease with somatic gain-of-function mutations in *NOTCH1* contributing to almost 60% of the cases [550]. Despite the high prevalence of activating *NOTCH1* mutations in T-ALL, *NOTCH1* mutations are not associated with unfavorable outcome and in some series they may even confer better prognosis [551,552]. On the contrary, *NOTCH1* mutations confer a dismal prognosis with a reduction in the OS in CLL patients. Based on current knowledge, *NOTCH1* mutations occur in 11% of CLL patients and are mutually exclusive with tumor protein 53 (TP53) disruptions in 90% of the cases [553]. Intriguingly, their frequency increases in advanced disease phases, as exemplified by the case of RT [554]. Unlike T-ALL, the most common *NOTCH1* mutation in CLL affects the C-terminal PEST domain causing prolonged half-life of the cleaved protein [555]. Unsurprisingly, several studies support that *NOTCH1* mutations as a negative predictor factor for CLL patients [556,557]. Accumulating evidence suggests that an anti-Notch1 treatment might be able to kill not only mature CLL cells but also their corresponding LSCs, favoring disease eradication for a definitive cure (558). As mentioned earlier, Notch signaling is an important pathway with both oncogenic and tumor-suppressive potential in AML [559]. Based on current knowledge, *NOTCH1* is mutated in 12% of AML patients but its impact on the OS is a debating matter [560,561]. Nevertheless, recent research showed that Notch signaling promotes chemoresistance in *FLT3*-amplified AML [562]. Intriguingly, Li et al., demonstrated that the combined inhibition of Notch and *FLT3* produces synergistic cytotoxic effects in *FLT3*-ITD positive AML [563]. In addition, Fischer et al., uncovered the oncogenic relevance of the Notch1 pathway in leukemia with rearrangements of the KMT2A (Lysine

methyltransferase 2A) gene (KMT2A-R). By using the Notch1 inhibitor CAD204520, their study demonstrated the successful inhibition of the Notch1 pathway, resulting in convincing anti-leukemic effects, which provides a promising target in the treatment of KMT2A-R AML [564]. Mechanistically, Notch signaling alters the levels of glycosyltransferases that are involved in O-fucosylation and O-glucosylation, which is eventually resulting in a positive feedback loop in AML (565,566,567,568). Furthermore, Notch2 signaling has been shown to play a key role in marginal zone B-cell development in the spleen, and to be dispensable for the development of other B-cell lineages [569,570]. In this context, NOTCH2 mutations have been found in other B-NHL subtypes, such as splenic marginal zone lymphoma (SMZL) and DLBCL. In DLBCL, NOTCH2 mutations affect approximately 8% of patients with some cases having increased copies of the mutated NOTCH2 allele [571]. In SMZL, NOTCH2 mutations represent the most recurrent genetic lesion accounting for approximately 20–25% of cases [572,573,574]. Unfortunately, Notch-related therapies have not gathered momentum due to the toxicities seen with current therapeutic strategies and the difficulty of targeting multiple Notch ligand-receptor interactions [575]. Hence, I believe that there is a great hope with the employment of glycobiology in creating novel Notch-related therapies.

## Structures common to different glycans

### Polysialic acid (PSA)

Polysialic acid is a linear polymer of sialic acid, with α2,8 and α2,9 linkages and a length ranging from 8 to 400 units. In mammalian cells, three sialyltransferases (ST8Sia II, ST8Sia III, and ST8Sia IV) are responsible for the extension of polysialic acid glycans [576]. Polysialylation is an essential glycosylation modification of several important glycoproteins, including the Neural Cell Adhesion Molecules (NCAMs) [577,578], chemokine receptor 7 (CCR7) [579,580], CD36 [581], and E-selectin ligand 1 (ESL-1) [582]. Because of the large negative charge of PSA, presence of PSA attenuates the adhesive property of NCAM (CD56) and increases the cellular motility. In addition, PSA plays important roles in formation and remodeling of the neural system through regulation of the adhesive property of NCAM. In tumor cells, the level of polysialic acid chains correlates with an aggressive phenotype and the resistance of cancer treatment [583]. Expression of the polysialated form of NCAM has been also demonstrated in some malignant tumors, such as Wilms' tumor and small cell lung cancer [584]. The polysialic upregulation in tumors is seen in breast, astrocytoma, and CML [585]. In general, polysialic acid expression correlates with metastatic disease and poor clinical prognosis [586,587,588,589,590].

### Type 1 and 2 glycan structures

Type 1 and 2 structures are present on O- and N-glycoproteins as well as on glycolipids.

A Type-2 unit composed of Galβ1-4GlcNAc, also called N-acetyllactosamine (LacNAc) and a Type-1 unit composed of Galβ1-3GlcNAc. Type 2 structures are ubiquitous, while type 1 structures are found in the GI tract. Types 1 and 2 can both be found in polymers of (Type 1)n and (Type 2)n, with the latter forming polyLacNAc chains, also called i blood group [591].

### Poly-LacNAc (poly-N-acetyl-lactosamine) structures

Poly-LacNAcs occur in mammalian glycoproteins in both N- and O-linked glycans. Enzymatically, the action of β-1,6-N-acetylglucosaminyltransferase V enzyme (GnT-5/*MGAT5*) which catalyzes the addition of ß1,6-N-acetylglucosamine to the α-linked mannose of biantennary *N*-glycans and core 2 β-1,6-N-acetylglucosaminyltransferase 1 (C2GNT1/GCNT1) which create the ß1,6 branch on Core 2 *O*-glycans provide added antennae scaffolds for LacNAc formation. Biochemically, both GnT-5/*MGAT5* and C2GNT1 enhance the avidity for galectins by promoting poly-N-acetyllactosamine production. N-Glycans generally have longer poly-LacNAc extensions than *O*-glycans, and both may receive sialic acid or Fuc residues or sulfate. Poly-LacNAcs represent a backbone for additional modifications by fucosyltransferases, sialyltransferases and sulfotransferases. Poly-LacNAcs have been suggested to be involved in biospecific interactions with selectins and galectins [592]. Poly-LacNAcs are more commonly found on core 2 *O*-glycans and serve as scaffolds for synthesis of glycan functional groups such as sLeX. Interestingly, the human blood group i and I antigens are determined by linear and branched poly-N-acetyllactosamine structures, respectively. In erythrocytes, the fetal i antigen (linear Poly-LacNAc chain) is converted to the I-blood group antigen (branched Poly-LacNAc chain) by Gcnt2 during development. Dysfunction of the I-branching enzyme may result in the adult i phenotype in erythrocytes [593]. *GCNT2* is the gene encoding Gcnt2 responsible for formation of the blood group I antigen. Gcnt2 is an N-acetylglucosaminyltransferase but does not exhibit core 2 activity. Nevertheless, *GCNT2* has a critical biological function in modulating EMT and promoting breast cancer metastasis [594].

### Lewis antigens

Lewis antigens are synthesized primarily by endodermal epithelia, such as GI epithelia, but are found in endodermal epithelia and RBCs due to transfer of glycolipids to RBCs [595]. Lewis structures are found on type 1 (Galβ1–3GlcNAc-R) and 2 chains (Galβ1–4GlcNAc-R) of

*O*-glycans, *N*-glycans, and glycolipids. Type 1 chains contain Lewisa/b, while type 2 chains contain Lewis X/Y .The fucosyltransferases are responsible for synthesizing the Lewis antigens [596]. Lewis antigens can also be sialylated and/or sulfated to form sialyl and sulfo Lewis antigens. Sialylation most often occurs at the 3 position of the terminal galactose of the type 1 or 2 chain to form sLeA/X. Sulfo, sialyl, and sulfo sialyl Lewis antigens are important in physiological processes such as inflammation, in particular, because of their role in leukocyte rolling and as selectin ligands. These antigens also play an important role in cancer, which additionally express dimeric Lewis antigens such as sialyl-dimeric Lewis x [597]. LeY antigen is overexpressed by malignant myeloid cells. A second-generation CAR-T anti-LeY evaluated in AML, had already demonstrated feasibility and durable *in vivo* persistence [598]. The increased expression of the sialylated Lewis antigens sLeX and its isomer sLeA, has been vastly documented in the majority of cancer types mainly due to the expression of sialyltransferases involved in their intracellular biosynthesis [599]. Noteworthily, sLeA and sLeX are the E-selectin glycan ligands. In particular, overexpression of sLeX is associated with poor prognosis and malignant relapse [600]. Mechanistically, sLeX can promote metastasis by inducing overexpression of E-selectin, resulting in hematogenous metastasis [601]. In fact, by mediating tumor cell attachment to endothelia, platelets, and leukocytes [602,603], sLeA and sLeX enable cancer cells to leave the bloodstream and colonise other organs [604,605,606]. Precisely, attachment to

endothelia contributes to vessel invasion, whereas attachment to platelets, and possibly leukocytes, contributes to survival in the vasculature. Interestingly, the leukocyte adhesion deficiency II (LAD II) [also known as Congenital Disorder of Glycosylation IIc (CDG IIc)], in which almost complete deficiency of sLeX expression can be observed, leads to immunodeficiency resulting from interrupting the selectin-mediated leukocyte tethering and rolling on endothelium [607]. In addition, loss of sLeX led to reduced trafficking of lymphocytes to inflamed peritoneum, and reduced lymphocyte homing to lymph nodes [608,609]. Strikingly, the major carriers of selectin ligands are mucins that are heavily O-glycosylated (i.e., the majority of selectin ligands are presented on mucins) [610]. However, the spectrum of selectin ligands on tumor cells is rather broad, encompassing glycolipids, proteins, and glycosaminoglycans [611]. Not surprisingly, the degree of selectin ligand expression by cancer cells is well correlated with metastasis and poor prognosis in cancer patients [612]. E-selectin, a cytoadhesive glycoprotein, is expressed on venular endothelial cells and mediates leukocyte localization to inflamed endothelium, the first step in inflammatory cell extravasation into tissue. Constitutive marrow endothelial E-selectin expression, a key endothelial cell factor, also supports BM hematopoiesis *via* NF-κB-mediated signaling. As an adhesion molecule expressed exclusively by endothelial cells, studies indicate E-selectin as a promoter of the proliferation of HSCs [613]. Experiments involving administration of an E-selectin antagonist or observation of E-selectin knockout mice reported improvement in the dormant state of HSCs as well as potentiation of the self-renewal capacity, strengthening the idea that E-selectin plays a central role in the proliferation of HSCs [614]. In a similar vein, a growing body of literature indicates that binding of E-selectin to sLeX/sLeA on LSCs activates multiple pro-survival signaling pathways and promotes chemoresistance in AML [615,616,617]. Mechanistically, the upregulation of endothelial E-selectin in response to TNF-α released by AML blasts was shown to provide leukemic cells with a pro-survival signal through Akt/NF-κB signaling, conferring chemoresistance [618]. These findings support that constitutive expression of E-selectin in the vascular compartment of BM is a key vascular niche component mediating leukemia survival and chemoresistance *via* E-selectin ligand/receptors [619]. Not surprisingly, the expression of E-selectin or its binding epitopes sLeX/sLeA may predict the clinical course and patient outcomes in AML [620,621,622]. Within this context, elevated sLeX/sLeA levels is a hallmark of AML M5 that positively correlated with the expression of transcription factors *CEBPA/SPI1*. Intriguingly, high expression of sLeX-associated fucosyltransferases *FUT3, FUT6, FUT7* and *ST3GAL4* have been linked to dismal prognosis in AML in monovariate analyses [623]. Noteworthily, ST3GAL4 is the main sialyltransferase involved in the synthesis of sLeX in myeloid leukocytes [624]. In this vein, transcriptome profiling of multiple genes involved in the synthesis of sLeX from 1074 pediatric patients treated in COG AAML 1031 identified that the increased expression of *FUT7* and *ST3GAL4* is associated with increased cell surface E-selectin ligand expression and poor prognosis [625]. This renders *ST3GAL4/FUT7* as well as their biosynthetic products potentially promising targets for the development of novel glycan-targeting therapies, especially to prevent or overcome the resistance to treatment of high sLeX-expressing AML subtypes such as AML M5 [626]. Not surprisingly, the sLeX/E-selectin axis is an attractive target in AML. One approach employed to target this axis was to exploit the glycomimetic drug uproleselan (GMI-1271), a carbohydrate analog of sLeX that blocks its interaction with E-selectin, which by disrupting the vascular niche-mediated chemoresistance improved survival of AML patients. In vitro mechanistic studies demonstrated that cytarabine-sensitive AML blasts become chemoresistant upon adherence to E-selectin, but that chemosensitivity can be restored with concomitant incubation with uproleselan. Additional studies showed that the uproleselan-mediated inhibition of E-selectin binding inhibited the activation of NF-κB and Akt and resulted in the attenuation of pro-survival pathways in the leukemic blasts [627]. After showing promising results in a phase I/II study enrolling R/R AML patients (NCT02306291), a phase 3 trial is currently underway to evaluate the efficacy of uproleselan administered with chemotherapy versus chemotherapy alone in patients with R/R AML (NCT03616470) [628,629,630]. In addition, uproleselan may reduce severe and other adverse events associated with AML chemotherapy and HSCT conditioning including including mucositis and diarrhea [631]. Furthermore, it was shown that MM cells enriched for E-selectin ligands recognized by the mAb Heca452 ($MM^{Heca452Enriched}$) were resistant to bortezomib treatment *in vivo*, and this resistance was reversed by a small glycomimetic molecule, GMI-1271, which inhibits E-selectin/E-selectin ligand interaction [632]. Currently, E-selectin inhibition in MM, by using the specific E-selectin inhibitor GMI1271, is also in clinical trials (NCT02811822).

## Glycoconjugates

### Glycosphingolipids

Glycosphingolipids are found in the outer leaflet of the plasma membrane of all vertebrate cells and are thought to play functional roles in the regulation of cellular proliferation and differentiation. A number of studies have examined the role of lipid rafts in physical properties and signaling [633]. Glycosphingolipids (GSLs) are a subclass of glycolipids composed of carbohydrates covalently linked to a ceramide (Cer, N-acylsphingosine) lipid tail that anchors the molecule within the cell membrane. Biologically, these ceramide-linked glycans are major components of the outer cell plasma membrane that play essential roles in cell signaling, apoptosis, adhesion, receptor modulation, growth and differentiation [634,635,636]. Cellular differentiation and malignant transformation are often accompanied by dramatic changes in GSL expression. Many GSLs are capable of inducing differentiation, apoptosis, BM suppression and metastasis [637,638,639]. Abnormal GSL expression is associated with the development of many types of cancers including leukemia [640]. GSLs are usually divided into two major families, known as galactosylated (galactocerebroside; GalCer) or glucosylated ceramides (glucocerebroside; GlcCer). Further extension and modifications of these core structures, including elongation, sulfation, and sialic acid acetylation, contributes to the diversity of the repertoire expressed in (immune) cells. Glucosylceramide-related GSLs are further divided into three major classes based on the action of specific glycosyltransferases; (iso)globo- (A4GALT), ganglio- (B4GALNT1 and ST3GAL5), and (neo-) lacto (B3GNT5) –series [641]. The (iso)globosides globotriaosylceramide (Gb3) and isoglobotriaosylceramide (isoGb3) are generated by the addition of a galactose to lactosylceramide (LacCer) (also known as CD17/CDw17) in α1,4 and α1,3 linkages by α1,4-galactosyltransferase (A4GALT) and α1,3-galactosyltransferase 2 (A3GALT2) respectively. The B3GNT5 gene encodes the glycosyltransferase

β1,3-N-acetylglucosaminyltransferase (β3Gn-T5), a lactotriaosylceramide (Lc3Cer) synthase, is a key enzyme for the biosynthesis of (neo)lacto-series GSLs (Lc3 and nLc4) [642]. Lc3Cer is a precursor structure for lacto-/neolacto-series glycolipid and polylactosamine chains elongated on Lc3Cer. β3Gn-T5 exhibits the strongest activity to transfer GlcNAc to glycolipid substrates, such as LacCer and neolactotetraosylceramide (nLc4Cer; paragloboside), resulting in the synthesis of Lc3Cer and neolactopentaosylceramide (nLc5Cer) repectively [643]. β3Gn-T5, together with its associated glycosidic product (Lc3), plays critical roles in embryonic development and differentiation. Its expression in leukemia cell lines has been reported previously [644]. It has also been suggested as a differentiation-associated GSL in the BM of AML patients with corresponding elevated B3GNT5 expression [645]. Previous studies have indicated that certain GSLs play a critical role in the differentiation of AML cells. Within this context, the best described myeloid-specific GSL is nLc4 (a fucosylated neolacto-series GSL which is known as the CD65 antigen) [646,647,648]. CD65 is expressed on most myeloid cells during development, highly on granulocytes and weakly on monocytes in Peripheral Blood (PB). The sialylated form of CD65 (CD65s) is expressed when the myeloid progenitor antigen CD34 disappears, indicating that CD65s expression marks a turning point in myeloid cell differentiation [649].

### Gangliosides

GSLs are further subclassified as neutral (no charged sugars or ionic groups), sialylated (having one or more sialic acid residues), or sulfated. Traditionally, all sialylated GSLs are known as "gangliosides" regardless of whether they are based on the ganglio-series neutral sugar core [650]. Gangliosides participate in the regulation of various cellular functions, including cell proliferation, apoptosis, migration and invasion. Moreover, they have been shown to regulate RTK signaling [651]; and their expression changes during malignant transformation, both at the quantitative and qualitative levels [652]. Gangliosides are a family of glucosylceramide-related GSLs characterized by an α2-3 linked sialic acid that is added onto the core GSL structure lactosylceramide (Lac-cer) by the sialyltransferase ST3GAL5 [653].The product of ST3GALT5 action, known as GM3, serves as a precursor for most of the more complex ganglioside species (GM3 is the parent structure for a- , b-, and c-series gangliosides). Moreover, β1,4-N-acetylgalactosaminyltransferase (GM2/GD2 synthase) is a key enzyme which catalyzes the conversion of GM3, GD3 (disialolactosylceramide) and lactosylceramide (LacCer) to GM2, GD2 and asialo-GM2 (GA2), respectively. This step is critical for the synthesis of all complex gangliosides enriched in the nervous system of vertebrates [654]. Overwhelming evidence indicate that AML cells have high expression of GM3 which was found to induce monocytic differentiation in leukemia cells [655]. In a recent study by Wang et al., GSLs with Neu5Gc were found in most AML cell lines, including GM3 (Neu5Gc), GD3 (Neu5Gc), GM1a (Neu5Gc), and two glycans in the (neo)lacto-series. However, the abundance of glycans with Neu5Gc varied between cell lines. The cell lines of the M6 subtype showed a high expression of gangliosides with α2,3-sialylation and Neu5Gc, as compared to the M2 and M5 subtypes which were characterized by high expression of (neo)lacto-series glycans and Lewis A/X antigens (an average Neu5Gc expression of 2.3% in M6 cell lines vs. only 0.8% in the rest of the AML cell lines). The authors conclude that glycans with Neu5Gc could be potential therapeutic targets for M6-stage AML [656]. In a similar vein, the GSL and gangliosides expression profiles were analyzed in the BM samples of AML patients in previous important study (Table-3). Interestingly, AML patients had 16-fold higher expression of the Lc3 synthase β3Gn-T5 than healthy subjects ($P < 0.05$). The authors suggested the exploitation of Lc3 as a potential biomarker and a target for therapy since it is highly expressed in primary AML cell lines [657]. Furthermore, GD3 is increased in lymphoblasts with a T-cell immunophenotype compared to non-T-ALL blasts. Consequently, GD3 expression was observed in T-ALL [658,659], and ATLL cells [660]. Depite that the differential expression of GM2 and GD2 in malignant cells is regulated by the enzyme activity of GM2/GD2 synthase, the amount of precursor structure present in individual cell lines is also a very important factor in determining the ganglioside profile [661]. Within this context, ATLL cell lines specifically express GD2 but not GM2 [662]. On the other hand, GM2 is an ideal target for anti-cancer therapy since normal cells express little GM2. Interestingly, DMF10.167.4, a hamster anti-GM2 mAb raised against a murine T-cell lymphoma cell line, has been shown to induce apoptosis *in vitro* [663].

**Table 3:** Expression GSLs and gangliosides according to the AML FAB subtypes

| AML subtype | Glycosphingolipids | Ganglioside(s) |
|---|---|---|
| M1 | Gb3, Lc3[1], and nLc4 | GM3 |
| M2a[2] | nLc4 | |
| M3a | Lc3 and nLc4 | |
| M4 | nLc4 | |
| M5 | Gb3[3], Lc3, and nLc4 | GM3 |

**Note:** [1]The significantly higher expression of Lc3 in the M1 subtype than other subtypes indicates that the expression of Lc3 is closely related to cell differentiation in human bone marrow.
[2]Acute myeloblastic leukemia with granulocytic maturation.
[3]Gb3 did not differ significantly between the control and AML groups, whereas Lc3, GM3 and nLc4 had significantly higher expression in the bone marrow samples of AML patients.
FAB, French–American–British; Gb3, globotrihexosylceramide; GM3, monosialodihexosylganglioside; GSL, glycosphingolipid; Lc3, lactotriaosylceramide; Lc4, lactotetraosylceramide; nLc4, neolactotetraosylceramide

### O-acetylation

O-acetylation of the sialic acid residues is one of the most common modifications of gangliosides [664]. O-acetylated ganglioside species represent therapeutic targets of interest as an alternative strategy to non-O-acetylated ganglioside species. For example, targeting OAcGD2 rather than GD2 seems to be a better strategy due to exclusive OAcGD2 expression in cancer tissue [665]. In a similar vein, targeting 9-O-Ac-GD2 ganglioside, a modified GD2 ganglioside which is expressed in neuroblastoma, SCLC, melanoma, renal carcinoma and lymphoma [666], cirmcumvent the significant neuropathic pain secondary to complement activation on anti-GD2 bound peripheral nerves [667], that limited the therapeutic application of anti-GD2 mAbs [668]. In particular, the 9-O-acetylation of gangliosides has been extensively associated with cancer, and hence considered as a marker of cell

and tissue growth. The most prominent one is 9-O-Ac-GD3 (also called CD60b), which is considered as an oncofetal marker in animal and human tumors like neuronal tumors, melanoma, basalioma or breast cancer, as well as in psoriatic lesions [669]. Similar to melanoma and glioblastoma, O-acetyl-GD3 seems to contribute to drug resistance capacity in ALL cells [670]. As a matter of fact, the survival and drug resistance of lymphoblasts critically depend on 9-O-acetylation, which was found on both GD3 and sialoglycoproteins [671,672]. Specifically, pre-B ALL cells surviving chemotherapy have increased cell surface 9-O-Ac-GD3 and 9-O-acetylated α2,3 or α2,6-linked sialoglycoproteins as reported by CCA lectin. Later, Joo et al., identified nucleolin (NCL), a multifunctional nucleolar protein, as a sialoglycoprotein modified by 9-O-acetylation in pre-B ALL, and proposed it as a possible therapeutic target [673]. Interestingly, recent clinical and experimental evidence suggested that overexpression of NCL is linked to drug resistance in B-ALL [674].

**Glycosaminoglycans and proteoglycans**

Rather than existing in glycoconjugates, glycans can also be secreted without conjugation to other macromolecules in the form of glycosaminoglycans (GAGs).

GAGs are a family of highly sulfated, complex, unbranched (linear), often long, polysaccharides with a repeating disaccharide unit. GAG chains, the essential functional parts, are often highly sulfated, with resulting capability to bind cytokines, chemokines, or growth factors. As such, GAGs are extremely important biomolecules of the ECM, as they modulate protein function and stability. GAGs can tether ligands to RTKs, resulting in constitutive activation independent of protein/RNA levels. GAGs regulate a variety of cellular interactions in the BM because they are expressed by both the BM stroma and by normal hematopoietic cells [675,676]. In industry, incorporating GAGs into biomaterials has emerged as a widely adopted strategy in medical applications, owing to their biocompatibility and ability to control the release of bioactive molecules [677]. Based on the difference of repeating disaccharide units, GAGs can be categorized into four main groups: Heparin/Heparan Sulfate (HS), Chondroitin Sulfate (CS)/Dermatan Sulfate (DS), Keratan Sulfate (KS), and hyaluronan (also known as hyaluronic acid, HA). GAGs can be covalently connected to a core protein forming Proteoglycans (PGs) or secreted, like hyaluronic acid (HA). HA does not form covalent links with proteins but instead interacts noncovalently with proteoglycans *via* hyaluronan-binding motifs [678,679]. HA and HS are two typical GAGs found in the ECM and on the cell surface with the basic repeating disaccharide unit composed of a uronic acid residue and a glucosamine residue [680]. CD44 , a type I transmembrane protein and member of the cartilage link protein family, is the principal cell surface receptor for HA [681]. Interestingly, the discovery of CD44 as a receptor for HA made possible to understand why one of the HA physiological functions was to capture circulating cells such as lymphocytes and lead them to inflamed sites. The interactions between HA and CD44 leads to cell survival, cell growth, invasion, and metastasis *via* signaling networks include; RhoGTPases and PI3K/AKT pathway and other chemoresistance pathways *via* ROK activation [682]. Intriguingly, heparin, the most acidic macromolecule of human body acting as an anticoagulant, is a highly sulphated variant of HS [683]. Despite that heparin and heparan sulphate differ significantly with regard to their chemical composition [684], heparin is often considered an analogue of heparan sulphate that commonly substitutes it in experimental models studying HS [685]. HS is produced by virtually all cells in the body; in contrast, heparin is confined to connective-tissue-type mast cells [686]. Moreover, HS regulates a wide array of functions, during both developmental and physiological processes, including cell adhesion, migration, proliferation and differentiation, cellular signaling, ECM assembly, and also during numerous pathological disorders, such as cancer or infectious and neurodegenerative diseases [687]. On the other hand, KS is involved in a range of biological processes such as cornea transparency, embryonic development, wound healing, cell adhesion, and migration; and dysregulation of its biosynthesis has been associated with a poor prognosis of various cancers [688]. Ubiquitous on cell surfaces and within the ECM in higher eukaryotes, proteoglycans are large biomolecules that consist of a protein part, the so-called core protein, which is glycosylated with sulfated and thereby negatively charged GAGs. By participating in the organization of ECM and regulating its mechanical properties, proteoglycans provide structural support in connective tissues such as cartilage. In addition, proteoglycans are well established as key players in supporting the dynamic ECM. In this regard, proteoglycans interact with growth factors, cytokines and chemokines protecting them from degradation and form effective gradients of these components in ECM [689]. Mechanistically, proteoglycans act as co-receptors for these molecules promoting their signaling. In fact, the vast majority of signaling events between cells or with the ECM are modulated by the associated GAG chains [690]. For instance, growth factors, neurotrophic factors and chemokines can be recruited to target cells through GAG binding sites, rendering proteoglycans important determinants for development [691,692]. Furthermore, proteoglycans regulate cell behavior and phenotype, and are involved in cell proliferation, adhesion, migration and invasion [693]. It is worth noting that changes in proteoglycans and GAGs modulate virtually all the hallmarks of cancer, highlighting their relevance to malignant disease [694]. A textbook example is the role of cell surface heparan sulfate proteoglycans (HSPGs) in sustaining proliferative signaling, the first hallmark of cancer [695]. Not surprisingly, HSPGs have emerged as key molecules in tumor progression and communication [696]. HSPGs are ubiquitously found at the cell surface and ECM in all the animal species. In addition, HSPGs are key regulators of the BM niche of normal hematopoietic stem cells [697]. It is worth noting that HSPGs can be roughly divided into into three groups according to their location: cell surface or membrane HSPGs, such as syndecans and glycosylphosphatidylinositol-anchored proteoglycans (glypicans), the secreted ECM HSPGs (agrin, perlecan, type XVIII collagen), and the secretory vesicle proteoglycan, serglycin [698]. Noteworthily, perlecan is the main HSPG in the blood vessels ECM. Cell surface HSPGs may also be secreted into the matrix because of enzymatic cleavage of core proteins. Other cell surface HSPGs include CD44 and beta glycan [699]. Intriguingly, tumor-specific HSPGs differ in composition from HSPGs in corresponding normal tissue which suggests that agents that bind HS or modify its synthesis could lead to selective targeting of tumor cells and tumor micro-vasculature [700]. In this vein, HSPGs play important roles in cancer initiation and progression, by interacting with the signaling pathways that affect proliferation, adhesion, invasion and angiogenesis. Not surprisingly, overexpression of HSPGs is associated with increased tumorigenesis, angiogenesis and invasiveness in several cancers including, MM, breast, and

pancreatic cancer [701,702]. Mechanistically, cell surface HSPGs act as coreceptors for growth factor-mediated RTK signaling, where the HS chain aids in the formation of a ternary complex of growth factor, receptor tyrosine kinase, and the GAG chain, which substantially promotes and enhances mitogenic signaling promoting tumor growth [703]. Interestingly, growth factor binding to HS is driven by heparan sulfation, the addition of negatively charged sulfate groups to the HS chain. Misexpression of the enzymes that catalyze heparan sulfation is associated with invasion, metastasis, and angiogenesis in solid tumors. Nevertheless, pediatric AML patient cohort analyses demonstrated that increased 6-O-heparan sulfotransferase 1 (HS6ST1) expression is associated with worse patient survival, suggesting that HS6ST1 influences AML chemosensitivity. It is worth noting that HS6ST1 is responsible for 6-O-sulfation of heparan sulfate (a specific form of heparan sulfation). Within this context, Termini lab used CRISPR/Cas-9 editing to knockout HS6ST1 from MOLM-13 AML cells to show that HS6ST1-knockout cells had a significantly increased percentage of necrotic cells than Control cells upon cytarabine (Ara-C) treatment. Bulk RNA sequencing revealed that IL2-STAT5 signaling is significantly downregulated in HS6ST1-knockout cells than Control cells. These results indicated that 6-O sulfation inhibits Ara-C-mediated cell death *via* STAT5 [704]. In a similar vein, many anti-cancer drugs alter HSPGs expression, have an anti-tumor effect and decrease or inhibit the activity of HSPGs or enzymes responsible for their regulation, which suggests HSPGs as a promising anti-cancer drug targets for the treatment of several cancers including hematologic malignancies [705].

Serglycin is emerging as the dominant proteoglycan species expressed by immune cells that play crucial roles in diverse immunological processes. Despite being originally regarded as a hematopoietic cell proteoglycan, serglycin is expressed by several nonhematopoietic cell types. A unique property of serglycin is its ability to change its structural and functional characteristics, likely because of its remarkably variable glycosylation pattern in different serglycin-expressing cell types [706]. Notably, heparin is the the most well-known serglycin-associated GAG and heparin PG serglycin occurs in the granules of connective-tissue-type mast cells. However, serglycin may also contain CS chains. Whereas the connective-tissue-type mast cells predominantly synthesize GAG chains of heparin type, the mucosal-type mast cells synthesize mainly CS chains [707]. Interestingly, serglycin bearing CS chains occur in most blood cells. Strikingly, serglycin exclusively carrying CS side chains is constitutively secreted by MM cells. Noteworthily, serglycin is the major proteoglycan secreted by MM cells, but is also present on the cell surface of myeloma plasma cells and affects bone mineralization [708,709]. Moreover, serglycin can be a useful marker in the diagnosis of AML where it was more specific than Myeloperoxidase (MPO) in distinguishing AML from Philadelphia chromosome-negative chronic myeloproliferative disorders [710]. Furthermore, syndecans and glypicans are the two major families of cell-surface HSPGs. Syndecans (SDCs) are a family of four transmembrane HSPGs that act in cooperation with key transmembrane receptors and ECM molecules mediating pleiotropic functions, such as signaling, adhesion, proliferation, migration, apoptosis, and differentiation [711]. In terms of structure and sequence, syndecan-1 (CD138) and syndecan-3 can be considered one subfamily and syndecan-2 (CD362) and syndecan-4 another. Although all syndecans bear HS glycan chains, only syndecan-1 and syndecan-3 can also bear CS glycan chains [712]. Syndecan-1 is highly expressed in MM cells [713]. In fact, syndecan-1 is the dominant HSPG expressed on the surface of myeloma cells and is used as a standard marker by many laboratories for identification and purification of these tumor cells [714,715,716,717]. In addition, cell surface syndecan-1 is shed from myeloma cells and is present at high levels in the serum of some myeloma patients [718]. Due to the high levels of syndecan-1 on the surface of myeloma cells and the abundance of shed syndecan-1 that accumulates within the TME, myeloma cells in the BM are literally bathed in biologically active HS [719]. Seidel et al., demonstrated that high levels (approximately five times the level of normal controls) of syndecan-1 in the serum of MM patients are an independent predictor of poor prognosis [720]. Strikingly, high-serum syndecan-1 enhances both the growth and metastasis of myeloma tumors [721,722]. Syndecan-1 exerts its growth-promoting effects by regulating the activity of many effector molecules important for myeloma growth and survival, including Hepatocyte Growth Factor (HGF), a growth factor known to be up-regulated in many myeloma tumors [723], that binds to the heparan sulfate of syndecan-1 and helps potentiate signaling *via* the cMET receptor with resulting cell proliferation [724].

Furthermore, Spinler et al., identified syndecan-1 as an important marker for aggressive CML cell populations, indicating that syndecan-1 may be a viable biomarker for disease risk or a potential clinical target to control CML [725].

**Heparanase (HPSE)**

Heparanase is the only mammalian endoglycosidase that cleaves heparan sulphate releasing biologically active fragments of heparan sulfate. Acting together, heparanase and heparan sulfate facilitate tumor cell arrest, extravasation, and metastasis. Heparanase is upregulated in essentially all human tumors in which the severity of tumor metastasis is directly proportional to heparanase levels [726]. Mechanistically, the enzyme promotes metastasis by degrading HSPGs in basement membranes, facilitating passage of tumor cells through the vascular wall [727]. As the enzyme releases HS-bound angiogenic factors from the ECM, heparanase upregulation also correlates with increased tumor vascularity and poor postoperative survival of patients with cancer [728]. Not surprisingly, heparanase is considered a master regulator of the aggressive cancer phenotype [729,730,731,732]. Noteworthily, heparanase is upregulated in response to chemotherapy which promotes chemoresistance coupled with poor prognosis. Mechanistically, the surviving cells with heparanase upregulation acquire chemoresistance, at least in part, due to autophagy. Consequently, heparanase inhibitors used in tandem with chemotherapeutic drugs overcome initial chemoresistance, providing a strong rationale for applying anti-heparanase therapy in combination with conventional anti-cancer drugs [733,734]. In fact, several studies have shown that heparanase inhibition by heparin derivatives attenuates tumor growth and metastasis [735,736,737,738,739]. Intriguingly, heparanase activity has been strongly implicated in the progression of MM [740,741]. Mechanistically, heparanase synergizes with syndecan-1 in promoting myeloma progression [742]. Heparanase also enhances myeloma progression *via* CXCL10 down-regulation, suggesting that this chemokine exerts tumor-suppressor properties in myeloma [743]. In a similar vein, heparanase promotes myeloma progression by inducing mesenchymal features and motility of myeloma cells [744]. Further, heparanase promotes myeloma stemness and *in vivo* tumorigenesis [745]. Strikingly,

heparanase promotes the spontaneous metastasis of myeloma cells to the bone [746]. Heparanase is present in the BM of most MM patients where high levels of heparanase enzyme activity correlates with elevated angiogenic activity, an important promoter of myeloma growth and progression [747]. Ramani et al., discovered that gene expression profiling of tumor cells from myeloma patients revealed that heparanase expression was high in the cells that survived and grew following chemotherapy. Strikingly, tumor cells that survive intensive chemotherapy in myeloma patients express high heparanase. They also found that heparanase enhances myeloma drug resistance while blocking heparanase-driven ERK signaling sensitizes myeloma cells to chemotherapy [748]. Mechanistically, frontline anti-myeloma drugs, bortezomib and carfilzomib activate the NF-κB pathway to trigger heparanase expression in tumor cells. Activated NF-κB signaling was also found to drive high heparanase expression in drug resistant myeloma cell lines. In addition to enhancing heparanase expression, chemotherapy also caused release of heparanase by tumor cells into the conditioned medium. This soluble heparanase was taken up by macrophages and triggered an increase in TNF-α production. Heparanase is also taken up by tumor cells where it induced expression of HGF, VEGF and MMP-9 and activated ERK and Akt signaling pathways. These changes induced by heparanase are known to be associated with the promotion of an aggressive tumor phenotype [749]. On the other hand, heparin-derived compounds with heparanase inhibitory activity have been shown to effectively attenuate myeloma tumor growth and bone metastasis [750,751]. Interestingly, the development of these compounds began by observing heparin capacity to inhibit HPSE activity because of its competition with HS for binding to the enzyme [752]. In this context, targeting heparanase activity using Roneparstat (SST0001), a chemically modified non-anticoagulant heparin (that is devoid of any significant anticoagulant activity) with potent anti-heparanase activity, blocks the multiple pathways that are stimulated by heparanase (e.g., syndecan shedding, angiogenesis) resulting in decreased drug resistance and inhibition of myeloma growth *in vivo* [753]. Analysis of myeloma tumors from animals treated with Roneparstat demonstrated that these tumors have diminished levels of VEGF, HGF and MMP-9, reduced angiogenesis and reduced levels of shed syndecan-1 compared to animals treated with vehicle. This highlights that the mechanism of action of Roneparstat is consistent with it having anti-heparanase activity *in vivo* [754]. However, heparanase inhibition is not expected to cause direct MM cell killing as demonstrated in phase I, first-in-human trial designed to assess the safety and tolerability profile of Roneparstat in patients with R/R MM (NCT01764880) [755]. Instead, exploration of roneparstat in combination regimens for the treatment of MM should be the next step in this field. In this vein, Ramani et al., demonstrated the synergistic effect of Roneparstat when associated with bortezomib or melphalan. By using an *in vivo* model of disseminated myeloma, where MM cells expressing a high level of heparanase home and grow exclusively in bone, Roneparstat in combination with either bortezomib or melphalan, significantly decreased both the number of animals with detectable tumors and tumor burden compared to animals treated with either of these drugs alone. Weissmann et al., found that heparanase is expressed by human follicular and diffused non-Hodgkin's B-lymphomas, and heparanase inhibitors restrain the growth of tumor xenografts produced by lymphoma cell lines [756]. It is worth noting that pixatimod (PG545) is another potent inhibitor of heparanase [757] as well as a novel clinical-stage immunomodulatory agent, which was found to stimulate innate immune responses against tumors in preclinical cancer models. Pixatimod is capable of inhibiting the infiltration of TAMs *via* the inhibition of heparanase yet it also activates NK cells through toll-like receptor 9 (TLR9)-dependent stimulation of DCs [758]. Pixatimod is a cholestanol-sulfo-tetrasaccharide conjugated small molecule compound. The oligosaccharide backbone of pixatimod is derived from starch, and retains the amylose structure of α(1→4)-linked glucose residues. Coupling the sulfated oligosaccharide to a lipophilic cholestanol aglycone significantly increased the elimination half-life *in vivo*, while reducing the unwanted anticoagulant activity associated with similar compounds but retaining the potent inhibition of heparanase [759]. Due to lack of objective responses using pixatimod as a monotherapy [760], pixatimod has been tested in combination with a number of approved anti-cancer drugs demonstrating its clinical potential, including with gemcitabine, paclitaxel, sorafenib, platinum agents and an anti-PD-1 antibody [761]. Brennan et al., found that pixatimod had potent anti-tumor activity in murine models of B-cell and T-cell lymphomas. Investigation into the mechanism revealed that the *in vivo* anti-tumor effect of pixatimod was critically dependent on NK cell activation and that NK cell activation by pixatimod was mediated through myeloid differentiation primary response 88 (MyD88)-dependent TLR9 pathway *in vivo*, thus suggesting the significance of capitalizing on pixatimod as a novel and effective NK-activating agent for the treatment of lymphomas [762].

**The cell surface proteoglycan CD44 (H-CAM)**

The most studied form of Tn antigen is found in mucins (particularly MUC1). However, Tn antigen is also expressed on the adhesion molecule CD44 that mediate the response of cells to their cellular microenvironment [763]. Activation of CD44, a cell surface adhesion receptor (referred to as the lymphocyte homing-associated cell adhesion molecule, H-CAM) that is highly expressed in many cancers [764], is initiated by binding to its ligand HA [765]. In addition, the hyaluronate receptor CD44 also binds to other components of ECM including other GAGs, serglycin, fibronectin, collagen type I and type IV, laminin, and osteopontin (OPN). In this way, CD44 functions as an adhesion molecule for cell-cell and cell-ECM interactions [766]. In particular, serglycin serve as a novel ligand for CD44 to regulate lymphoid cell adherence and activation [767]. Guo et al., showed that serglycin is frequently overexpressed in lung adenocarcinomas, and functions in promoting NSCLC cell migration, invasion and stemness in a CD44-dependent manner [768]. In addition to tethering cells to extracellular ligands as cell-adhesion molecule, CD44 also participate in cellular signaling cascades through association with the actin cytoskeleton [769]. Interestingly, CD44 is a heavily glycosylated protein (class I transmembrane glycoprotein). N-glycosylation and sialylation regulate CD44 binding to HA; CD44 O-glycosylation regulates the tumor aggressiveness, and fucosyltransferase-mediated CD44 fucosylation promotes tumor progression [770,771]. Hematopoietic cell E/L-selectin ligand (HCELL) is a specific glycated form of sialofucosylated CD44 that is characteristically expressed on human hematopoietic stem cells and is the most potent E-selectin and L-selectin expressed on human cell prime ligands [772]. HCELLs have been shown to be present at high levels in human malignant hematopoietic cells, including neonatal Acute Myeloid Leukemia (AML) cells and the AML-

derived primitive human hematopoietic progenitor cell line KG1a [773,774]. Strikingly, aberrant expression and dysregulation of CD44 enhance tumor initiation and progression [775]. CD44 can directly potentiate RTK signaling pathways and act as a coreceptor for several growth factors, such as Met, VEGFR-2 and EGFR, thus enhancing cancer cell proliferation and correlating with poor prognosis and metastatic potential [776]. Moreover, HA-CD44 interactions induce highly malignant, chemotherapy-resistant cancer stem-like cells [777]. Mechanistically, HA-CD44 interactions promote cancer cell migration through SRC-induced cortactin cytoskeleton function [778]. CD44 is overexpressed in many cancers of hematopoietic and epithelial origins [779]; where its expression is correlated with the tumor biological behaviour including tumorigenesis, growth, metastasis and prognosis [780]. As CD44 contributes to the cancer stem/initiating phenotype, CD44 was identified as stem cell marker of HSCs [781], as well as a universal CSC marker in many cancers [782,783]. Not surprisingly, cells overexpressing CD44 possess several CSC traits, such as self-renewal and Epithelial-Mesenchymal Transition (EMT) capability, as well as a resistance to chemo- and radiotherapy [784]. The importance of adhesive interaction between CD44 and HA (which is a component of the BM ECM) to maintain Leukemia-Initiating Cells (LICs) in the BM niche has been confirmed using an anti-CD44 antibody, soluble HA, or hyaluronidase [785,786]. In AML, the CD44 cell surface antigen is expressed on leukemic blasts in all subtypes. As a CD44 is a key regulator of AML LSC function, targeting of CD44 eradicates human acute myeloid leukemic stem cells [787]. In a similar vein, CD44 is also involved in the arrest of myeloid differentiation; Charrad et al., demonstrated that CD44 ligation (by HA as well as CD44 antibodies) can reverse the differentiation blockage in AML M1/2 to AML M5 subtypes, and in this scenario CD44-targeted differentiation was comparable to that obtained in AML M3 with retinoic acid [788]. In ALL, high CD44 expression is seen in high risk T-ALL while CD44 expression was significantly lower in the TEL/AML1 (ETV6-RUNX1) ALL subtype (expressed from the t(12;21) translocation) that defines a subgroup of patients with an excellent prognosis [789]. In addition, CD44 signaling plays a pivotal role in regulating the proliferation of CML cells by modulating the expression and activity of the Wnt/β-catenin signaling pathway [790]. The full-length CD44 gene consists of 20 exons in mice but 19 exons in humans (exon 6 is missing in humans. Exons 6–14 of the CD44 gene in humans (known as variant or variable exons, CD44v2-v10) undergo extensive Alternative Splicing (AS) *via* excision or inclusion in various combinations in the membrane-proximal stem region to generate splicing variants (CD44v isoforms) [791]. The smallest and the most expressed CD44 isoform is the CD44 standard (CD44s), constructed of ten constant exons with no variant exons [792]. CD44s, referred to as hematopoietic CD44 (CD44H), is expressed mainly on cells of lymphohematopoietic origin [793]; while, CD44v are predominantly expressed on epithelial cells [794], including epithelial-type carcinomas, particularly those in advanced stages [795]. Furthermore, serum soluble CD44 (sCD44) levels can be used as as circulating tumor markers. Elevated levels of sCD44s and sCD44v6 were associated with an advanced disease in B-CLL [796]. Patients with higher than median sCD44 levels had a more advanced clinical disease stage, and had a median Progression-Free Survival (PFS) of 36 months, whereas patients with an sCD44 level < 642 ng/ml experienced a longer PFS of the average of 8 years. This indicated that serum sCD44 levels may represent a reliable prognostic marker that might be used for predicting the risk of disease progression in patients with early B-CLL [797]. Elevated levels of serum soluble CD44 (sCD44) were also reported in adult lymphomas and leukemias with a poorer treatment outcome [798,799]. Similarly, Tacyildiz et al., found that serum sCD44 levels were significantly high in pediatric patients with Hodgkin lymphoma (HL) and NHL who were in advanced stages of disease in contrast to significantly low levels in patients who were in complete remission (CR) [800]. Despite that CD44 blockade can lead to the elimination of leukemia initiating cells, anti-panCD44 can interfere with hematopoiesis. Hence, CD44v-specific targeting is a better option that targeting CD44 itself [801]. The extra domain formed by variant exons after distinct AS and assembly is able to interact with and sequester different growth factors, as well as cytokines, thus endowing CD44 with additional functions [802]. Mechanistically, CD44v displays a greater affinity to HA compared to CD44s [803]. In this context, compelling evidence indicates that major HA-CD44 signaling pathways involve a specific variant of CD44 isoforms. For example, HA/CD44v6 interaction can drive tumor metastasis by activating RTKs signaling pathways [804,805]. Consequently, CD44v expression is directly proportional to increased metastatic spread in several hematologic and solid malignancies and poor prognosis [806]. At instance, CD44v surface levels in CLL can identify a subgroup of patients with significantly worse prognostic features [807]. Within this context, targeting and inhibiting CD44 through neutralizing antibodies was shown to be cytotoxic in CLL cells, particularly in patients with CLL that express ZAP-70, but had little effect on normal B-cells [808]. Among the various CD44 isoforms, the v6 exon-containing isoforms (CD44v6) is implicated in tumorigenesis, tumor cell invasion and metastasis [809]. In fact, CD44v6 is currently the most established tumor antigen among the CD44 splice variants [810]. CD44v6 is found to confer metastatic potential to non-metastatic tumor cells [811]. CD44v6 is relatively tumor- restricted and associated with poor prognosis in AML [812,813], and MM [814]. Interestingly, Casucci et al., showed that CD44v6 is required for AML and MM cell growth *in vivo* and appealing target to select in order to avoid immune evasion as a result of antigen-loss variants. In *in vivo* models of AML and MM, CD44v6 CAR T-cells were found to provide significant anti-tumor activity without affecting either CD44v6-expressing keratinocytes or hematopoietic stem cells [815,816]. CD44v6 facilitates homing of MM cells to the BM and their adhesion to BM stroma is dependent on CD44v6 expression which is upregulated by contact of the MM cells to BM endothelial cells [817]. Furthermore, CD44v6 expression was observed predominantly in aggressive NHLs (aNHLs) where it display strong prognostic potential and identify patients with an unfavourable outcome [818,819,820]. For example, CD44v6 is particularly important for predicting worse prognosis in DLBCL [821]. Likwise, surface CD44v6 expression was significantly correlated to poorer OS in B-CLL [822] and ALL [823,824]. In addition to the Tn antigen, CD44v6 can also carry TF [825], sTn [826], and sLeA antigens [827]; where it correlates with the metastatic potential of several cancers. Intriguingly, overexpression of CD44v9 is related to an unfavorable clinical presentation in MM and high-grade NHL [828]. In MM, acquired CD44v9 expression can occur during disease progression [829]. The CD44v10 isoform displays prognostic relevance by being correlated to initial BM involvement and risk of relapse in

Nodular Sclerosing HL (NSHL) [830]. In CML, Holm el al, showed that CD44v3 (containing variant exons 8–10) is elevated during CML progression from chronic phase to blast crisis. Furthermore, although CD44 mAb and dasatinib treatment significantly reduced blast crisis chronic myeloid leukemia stem cells (BC LSCs) self-renewal in the splenic niche and lowers self-renewal in BM, some BCR-ABL1– and CD44v3-expressing cells persist in the BM niche following combination therapy, suggesting that a CD44v3-specific mAb may be more effective at eradicating BC LSCs from the more recalcitrant BM niche in CML [831].

**The B cell receptor and immunoglobulins**

The B-cell Receptor (BCR) and its secreted counterpart, Immunoglobulins (Igs) (also called antibodies (Abs)) are two important glycoproteins involved in B-cell biology. It has been indicated that glycans expressed by these B-cell-specific molecules can modulate immune activation *via* glycan-binding proteins [832]. Compelling evidence indicate that the BCR pathway is activated in CLL, DLBCL, *Burkitt Lymphoma (BL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Marginal Zone Lymphoma (MZL),* and *Waldenstrom's Macroglobulinemia (WM)*, which represent a potential therapeutic target [833]. Unfortunetely, BCR-targeting drugs often fail to produce durable responses despite their initial effectiveness [834]. It has been repeatedly demonstrated that the development and function of B-cells depend on signals from the BCR. Indeed, healthy B-cells depend on surface BCR for survival and metabolic fitness. To reiterate, there are two principal types of BCR signaling, antigen-dependent and antigen-independent or "tonic" BCR signaling. Tonic BCR signaling is a constitutive signaling that mainly relies on the PI3K/AKT pathway and is crucial for B-cell survival. By contrast, antigen-dependent BCR signaling relies on the NF-κB pathway and plays an important role in humoral responses inducing B-cell proliferation, cytidine deaminase (AID) expression, affinity maturation and differentiation [835]. Similar to normal B lymphocytes, B-cell lymphomas including CLL and other NHLs also depend on the presence of an intact BCR signal transduction pathway encompassing both types of BCR signaling [836]. Structurally, the BCR is made of surface-bound Ig (either IgA, IgD, IgE, IgG or IgM) in association with a heterodimeric signaling unit comprised of Ig-α (CD79A) and Ig-β (CD79B), thereby combining antigen recognition with signal transduction [837,838]. In particular, surface IgM is a key component of the BCR and mediates intracellular signals important for proliferation or apoptosis [839]. The CD79A/B heterodimer transmits an activating signal when antigen binds to the BCR in $CD20^{+}$ B-cells and in CD20-negative plasmablasts and plasma cells [840,841]. In addition, CD79A and CD79B are essential for BCR assembly and expression in human B-cells. Consequently, aberrant activation of BCR signaling plays a critical role in the pathogenesis of many B-cell malignancies. Compelling evidence suggests that B-cell malignancies arising from mature B-cells usually retain BCR expression on the surface [842]. In fact, expression of surface Ig (sIg) appears to be critical for the majority of B-cell malignancies [843]. However, in agreement with previous reports suggesting that CD79A and CD79B are essential in lymphoma cell lines representing DLBCL [844,845,846], the mechanistic link between the IgM surface level and B-cell survival was recently unveiled. Through combining CRISPR/Cas9 deletion of CD79A or CD79B with studies of glycan maturation in MCL cell lines, Huse et al., demonstrated that CD79A and CD79B are equally required for surface IgM expression in human B-cells, and if one of these proteins was deleted, it causes a block in N-glycan maturation of the other CD79 protein as well as IgM, resulting in subsequent blocked transportation of the IgM complex to the plasma membrane and accumulation of immature proteins in the ER [847]. Interestingly, MCL cells usually overexpress IgM as compared to normal B-cells, which likely contribute to the pathogenesis of this lymphoma type [848]. As loss of IgM surface expression due to CD79A/B depletion reduced the survival and fitness of lymphoma cell lines, the CD79A/B signaling pathway is a potential therapeutic target. Moreover, B-CLL depends on BCR signaling for survival and proliferation [849]. As the case with B-cell lymphomas, surface expression of IgM has an important influence on the clinical behavior of CLL [850]. However, contrary to DLBCL and MCL, low surface expression of IgM is a characteristic feature of B-CLL [851,852,853]. Mechanistically, the impaired glycosylation and folding of the mu and CD79a chains leads to the retention of both chains in the ER and lower levels of surface IgM expression [854]. Although the t(14;18) translocation disrupts one Ig allele, expression of sIg is retained, indicating that sIg of FL is vital for tumor cell survival. Initially this retention and the ongoing somatic hypermutation led to speculation about a role for persistent antigen in FL, which was difficult to explain, given the high variability of the Immunoglobulin Variable Region (IGV) gene usage and the sequence changes resulting from somatic hypermutation. A striking observation on the nature of sIg in FL has revealed a possible explanation both for retention of sIg and for an influence of microenvironmental factors. This involves a "universal" antigen-independent mechanism able to engage sIg of all cases of FL [855]. Specifically, one of the key features of FL is the almost universal acquisition of N-linked glycosylation sites in the Ig variable region, most commonly in the Ig complementarity-determining regions (CDRs) of the heavy chains and less frequently in the light chains [856]. The acquired N-glycosylation sites are tumor-specific and are introduced during somatic hypermutation in FL [857]. Strikingly, the glycans acquired on the sIg variable region are unusual in that their biosynthetic processing terminate at the initial oligomannose-type state, indicating that they do not fully mature in the Golgi apparatus, most probably due to their inaccessibility to the appropriate Golgi enzymes [858,859]. The presence of high-mannose glycans in surface Ig elucidates the mechanism by which surface Ig may activate the malignant cells even in the absence of antigen, hence promote tumor progression. Mechanistically, mannosylated sIg (sIg-Mann) interacts with the C-type lectin dendritic cell–specific intercellular adhesion molecule 3 grabbing non-integrin (DC-SIGN) [860]. In contrast to normal B-cells, exposure of FL samples to DC-SIGN triggered prolonged phosphorylation of AKT, ERK, and phospholipase C-γ-2 (PLCγ2) and increased expression of cMYC, supporting the concept that DC-SIGN is able to activate and maintain proliferation signals that could promote disease progression [861,862]. Hence, lectins within the TME promote tumor survival and progression through antigen-independent interactions with the BCR. Interestingly, Chiodin et al., report that the same modification is seen in a subset of DLBCLs, occurring in about 50% of germinal center B-cell (GCB)-type, but only 6% of activated B-cell (ABC)-type DLBCLs and conferring poor prognosis which identifies an aggressive form of DLBCL that may be targeted therapeutically. Similar to FL, this modification facilitates a chronic antigen-independent-BCR activation through interactions with microenvironmental

DC-SIGN [863]. In conculsion, therapeutic approaches designed to selectively block interaction between DC-SIGN and high-mannose residues would also be of potential relevance in FL and DLBCL patients.

**Immunoglobulins**

As the secreted form of the BCR [864], antibodies are the most abundant glycoproteins in the blood. Antibodies are made up of two identical heavy and light chains [865] and consist of a constant (Fc for Fragment crystallizable) and a variable (Fab for Fragment antigen binding) region. While the binding specificity of the antibody is determined by the sequence and conformation of the Fab domain, its effector functions are largely determined by the Fc domain and its ability to interact with Fc receptors (FcγRs) expressed on discrete populations of immune and non-immune cells. Classical FcγRs can be broadly divided into activating or inhibitory depending on the presence of Immunoreceptor Tyrosine-based Activation (ITAM) or Inhibitory (ITIM) Motifs in the cytoplasmic tail. Interestingly, all antibodies contain glycans that are linked to conserved motifs in the Fc region which are essential for their effector functions [866,867]. Mechanistically, immunoglobulin glycans impact the effector functions of antibodies depending on the branching of *N*-glycans and/or the terminal sugars of *N*-glycans or *O*-glycans, which include galactose and sialic acid [868]. As the most abundant class of antibody in serum, IgG plays a central role in systemic immunity. Interestingly, IgGs are the most abundant N-glycosylated proteins in human serum with the conserved N-glycosylation site at Asn297 of their constant region [869]. These Fc glycans have a substantial impact on the structure of soluble IgG molecules; and without them IgG cannot bind to FcγRs or complement factors (870). In a similar vein, it was shown that Siglecs limit the effectiveness of tumor-targeting antibodies by antagonizing FcγRs [871]. Notably, variation in N-glycosylation of IgG, has physiological significance in hematologic malignancies. For instance, it is well-known that M-proteins from MM patients have similar structure to antibodies. Interestingly, glycosylation, based on the attachment of an oligosaccharide to M-proteins, is the most prevalent PTM of M-proteins [872]. While the the exact role of Fab N-glycosylation remain poorly understood [873], recent evidence has emerged suggesting that N-glycosylation of the M-protein variable (Fab) region contributes to M-protein pathogenicity, and that it is a risk factor for disease progression of plasma cell disorders [874]. In a similar vein, M-protein glycosylation may influence the development of amyloid deposits in patients with light chain amyloidosis [875]. In fact, monoclonal light chain glycosylation has been reported as a risk factor of progression to MM and amyloidosis [876,877]. In addition, IgG N-glycan profiles can stage plasma cell disorder disease and identify patients who relapse following treatment [878]. The IgG *N*-glycans present at each of these stages was found to correlate disease severity with increased agalactosylated and afucosylated N-glycan content [879]. MM in remission appeared to have recovered more of the normal galactose and fucose content, closely correlating with the traditional M-protein biomarker of MM. The agalactose content subsequently increased during MM relapse. In the SMM stage, more galactose and sialic acid was observed on IgG Fc regions compared to either MUGS or MM.

## Immune-related lectin receptors

Lectins, non-enzymatic, non-immunoglobulin, sugar-binding proteins, selectively interact with small subsets of the vast set of possible glycoforms and thereby facilitate diverse biological processes [880]. In particular, lectin-glycan (protein-carbohydrate) interactions serve multiple functions in the immune system [881]. In oncology, TACAs interact with Antigen-Presenting Cells (APCs) through their engagement with several lectin families of the immune system. In addition to mediating tumor cell recognition by the immune system [882], these interactions also modulate the anti-tumor innate and adaptive immune responses (immunomodulatory effects). Notably, glyco-immune interactions mediate T-cell immunosuppression. As a notable example, the interactions between endogenous lectins with two of the most abundant transmembrane glycoproteins on the T-cell surface, the CD43 and CD45, modulate several T-cell responses including migration, T-cell receptor signaling, and apoptosis in a glycan-dependent manner [883]. It is worth noting that both CD45 and CD43 are considered as pan-hematopoietic markers in humans [884]. CD45, also known as protein tyrosine phosphatase receptor type C (PTPRC), is a large transmembrane glycoprotein expressed on all nucleated hematopoietic cells and an essential regulator of T- and B-cell receptor signaling through activation of various Src family kinases [885]. The leukocyte sialomucin CD43, also known as leukosialin or SPN (sialophorin), is one of adhesion inhibitory molecules that is abundantly expressed on most leukocytes [886]. In fact, there is substantial evidence for the the role of glycan–lectins interactions in immunosuppressive mechanisms that occur in tumor immune escape [887,888,889,890]. Such inhibitory glycan-lectin interactions constitute glyco-immune checkpoints that circumvent the potential drawbacks of CTLA-4 and PD-1 checkpoints and offer promising novel and improved cancer immunotherapeutic modalities [891]. Furthermore, aberrant lectin binding is capable of altering critical cellular functions. For example, expression of sLeX and sLeA enables circulating cancer cells to bind C-type lectins such as endothelial E-selectin, attach to endothelial cells, infiltrate distant sites, and establish metastasis [892,893]. Human lectins are classified according to their subcellular location and the structures of the CRDs they contain [894]. The most important lectin families are the C-type lectins, the S-type lectins (galectins), and the I-type lectins (Siglecs).

**C-type Lectin Receptors (CLRs)**

CLRs are $Ca^{++}$-dependent lectins that are defined by having one or more characteristic C-type lectin-like domains (CTLDs) [895]. CLRs on APCs facilitate uptake of carbohydrate antigens for antigen presentation, modulating the immune response in infection, homeostasis, autoimmunity, allergy, and cancer [896]. Both macrophages and B-cells can serve the antigen-presenting function. However, DCs are the superior professional APCs [897]. As professional APCs, DCs sense the microenvironment through different types of receptors to scan local environmental changes and eliminate incoming pathogens [898]. Interestingly, CLRs expressed by APCs and various non-immune cells are considered as non-classical FcRs (sometimes referred to as Type II FcR) [899,900]. CLRs can be divided into two main categories: Selectins and myeloid CLRs (expressed by cells of the myeloid lineage, such as DCs, macrophages, neutrophils, and monocytes). Both categories can function as both adhesion molecules and endocytic receptors on APCs, thus are involved in the uptake of pathogens for antigen processing and presentation, and subsequent T-cell activation [901,902,903]. Myeloid CLRs are further classified into four main groups depending on their intracellular signaling motifs [904]. Myeloid CLRs are important

sensors of endogenous (self) or exogenous (non-self) that work in concert with other PRRs [905,906]. Several myeloid C-type lectins, such as DC-SIGN and MGL contribute to tumor progression by inducing immunosuppressive responses upon sensing abnormal or altered tumor-associated carbohydrates [907]. Tumor-associated glycans recognized by myeloid CLRs in immune cells possess immunomodulatory properties which enable tumor growth and immune response evasion [908]. Noteworthily, there is evidence that leukemic blasts from B-ALL and T-ALL patients have increased binding with myeloid C-type lectins thereby affecting their immunological elimination [909]. The most important molecules from the C-type lectins family include:

***Myeloid C-type lectin receptors:***

**The Macrophage Galactose-type Lectin (MGL, CD301; also known as CLEC10A):** MGL is a Type II C-type lectin, and is the only lectin that exclusively binds terminal GalNAc residues [910]. MGL is typically expressed by immature DCs and alternatively activated macrophages (subtype M2a) conferring immune-suppressive (tolerogenic) signaling. The main ligands of MGL in cancer are truncated O-glycans including the Tn antigen (α-GalNAc-Ser/Thr) [911,912], the TF antigen (Galβ1–3GalNAc) [913], sTn [914], as well as N-GalNAc and galactose and core 2 structures [915,916]. Interestingly, MGL is the only C-type lectin receptor that recognizes and exhibits a high binding specificity for terminal α- and β-linked GalNAc residues found in Tn, sTn and LacdiNAc antigens [917,918]. Strikingly, the binding of MGL to altered glycosylation prevents an anti-tumor immune response, allowing cancer cells to escape the immune system. In this context, the expression of Tn antigen on tumor cells engaging MGL on APCs creates an immunosuppressive milieu. This suggests that the MGL-Tn axis is an immunosuppressive checkpoint axis in cancer [919,920]. Mechanistically, Tn antigen engagement by MGL results in the polarization of tolerogenic DCs and immunosuppressive macrophages [921,922,923]. In addition, MGL upregulation on tolerogenic DCs contributes to dampening T-cell immunity in an MGL-dependent manner through interacting with a Tn antigen on the CD45 molecules of effector T-cells. This binding suppresses the phosphatase activity of CD45 and inhibits lymphocyte protein tyrosine kinase (Lck) activation. In effector T-cells, CD45-mediated dephosphorylation of the C-terminal tail of Lck leads to the formation of its active form, which in turn is required for the initiation of T-cell receptor (TCR) signaling [924,925]. Therefore, the suppression of CD45 activity by MGL reduces TCR signaling pathways, thus leading to the inhibition of T-cell proliferation, reduction in pro-inflammatory cytokine synthesis, and, therefore, the acceleration of T-cell apoptosis [926,927,928]. On the other hand, binding of MGL to its ligands contributes to immune suppression by increasing IL-10 (an anti-inflammatory cytokine) secretion and induction of T-cell apoptosis [929]. Further, owing to its specificity for the truncated O-glycans, MGL is able to recognize the mucin MUC1. A study performed by Napoletano et al., showed that the interaction of MGL with the Tn-MUC1 glyco-peptide, with a high density of glycans (15 Tn residues), was stronger than MUC1 bearing lower amounts of GalNAc residues [930]. The binding of MGL to the truncated glycan structures on MUC1 leads to a defective T-helper (Th) cell-mediated response as well as to a reduction of cytotoxic T lymphocytes (CTLs) [931]. Besides, the tumor-associated MUC1 glycoform bearing the sialyl TF antigen was shown to impair the DC function by enhancing spontaneous apoptosis or defective antigen presentation [932]. Therefore, the MGL-Tn-CD45 and the MGL-Tn-MUC1 represent novel immunosuppressive checkpoint axes, especially in context of modulating the APC functions. In addition, the T-cell leukemia model cell line Jurkat is known to have a high level of Tn antigens (due to a mutation in Cosmc) which rendered acute T-cell leukemia cells a model system to study the immunoregulatory properties of MGL and the effect of its ligand recognition [933]. Both CD43 and CD45 have been described as the main carriers of the Tn antigen interacting with MGL in Jurkat cells [934]. Therefore, it can be inferred that both the Tn antigen and the MGL-Tn-CD43/ MGL-Tn-CD45 axes are potential therapeutic targets for treatment of T-ALL.

**The Dendritic Cell-specific Intercellular Adhesion Molecule 3-grabbing Non-integrin (DC-SIGN, CD209):** Similar to the MGL, DC-SIGN belong to the type II group of CLRs and is expressed on APCs (mainly immature DC and macrophages with M2 polarization) [935,936]. DC-SIGN is associated with antigen uptake and subsequent MHC (major histocompatibility complex) presentation for the potentiation of adaptive immune responses [937,938,939,940,941]. DC-SIGN is known to bind the tumor-associated Lewis antigens (LeX, LeY, LeA, LeB) [942,943]. DC-SIGN is involved in tumor immune evasion as well as promoting tumor development [944,945]. Mechanistically, the interaction between DC-SIGN with Lewis X (LeX; CD15) antigens on tumor cells leads to immune suppression through various mechanisms driven by TAMs, including increased PD-L1 expression [946,947]. As an example, the expression of DC-SIGN on DCs binds to LeX and LeY carbohydrates on tumor-associated carcinoembryonic antigens of colon cancer cells, suppressing the function of antitumor immunity of DCs and subsequently inducing immune evasion, which is in favor of the progression and metastasis of colon cancer cells [948,949]. In this context, CD15 was shown to be the ligand for DC-SIGN in some ALL cells. However, other ligands play a role in the interaction of ALL cells with DC-SIGN. It should be noted that B-ALL cells demonstrated increased binding to DC-SIGN and L-SIGN (liver/lymph node-SIGN, also called DC-SIGN-related or CD299), which correlated with poor prognosis, suggesting involvement of this interaction in pathogenesis [950]. Importantly, blockade of DC-SIGN can abrogate immunosuppressive activity from TAMs and increase anti-tumor activity of $CD8^+$ T-cells, while working synergistically with PD-1 immunotherapies *in vitro* [951]. In addition, BCRs in several B-cell malignancies carry high-mannose oligosaccharides which interact with mannose-binding lectins, especially with DC-SIGN, in the TME and initiate antigen-independent signaling that may drive tumor growth/survival. This lectin interaction with the BCR is critical for lectin-driven malignancies, particularly FL. At instance, the acquisition of new glycosylation motifs in the BCR due to gene rearrangement and/or somatic hypermutation is an early event in the genesis of FL [952]. In fact, most FL cases express a BCR that has acquired ≥1 N-linked glycosylation motifs (N-motifs) in their Fab portions by somatic hypermutation [953]. These N-motifs contain mannose-terminated glycans and can interact with lectins in the TME, activating the tumor BCR pathway [954,955,956]. However, insertion of N-glycosylation sites in Ig variable region genes has been detected in other germinal center (GC)-associated lymphomas, specifically in subsets of DLBCL and BL, suggesting involvement of altered glycans in pathogenesis of these malignancies as well. Strikingly, the BCR in CLL also carries high-mannose oligosaccharides, albeit in

the heavy chain constant rather than variable region. The high expression level of the unique glycoform, particularly in the more aggressive unmutated CLL subset, suggests a functional significance for this glycan in CLL. Hence, targeting BCR-lectin interaction is considered to be an interesting therapeutic strategy [957].

**The Myeloid Inhibitory C-type Lectin-like Receptor (MICL; also known as CLL-1, CLEC12A, DCAL-2, and KLRL-1):** Like MGL, MICL, also known as human C-type lectin-like molecule-1 (CLL-1), is a myeloid cell-expressed C-type lectin. Since it is overexpressed in over 90% of AML blasts and the majority of LSCs while absent on normal HSPCs, CLL-1/CD371 is a potential target for immunotherapy in AML [958,959]. Currently, researchers from the Memorial Sloan Kettering (MSK) cancer center are studying a new CAR T-cell therapy (CD371-CAR-IL18) that targets CLL-1 to treat AML (NCT06017258).

**Selectins**

Selectins belong to group IV of the CLRs. They play crucial roles in regulating the trafficking of leukocytes. These proteins are responsible for the initial capture (i.e., "rolling") of leukocytes from the circulation before extravasation across the vascular endothelium can occur. Selectins share a common ligand, the carbohydrate sLex, though their affinity is modulated by the nature of the carbohydrate scaffold and the backbone that carries sLex [960]. Each selectin is named according to its expression pattern. Overall, E-selectin (CD62E) binds leukocytes to activated endothelium, whereas P-selectin (CD62P) binds leukocytes to platelet-activated endothelium and platelets, and L-selectin (CD62L) binds leukocytes to lymph node HEVs. Broadly, selectins can be divided into two functional categories:

1. The interactions between P- and E-selectins with their ligands mediate leukocyte homing into non-lymphoid tissues in response to inflammation or tissue injury [961,962]. While P- selectin is stored in endothelial cell Weibel-Palade bodies and platelet storage granules, E-selectin expression is limited to endothelial cells but is not stored in any intracellular compartment. Hence, endothelial E-selectin expression is driven by inflammatory cytokines, whereas P-selectin secretion occurs *via* exocytosis of endothelial stores after stimulation by activated platelets [963,964]. P- and E-selectin ligands have a sLeX which contains a sialic acid bound to the terminal galactose of the Lewis antigen in an α2-3 linkage, catalyzed by the ST3GAL family of enzymes [965]. However, P-selectin recognizes with high affinity sLeX presented on Core2 *O*-glycans carried on threonine 57 of PSGL-1 [966].

2. L-selectin is a type-I transmembrane glycoprotein and cell adhesion molecule that is expressed on most circulating leukocytes [967]. Intriguingly, L-selectin-ligands interactions mediate steady-state lymphocyte homing into to secondary lymphoid organs. As a matter of fact, lymphocyte homing is regulated *via* adhesive interactions between lymphocytes and 6-sulfo-sLeX on HEVs. Mechanistically, the first interaction between naive lymphocytes and HEVs (specialized blood vessels mediating lymphocyte trafficking to lymph nodes and other secondary lymphoid organs) is initiated by lymphocyte L-selectin that recognizes a family of sulfated mucin-like glycoproteins known as HEV sialomucins including glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), CD34, podocalyxin, endoglycan, endomucin, and nepmucin which become effective L-selectin ligands when they are modified with 6-sulfo sLeX structures by a group of glycosyltransferases and sulfotransferases highly expressed in HEV endothelial cells (HECs) [968]. Indeed, the expression of high levels of the L-selectin-binding HEV-specific glycoforms of HEV sialomucins is undoubtedly one of the most important features of the HEV endothelium [969]. Within this context, the tetrasaccharide 6-sulfo-sLeX, abundantly produced in HEVs and is present on both *N*-glycans and extended core 1 and 2 *O*-glycans decorating HEV sialomucins [970,971,972], is the critical carbohydrate determinant for L-selectin recognition [973,974,975]. Consequently, it has been reported that GlcNAc6STs can control lymphocyte homing *via* the ligand 6-sulfo-sLeX synthesis on HEVs [976]. Noteworthily, L-selectin ligands expressed on HEVs in peripheral lymph nodes are collectively referred to as peripheral node addressin (PNAd), which is defined by its reactivity to the HEV-specific mAb "Mouse Endothelial Cell Antigen-79" (MECA-79) [977,978]. In fact, MECA-79 is a fantastic tool for HEV studies that specifically recognizes 6-sulfo sLeX structures on extended core 1 *O*-glycans [979]. In addition, selectins have key role in trafficking of T-cells to tissues. L-selectin controls the capacity for naive and memory T-cells to actively survey peripheral lymph nodes, whereas P- and E-selectin capture activated T-cells on inflamed vascular endothelium to initiate extravasation into non-lymphoid tissues. The capacity for T-cells to interact with all of these selectins depends on the enzymatic synthesis of complex *O*-glycans, and thus, this protein modification plays an indispensable role in regulating the distribution and homing of both naive and previously activated T-cells *in vivo* [980].

The best characterized selectin ligand is P-selectin glycoprotein ligand-1 (PSGL-1) that is mostly expressed on the surface of all leukocytes where it facilitates rolling and tethering [981]. All three selectins bind to PSGL-1. However, binding of PSGL-1 to P-selectin (CD62P), but not E-selectin, is dependent on posttranslational modifications. P-selectin requires a very specific glycopeptide epitope to engage its glycoprotein partner PSGL-1. This epitope includes sLex on a core 2 residue with nearby sulfated tyrosine [982,983,984]. PSGL-1 represents a marker of plasmacytic differentiation since it is constantly expressed in MM cells as well as in lymphoproliferative disorders showing plasmacytic differentiation [985]. Importantly, interactions between PSGL-1 and P- and E-selectin regulate MM cell proliferation and homing and contribute to resistance to therapies [986]. PSGL-1 is also essential for hematogenous metastasis of lymphomas [987]. PSGL-1 can bind to V-domain immunoglobulin suppressor of T-cell activation (VISTA) to mediate T-cell suppression in acidic environments, characteristic of many TMEs [988]. Consequently, blockade with antibodies specific to this PSGL-1/VISTA axis reversed immunosuppression *in vivo*, and ongoing clinical trials are assessing the blockade of VISTA. In light of these findings, PSGL-1 could also be a promising therapeutic target to overcome T-cell suppression [989,990]. Physiologically, selectins are important for the interactions involving leukocytes, platelets, or endothelial cells [991]; and therefore, they play an essential role in tumor-promoting inflammation and cancer metastasis. During the the metastatic cascade, adhesion of circulating cancer cells to the walls of blood vessels is the function of selectins [992]. Notably, the role of E-selectin/ligand (sLeX and sLeA) interactions in initiating and enhancing the adhesion of cancer cells to the endothelium in tumor metastasis is well established [993]. For instance, it has also been shown that E-selectin drives cancer metastasis into the BM [994,995]. Noteworthily, Connolly et al., suggested that aberrant transcription of glycosylation

genes, involved predominantly in selectin ligand synthesis, is associated with inferior survival outcomes and may help identify patients likely to benefit from treatment with agents targeting aberrant glycosylation, e.g. E-selectin inhibitor in MM [996]. It is important to note that binding of E-selectin to a cell requires the presence of sLeX or sLeA tetrasaccharides at the termini of cell surface glycolipids, or glycoprotein *O*-glycans (Ser/Thr-linked) or *N*-glycans (Asn-linked) [997]. Strikingly, P-selectin and L-selectin-mediated interactions also contribute significantly to tumor metastasis (both are essential for creating an inflammatory metastatic microenvironment once cancer cells intravasate and circulate in the bloodstream) [998,999]. In this vein, accumulating evidence indicates that P-selectin-mediated interactions contribute to cancer progression [1000,1001].

**S-type lectins (Galectins)**

Galectins – previously known as "S-type lectins" and then named "galectins" in 1994- constitute an evolutionary conserved family of β-galactoside-binding lectins composed of one or two carbohydrate-recognition domains (CRDs). Unlike Siglecs and selectins (mostly cell-surface-bound receptors), galectins are soluble lectins [1002]. Since their discovery in the 1970s, their biological roles, initially thought that were limited to recognition of carbohydrate ligands in embryogenesis and development, have expanded in recent years by the discovery of their immunomodulatory activities [1003]. The minimal structure recognized by galectins is the disaccharide N-acetyllactosamine (lacNAc), which is found in *N*-glycans and O glycans and can be presented as multiple units (poly-lacNAc) on cell surface glycoconjugates [1004]. LacNAc is 5–10 times more active than lactose [1005,1006], and so *N*-glycans are good ligands for most galectins. However, substantial differences exist in the glycan-binding preferences of individual members of the galectin family, particularly in the recognition of sialylated and sulfated glycans [1007], which might be the basis of functional differences in their biological activity [1008]. The extent of N-glycan branching, the multiplicity of lacNAc residues and/or modifications (e.g., sialylation or fucosylation) on LacNAc or poly-LacNAc structures may alter galectin-glycan interactions [1009]. For instance, incorporation of α2- 6-linked sialic acid to cell surface glycoconjugates interrupts binding of some members of the family, including galectin-1 [1010]. Of particular interest, the affinity of galectins for *N*-glycans increases in correlation with β1-6 branching (mediated by GnT-5/*MGAT5*) and extension with poly-lacNAc. Galectins are expressed in a plethora of tissues and cell types, and their functions are highly context-dependent [1011]. In contrast to other chemokines, cytokines, or transcription factors, galectins mediate a multitude of vital activities through binding to the outermost grouping of carbohydrates on a glycoprotein or glycolipid oligosaccharide rather than specific receptors [1012]. Nevertheless, galectins are peculiar in that they also mediate their functions intracellularly. There is compelling evidence that galectins might have non-carbohydrate binding partners and functions. These CRD-independent functions have been particularly well documented for the intracellular galectins [1013,1014,1015]. By contrast, an important mechanism by which extracellular galectins regulate cellular events is by complexing with cell surface glycoprotein receptors to create galectin–glycoprotein lattices [1016]. These lattices are vital for organization of glycoprotein assemblies on the cell surface [1017] as well as signaling [1018]. Mechanistically, lattices can affect cell signaling in several ways. Galectin lattices can retain glycoproteins on the cell surface by retarding endocytosis and thus increase the effective concentration of the receptor, or galectins can alter signaling by the receptors [1019]. For instance, galectin-glycan lattice is known to regulate BCR signaling in lymphocytes. It is worth noting that in relation to BCR signaling, both BCR and CD45 are modified by *N*-glycans and act as galectin ligand. Interestingly, BCR interacts with CD45 (a ligand for both galectin-3 and galectin-1) through galectin bridging between the BCR and CD45. Since BCR signaling is known to be involved in cell adhesion or migration, interaction between CD45 and BCR through the glycan-galectin lattice might be a foundation of BCR-mediated cell adhesion mechanism [1020]. In cancer, galectins play central roles in tumor progression as well as they are excellent negative regulators (checkpoints) of the immune cell functions, participating in the creation of a TME that promotes tumor escape [1021]. In the TME, the abundantly expressed galectins play essential role in the modulation of the antitumor immune response by regulating the innate and adaptive immune systems [1022,1023,1024]. In addition, galectins are also crucial for RTK activation; the altered glycosylation changes observed in RTKs are known to allow galectin recognition (mainly galectin-1, -3, and -9) [1025]; the latter are responsible for oncogenic activation of RTKs. Mechanistically, cancer cells utilize extracellular galectins to induce lattices on the cell surface where activated growth factor receptors are trapped which leads to sustained activation of the signaling pathways by preserving a constant flow of proliferative stimuli. Hence, the RTK-galectin interplay constitutes an attractive target for development of anti-cancer therapies [1026]. Amongst the 12 galectins identified in humans so far, galectin-1, galectin-3, and galectin-9 were most intensively studied in context of cancer [1027]. Table-4 outlines the multiple roles of these gelectins in hematologic malignancies.

**Table 4:** The multiple roles of galectins in hematologic malignancies

| Galectin | Malignancy | Significance | Therapeutic value | Reference(s) |
|---|---|---|---|---|
| | Multiple myeloma | Over-expressed in MM cells<br>Cell invasion | Knockdown of galectin-1 in MM cells resulted in smaller tumor formation and less lytic bone damage in an intra-tibeal injection model | [1028, 1029] |
| | Chronic lymphocytic leukemia | Secreted galectin-1 contributes to stimulate the activity of CLL cells and may help to establish the appropriate microenvironmental conditions for leukemic progression | Selective manipulation of galectin-1 expression in nurse-like cells may be able to influence CLL differentiation and survival | [1030, 1031] |
| Galectin-1 | Hodgkin's lymphoma | Play critical roles in disease progression<br>Facilitates immune escape<br>High galectin-1 is correlated with poor outcome | Can serve as a predictive biomarker for R/R HL<br>In clinical studies, neutralization of galectin-1 was an effective therapeutic strategy | [1032, 1033, 1034] |

| | | | | |
|---|---|---|---|---|
| | B-cell precursor acute lymphoblastic leukemia | Given the strong upregulation of galectin-1 in *KMT2A*-R cells, a cell surface remodeling towards higher levels of HS might also play an important role in *KMT2A*-R cell survival within the BM environment | PTX008 inhibits galectin-1-regulated cell aggregation, adhesion, migration of B-ALL cells, and sensitizes the ALL cells to treatment with chemotherapy | [1035, 1036] |
| | Leukemic cutaneous T-cell lymphoma | L-CTCL–derived galectin-1 may impair the viability, proliferation, and Th1 responses of nonmalignant T cells, leading to a systemic Th2 bias that favors tumor survival and probably contributes to the observed susceptibility of these patients to infections | Inhibition of galectin-1/ligand interactions may be an effective strategy for enhancing both anti-tumor and anti-pathogen responses in patients with L-CTCL | [1037] |
| Galectin-3 | Acute myeloid leukemia | High galectin-3 is important for MSCs to support leukemia cell survival in the TME<br>High galectin 3 is an independent prognostic factor for poor survival | Kiromic Biopharma's novel galectin-3 inhibitor CBP.001 reduces AML cell viability in the presence of MSC and sensitizes AML cells to Ara-C in co-culture suggesting targeting galectin-3 may be an effective microenvironment based strategy for AML therapy | [1038] |
| | | | The GCS-100/ABT-199 combination was effective against primary AML blast cells from patients with *FLT3*- ITD mutations | [1039] |
| | Chronic myeloid leukemia | Cell proliferation regulation and antiapoptosis Drug resistance | | [1040, 1041] |
| | Acute lymphoblastic leukemia | The stromal derived galectin-3 is critical for chemoresistance | | [1042] |
| | Multiple myeloma | Adhesion and migration, Angiogenesis, Anti-apoptotic, Invasion and metastasis, Regulation of bone homeostasis, Drug resistance | GCS-100, induces apoptosis in primary MM cells and HMCLs, reduces MM cell proliferation supported by adhesion to BMSCs and blocks HMCLs migration induced by VEGFA<br>GCS-100 overcomes resistance to the proteasome inhibitor, bortezomib, and increases the apoptosis induced by dexamethasone treatment | [1043] |
| | Diffuse large B-cell lymphoma | Expression and cell-surface localization of galectin-3, and interaction of cell-surface galectin-3 with CD45 to regulate CD45 phosphatase activity, is a novel mechanism of apoptosis resistance in DLBCL | Removal of cell-surface galectin-3 from CD45 with the polyvalent glycan inhibitor GCS-100 rendered DLBCL cells susceptible to chemotherapeutic agents | [1044] |
| Galectin-9 | Multiple myeloma | Galectin-9 has an antiproliferative effect on MM cell lines and patient-derived myeloma cells by inhibiting the JNK and p38 MAPK signaling pathways | Galectin-9 can be used as a new therapeutic option to treat MM | [1045] |
| | Acute myeloid leukemia | Galectin-9 impairs the anti-cancer activity of cytotoxic lymphoid cells including NK cells leading to immune evasion | The Tim-3-galectin-9 secretory pathway presents sTim-3 and galectin-9 as biomarkers for AML diagnostics and potential targets for AML immunotherapy | [1046] |

**Note:** MM, Multiple myeloma; CLL, Chronic lymphocytic leukemia; R/R HL, relapsed/refractory Hodgkin lymphoma; KMT2A, Histone-lysine N-methyltransferase 2A; KMT2A-rearranged, KMT2A-R; BM, bone marrow; B-ALL, B-cell precursor acute lymphoblastic leukemia; L-CTCL, Leukemic cutaneous T-cell lymphoma; Th1, type 1 T helper T cells; Th2, type 2 helper T cells; MSCs, mesenchymal stromal cells; TME, tumor microenvironment; AML, Acute myeloid leukemia; GCS-100, a modified pectin inhibitor of galectin-3; ABT-199, a BH3 mimetic; Ara-C, cytosine arabinoside; BH3, Bcl-2 homology 3; *FLT3*-ITD, FMS-like tyrosine kinase-3 internal tandem duplication; HMCLs, inter-human myeloma cell line; BMSCs, bone marrow stromal cells; VEGFA, vascular endothelial growth factor A; DLBCL, Diffuse large B cell lymphoma; JNK, Jun N-terminal kinase (also known as stress-activated protein kinase, SAPK) is one of the 3 major members of the mitogen-activated protein kinase (MAPK) superfamily; the others are extracellular signal-regulated kinase (ERK) and the p38 MAP kinase; TIM-3, T cell immunoglobulin and mucin-domain containing-3; NK cells, natural killer cells.

Noteworthily, galectin-1, -2 and -3 have important roles in the regulation of the adaptive immune response [1047]; particularly in T-cell activation and B-cell differentiation [1048]. Galectin-1 and -3 are expressed by most cell types in nearly every tissue [1049,1050], whereas galectin-9 is mainly expressed by gastrointestinal epithelial cells, the thymus and endothelial cells [1051,1052,1053]. These galectins are strongly implicated in cancer progression and immune escape; the latter is mediated by regulating T-cell activation and T-cell exhaustion [1054]. Indeed, galectin-1, -3, and -9 can all regulate T-cell death. Galectin-1 regulates T- cell death only *via* the extracellular route. By contrast, galectin-3 regulates cell death, both intra- and extracellularly. In this context, galectin-3 is the only family member with both pro- and anti-apoptotic activity: extracellular galectin-3 directly induces death of human thymocytes and T-cells, while intracellular galectin-3 blocks T-cell death (i.e., anti-apoptotic) [1055]. Mechanistically, the human TCRα/β-CD3 complex has 12 N-glycan sites [1056]. *N*-glycans on TCR binds both galectin-1 and galectin-3 [1057]. The galectin-glycoprotein lattice trengthened by GnT-5/*MGAT5*-modified glycan negatively regulates T-cell activation thresholds by inhibiting ligand-dependent TCR clustering at the immune synapse (T-cell activation requires clustering of a threshold number of TCRs at the site of antigen presentation). Consequently, a deficiency in GnT-5/*MGAT5*, the enzyme crucial in the N-glycosylation pathway, lowers the T-cell activation threshold by enhancing TCR clustering [1058]. On the other hand, galectin-9 induces T-cell death by mechanisms distinct from galectin-1 or -3 [1059,1060]. Furthermore, galectins were found to augment T-cell exhaustion induced by T-cell exhaustion markers/immune checkpoint receptors [1061]. For example, the engagement of galectin-3 and PD-1 leads to tumor-induced immune suppression, and both PD-L1 and galectin-3 have been implicated in M2-macrophage polarization and reduced $CD8^+$ T-cell recruitment to the tumor site [1062]. Galectin-9 also interacts with PD-1 which attenuates galectin-9/TIM-3-induced T-cell apoptosis. This dual effect establishes galectin-9 as an important regulator of tumor immune response that can be targeted for cancer immunotherapy [1063]. In addition, some exhaustion markers are known ligands for galectins. Galectin-3 modulates the threshold of T-cell activation through binding to CTLA-4 and LAG-3/CD223 (lymphocyte activation gene 3) [1064,1065]. Noteworthily, LAG-3 is essential for galectin-3-mediated suppression of $CD8^+$ T cell-secreted interferon gamma (IFNγ) *in vitro* (the capability of galectin-3 to bind activated antigen-committed $CD8^+$ T-cells in the TME is only possible through galectin-3 binding to LAG-3 [1066,1067,1068]. Moreover, it is recognized that that galectin-9 is a ligand for TIM-3/CD366 (T-cell immunoglobulin and mucin-domain containing-3) [1069]; the latter plays a functional role in establishing T-cell exhaustion and is highly implicated in the regulation of anti-tumor immunity [1070]. Hence, galectin-9 –TIM-3 interaction is being developed as a new target for checkpoint blockade in cancer immunotherapy [1071]. To sum up, galectins have emerged as regulatory glyco-checkpoints that control anti-tumor immunity by inducing T-cell exhaustion [1072,1073]. That said, the immunomodulatory role of these galectins has drawn attention to the possibility of targeting them and/or their ligands to overcome the mechanisms of tumor immune escape [1074,1075]. Within this context, literature indicated that galectin inhibition induces effective anti-tumor effects, especially when combined with other strategies (e.g., irradiation, anti-angiogenic, chemotherapies, etc.). In addition, galectin inhibition alone or in combination with ICB is an attractive therapeutic strategy to reverse the immune escape mechanisms induced by T-cell inhibition [1076,1077,1078]. One of the first attempts to use galectin inhibitors in cancer consisted of administering a β-D-lactosyl-steroid with antimigratory activity (i.e., with antimetastatic and/or anti-invasive effects). This treatment significantly increased the survival of mice grafted with lymphoma and glioblastoma cells [1079,1080]. β-D-lactosyl-steroid belongs to a class of molecules capable of binding to the CRD and thus preventing further ligand binding. Galectin inhibitors based on these competitive interactions include thiodigalactose (TDG) which underwent chemical modifications improve its inhibitory properties. The most advanced TDG in clinical studies is TD139 (also called GB0139, developed by Galecto Biotech) which was initially evaluated in pre-clinical models of lung fibrosis [1081,1082]. TD139 recognizes galectin-3 CDR with high affinity (Kd 68 nM) but its absolute selectivity for galectin-3 is relative since it also binds to galectin-1 CDR (Kd 220 nM) and other galectins with lower affinities [1083]. Zetterberg et al., discovered a new class of 1,3-substituted α-d-monogalactopyranosides with surprisingly high affinity for galectin-3 [1084]. In this series, GB1107 and GB1211 (shares a chemical template with GB1107) have good affinity (Kd 37 nM) and bind to the CRD of galectin-3. In contrast to GB0139 has limited oral bioavailability, GB1107 is characterized by good biodisponibility upon oral administration [1085]. Mechanistically, GB1107 promotes tumor M1 macrophage polarization and $CD8^+$ T-cell infiltration. In addition, GB1107 potentiated the effects of a PD-L1 immune checkpoint inhibitor to increase expression of cytotoxic (IFNγ, granzyme B, perforin-1, Fas ligand) and apoptotic (cleaved caspase-3) effector molecules [1086,1087]. Furthermore, the Modified Citrus Pectin (MCP), which is obtained by partial hydrolysis of citrus pectin is one of the most studied galectin inhibitors. In vitro studies demonstrated that MCP binds galectin-3 through galactoside residues [1088,1089]. However, due to the high chemical variability of dietary MCP supplements on the market, more defined MCP variants have been described including: PectaSol-C, GCS-100, GM-CT-01 and GR-MD-02. Noteworthily, GCS-100 is a complex polysaccharide prepared from MCP and has been shown to have great potential to treat MM cells, including those resistant to dexamethasone, melphalan, or doxorubicin by La Jolla Pharmaceuticals. Mechanistically, GCS-100 detaches galectin-3 from $CD4^+$ and $CD8^+$ tumor-infiltrating lymphocytes, boosts cytotoxicity and restores IFNγ secretion [1090]. Interestingly, the biological effects of both MCP and GCS-100 are carbohydrate-dependent. Unfortunately, La Jolla Pharmaceuticals announced that they were discontinuing the development of GCS-100 in 2015 after the FDA required a more complex characterization of the compound to advance into late-stage development (NCT00776802 and NCT00609817). The details of galectin inhibitors are beyond the scope of this article but are reviewed elsewhere [1091].

**Galectin-1**

Human galectin-1 is a 14-kDa protein that contains 135 amino acids and is encoded by the LGALS1 gene [1092. Galectin-1 is a proto-type member of the galectin family with a single CRD that was first discovered in 1975 after isolation from an electric eel, and thus, named “electrolectin” [1093]. Galectin-1 has protumorigenic activity. Given that the immunosuppressive TME is one of the major culprits accounting for the progression of cancer, galectin-1, an immunosuppressive biomarker, has

received a great deal of attention. Mechanistically, cancer cells hijack galectin-1 to evade immune surveillance. That galectin-1 is a critical determinant of T-cell apoptosis has been demonstrated since 1995; and hence, targeting galectin-1 possesses a potent efficacy in immune-associated diseases from experimental data, such as cancer [1094]. In this context, elevations of galectin-1 in the TME were well documented in various malignancies [1095], including lung and pancreatic carcinoma, melanoma, and neuroblastoma [1096,1097,1098]. Three glycoprotein counter-receptors, CD43, CD45, and CD7 are involved in T-cell death induced by galectin-1 [1099,1100,1101,1102]. While the expression of CD7, a small glycoprotein that is exclusively N-glycosylated, on human T-cells is esential for galectin-1- induced T-cell apoptosis [1103], expression of both CD43 [1104] and CD45 [1105] enhances (but is not required for) apoptosis induced by galectin-1. Interestingly, CD45- galectin-1-induced T-cell death is dependent on the relative amount and type of glycans present on these glycoproteins. Mechanistically, core 2 *O*-glycans provide galectin-1-binding moieties to induce the clustering of CD45 and T-cell death [1106,1107]. Furthermore, galectin-1 binding to *N*-glycans in general and to *N*-glycans on CD45 in particular (CD45 bears abundant *N*-glycans) is required for galectin-1 signaling and T-cell death. N-acetyllactosamine (Galβ1–4GlcNAc) that is not capped by α2,6-linked sialic acid (found on branched core 2 *O*-glycans and abundant on N-linked glycans) is the preferred minimal saccharide ligand bound by galectin-1. As this disaccharide is ubiquitously expressed on a variety of cell surface glycoproteins, galectins bind N-acetyllactosamine, with avidity increasing in proportion to the number of N-acetyllactosamine units i.e. GlcNAc branching (galectins do not bind soluble lactosamine disaccharides). This entails that glycans must contain multiple N-acetyllactosamine units in order to bind galectin-1 with high avidity (galectin-1 preferentially binds glycoproteins containing linear Poly-N-acetyllactosamine sequences) [1108,1109,1110,1111,1112]. Furthermore, the regulated expression of glycosyltransferases during development and activation, creating N-acetyllactosamine ligands, may determine T-cell susceptibility to galectin-1-induced cell death [1113]. In this context, the expression of the GCNT1 (which creates a branched structure on *O*-glycans that can be elongated to present multiple lactosamine sequences) is required for galectin-1 mechanism of inducing T-cell death [1114]. Conversely, galectin-1-induced T-cell death is inhibited by the expression of ST6GAL1 that preferentially utilizes *N*-glycans as acceptor substrates [1115,1116] resulting in increased sialylation of *N*-glycans on CD45 (CD45 is an established acceptor substrate for ST6GAL1). Interestingly, sialylation of core 1 *O*-glycans also antagonizes susceptibility to galectin-1-induced cell death [1117]. Noteworthily, core 2 O-glycan expression is only required for galectin-1 T-cell death if the cells express CD45. Mechanistically, core 2 *O*-glycans was essential for the galectin-1-induced reduction in CD45 phosphatase activity that is necessary for galectin-1 T-cell death. However, changes in glycosylation of CD45, rather than the expression level of CD45, may be the primary factor that regulates susceptibility to galectin-1 death during thymocyte development [1118]. On the other hand, CD43, which is heavily O-glycosylated, contributes a significant fraction of galectin-1 binding sites on T-cells, as T-cells lacking CD43 bound approximately 50% less galectin-1 than T-cells expressing CD43. While galectin-1 binds to both *N*-glycans and *O*-glycans on CD45, O-glycosylation is primarily responsible for galectin-1 binding to CD43 (CD43 bears only a single N-glycan). Surprisingly, galectin-1 can bind to core 1 *O*-glycans on CD43 even in the absence of core 2 O-glycan modifications (addition of core 2 *O*-glycans specifically to CD43 is not essential for galectin-1 death) [1119]. Despite that lactosamine is not present in core 1 *O*-glycans and the the affinity of galectin-1 for isolated Galβ1,3GalNAc sequences found in core 1 *O*-glycans was 125-fold lower than for Galβ1,4GlcNAc (lactosamine) sequences [1120], galectin-1 is able to bind the extracellular domain of CD43 decorated with either core 1 *O*-glycans or core 2 *O*-glycans with roughly equivalent affinities leading to activation of apoptotic signaling [1121]. In this case, low affinity/high avidity binding to a highly abundant but less preferred glycan ligand, Galβ1,3GalNAc, is sufficient to induce T-cell death. Although T-cells dying in response to galectin-1 display characteristics common to other death pathways, galectin-1 does not trigger death *via* known T-cell surface apoptotic triggers such as Fas or CD3 [1122,1123]. As a negative regulator of T-cell activation and survival, galectin-1, plays a critical role in promoting escape from T cell-dependent immunity, thus conferring immune privilege to tumor cells that leads to tumor development and progression [1124]. Within this context, tumor-secreted galectin-1 mediates immune evasion by preventing T-cell migration into the tumor. Mechanistically, galectin-1 reprograms the tumor endothelium to upregulate cell-surface PD-L1 and galectin-9 [1125]. Although the immune-inhibitory effects of galectin-1 have been primarily attributed to the modulation of T-cells, galectin-1 aslo induces a TAM-like phenotype with a combination of pro-inflammatory features and upregulation of immunomodulators such as checkpoint protein PD-L1/CD274 and the indoleamine 2,3-dioxygenase-1 (IDO1) [1126]. Intriguingly, galectin-1 may promote survival of hematological malignancies through direct action on tumor cells but also through effects on the TME. High galectin-1 expression was reported in *KMT2A*-R B-ALL and HL [1127,1128]. In B-ALL, galectin-1 is a highly sensitive and specific biomarker of *KMT2A* rearrangement that is likely induced by a *KMT2A*-dependent epigenetic modification [1129]. Recently, Li et al., identified galectin-1 as a striking biomarker of progression to MF and poor survival in multiple patient cohorts. Interestingly, galectin-1 inhibition ameliorated disease features with a similar impact on splenomegaly and myeloproliferation to JAK-inhibition, reducing myeloproliferation and fibrosis *in vitro* and *in vivo*. Likewise, a clear correlation between *LGALS1* expression level and poor survival was found in AML, suggesting a role beyond MPN. Therefore, galectin-1 inhibition is a promising therapeutic strategy in both myeloid malignancies [1130]. Taken together, galectin-1 inhibitors represent an attractive opportunity in order to suppress tumor growth and progression by thwarting tumor-immune escape, attenuating aberrant angiogenesis and circumventing resistance to anti-cancer therapies [1131].

**Galectin-3**

Galectin-3 is a central regulator of cell adhesion and inflammation in cancer. Human galectin-3 is a 35-kDa protein that contains 135 amino acids and is encoded by the LGALS3 gene [1132]. Like galectin-1, the preferential glycan ligand for galectin-3 is Poly-N-acetyllactosamine (poly-LacNAc); but unlike galectin-1, galectin -3-binding ability does not require a terminal β-galactose residue [1133]. An alternative to Poly-LacNAc chains is a chain composed of LacdiNAc glycan units [-3GalNAcβ1-4GlcNAcβ1-]n generated by the action of a β1-4GalNAc-transferase [1134]. LacdiNAc, a recently identified epitope in some O- and N-linked glycoproteins, can act as a selective galectin-3 ligand [1135]. Interestingly, terminal LacdiNAc expression on glycosylated

proteins has been reported to be upregulated in a variety of malignancies, suggesting its potential value as a cancer glycome biomarker [1136]. Again, sialylation is a major regulator of galectin-3–glycan ligand binding (inhibited by the action of ST6GAL1) [1137]. In a similar vein, the expression of sTn on *O*-glycans, a biosynthetic product of ST6GALNAC1, was able to decrease cell surface galectin-3 and galectin-3-binding sites leading to an accumulation of galectin-3 in the intracellular environment, which can account for the chemotherapeutic resistance observed in ST6GALNAC1-overexpressing tumor cells [1138]. Contrarily, galectin-3 still cooperates with sTn antigen to promote tumor metastasis by activating the Akt pathway leading to an increase in the transcription activity of β-catenin and protein synthesis (galectin-3 promote tumor metastasis mostly in an Akt-dependent way) [1139]. Galectin-3 is involved in the regulations of a wide range of cancer cell activities during cancer development, progression and metastasis [1140]. Mechanistically, most of the molecular mechanisms leading to galectin-3 activities emanate from its characteristic oligomerization ability [1141]. Owing to its unique CRD, galectin-3 molecules can oligomerize and form pentamers upon glycan binding to their CRDs [1142]. Galectin-3 oligomerization leads to three cross-linking modes of action including cell-cell adhesion, signal transduction through receptor clustering, and lattice formation [1143,1144]. Moreover, the oligomerization capacity of galectin-3 has been shown to be important for its function in endocytosis [1145]. Mechanistically, galectin-3 oligomerizes upon recognizing beta1,6-branched *N*-glycans on proteins (including integrin, N-cadherin, lysosomal associated membrane proteins, L1, Mac-2 binding protein, CD166, melanotransferrin). Oligomerized galectin-3 acquires the capacity to bind to plasma membrane GSLs that drive GSL-dependent narrow membrane bending and the biogenesis of tubular endocytic pits from which clathrin-independent endocytic carriers (CLICs) are formed (similar to the GSL-binding subunits of bacterial Shiga and cholera toxins and the VP1 protein of simian virus 40) [1146,1147,1148]. Remarkably, the complexity of the lattice that galectin-3 form with glycoproteins and glycolipids depends on GnT-5/*MGAT5*-mediated modifications [1149]. Intriguingly, galectin-3-dependent lattice formation induces persistence of a given receptor on the cell surface. The so called "receptor retention" tunes the function of different receptors, such as the EGFR, platelet-derived growth factor receptor (PDGFR), FGFR, VEGFR, and TGFBR [1150].

**Galectin-3 role in immunosuppressive TME**

Although both galectin-1 and galectin-3 can bind to T-cells and trigger T-cell death [1151,1152], these galectins induce two separate death pathways with distinct mechanisms. Notably, galectin-3 binds to a complement of T-cell surface glycoprotein receptors that differ from those recognized by galectin-1. CD45 and CD71, but not CD29 and CD43, contribute to galectin-3-induced T-cell death. Although CD45 is not required but regulates susceptibility to galectin-1, CD45 is required for galectin-3 cell death. By contrast, CD7 is not required for death triggered by galectin-3 [1153]. Unlike galectin-1 binding that result in clustering of CD45 during galectin-1-induced T-cell death [1154], galectin-3 induces clustering of CD71, but not CD45, on the T-cell surface. Instead, galectin-3 binding creates small patches of CD45 around the cell surface. In addition, galectin-3 has been proposed to separate CD45 and TCR into discrete domains on the T-cell surface during T-cell activation [1155].

Similar to galectin-1, specific glycosylation of CD45 is important for regulation of galectin-3 -mediated signaling. GCNT1 (C2GnT1) regulates galectin-3 binding to a subset of highly glycosylated CD45 glycoforms. In addition, galectin-3 has high affinity for β-1,6-N-acetylglucosamine branched glycans (complex *N*-glycans) formed by GnT-5/*MGAT5* modification [1156]. Increased branching of *N*-glycans can directly inhibit T-cell activation by GnT-5/*MGAT5*-dependent galectin-3 interaction [1157]. Mechanistically, β1,6GlcNAc-branched *N*-glycans attached to the TCR enhance binding to galectin-3, an interaction that limit TCR clustering at sites of immune synapse by restricting lateral TCR movement within the plane of the membrane, thus increasing agonist thresholds for TCR signaling (i.e., reducing TCR signaling) [1158,1159,1160], and vice versa; β1,6GlcNAc-branching deficiency in naive T-cells reduces activation thresholds by weakening the galectin lattice, enhancing TCR clustering, and signaling at the immune synapse [1161].

Furthermore, galectin-3 inhibits TCR-mediated activation of $CD4^+$ T-cells, by affecting the early events in signal transduction and potentiating down-regulation of TCR in cells activated by engagement of the receptor leading to lower levels of cytokine production [1162]. As a result, galectin-3 binding to the TCR in the immunological synapse is an important immunosuppressive mechanism in the TME, which highlights the potential use of galectin-3 as a therapeutic target capable of modulating anti-tumor immunity [1163]. Within this context, the galectin-3 ligand LAG-3 expression in the TME correlates with poor prognosis in MM and several hematologic malignancies [1164,1165]. Mechanistically, galectin-3 negatively regulates T-cell function and proliferation through interaction with LAG-3, especially on $CD8^+$ CTL, possibly by reducing the affinity of the T-cell receptor and its internalization. A phase I/IIa trial aiming at evaluating the safety and efficacy of LAG-3 blockade with Relatlimab, BMS-986016 (the first developed anti-LAG-3 mAb) with or without Nivolumab (PD-1 inhibitor) in the setting of refractory or recurrent B-cell malignancies including NHL, CLL, HL and MM has already been completed (NCT02061761). Another phase I/II randomized trial (NCT04150965) designed to evaluate anti-LAG-3 and anti-TIGIT (T-cell immunoreceptor with Ig and ITIM domains), in order to understand their immunologic effects and safety both as single agents and in combination with pomalidomide and dexamethasone, in patients with R/R MM is currently underway.

Strikingly, CD45 is the major receptor tyrosine phosphatase in B-cells. Not surprisingly, the BCR interacts with CD45 through galectin bridging between the BCR and CD45. Interestingly, CD45 regulates BCR and TCR activation in different ways: the higher level of CD45 favorably affects BCR signaling, unlike for TCR. Notably, the importance of CD45 synthesis by tumor cells in predicting the clinical outcome of patients with CLL, ALL, MM, and DLBCL has already been stated [1166]. In this vein, as galectin-3/CD45 interaction modulates apoptosis resistance in DLBCL, removal of cell-surface galectin-3 from CD45 with GCS-100 rendered DLBCL cells susceptible to chemotherapeutic agents [1167].

**Galectin-3 role in metastasis**

Circulating levels of galectin-3 are significantly higher in cancer patients, especially those with metastasis [1168]. Metastasis (the development of secondary tumors in a part of the body that is far from the original primary cancer) constitutes the primary cause of death for >90% of patients with cancer [1169,1170,1171]. Despite that metastasis is usually linked to epithelial cancers (known as

carcinomas), all cancers (including hematologic malignancies) have the capacity to metastasize [1172]. Numerous studies have indicated that galectin-3 is involved in multiple stages of cancer progression and metastasis and may render anticancer activities in several ways [1173,1174]:

1. The intracellular galectin-3 is anti-apoptotic (providing survival advantage to cancer cells).

2. Galectin-3 promotes tumor neoangiogenesis.

3. The extracellular galectin-3 is involved in homotypic aggregation.

4. Tumor–endothelial cell interactions required for metastasis are mediated by endothelium-associated galectin-3 and cancer cell-associated TF antigen.

5. Tumor cell secreted galectin-3 induces apoptosis of cancer-infiltrating T-cells to promote immune escape and tumor progression.

**The metastatic cascade**

The metastatic cascade can be broadly separated into three main processes: invasion, intravasation and extravasation. The metastatic cascade is dependent on the loss of adhesion between cells, which initiates the process of invasion, the first step of metastasis. Mechanistically, the loss of cell-cell adhesion capacity allows malignant tumor cells to dissociate from the primary tumor mass and changes in cell-matrix interaction enable the cells to invade the surrounding stroma [1175]. The blood vessel within the tumor's vicinity can then provide a route for the detached cells to enter the circulatory system and metastasize to distant sites; the process of intravasation [1176,1177]. Extravasation constitutes a multistep phenomenon that can be divided into different phases. The extravasation process is initialized by rolling, relatively low-affinity binding, of leukocytes mediated by the selectin family of adhesion molecules. Interestingly, tumor cells exploit these mechanisms used by leukocytes to roll, arrest and adhere to the vascular endothelium [1178,1179]. In this vein, compelling evidence indicates that selectins regulate adhesion of circulating cancer cells to the walls of blood vessels. In particular, the presence of E-selectin ligands on cancer cells correlates with enhanced adhesion to the activated endothelium [1180,1181,1182,1183]. Moreover, during selectin-mediated rolling, integrins are activated, and then bind to their endothelial ligands to mediate a tight adhesion (or arrest) of the leukocytes. Noteworthily, integrins ar a family of heterodimeric membrane glycoproteins composed of noncovalently associated α and β subunits that mediate cell-matrix and cell-cell interactions [1184,1185]. After adhesion, N-cadherin (also known as CDH2) mediate the final steps of extravasation (transmigrate tumor cells through the vascular endothelium by a procedure named diapedesis) [1186]. Intriguingly, tumor cells imitate leukocyte mechanisms for extravasation [1187]. However, the adhesion molecules and ligands involved in tumor cell extravasation are somehow different from leukocytes suggesting additionally or alternatively non-leukocyte-like mechanisms [1188]. For instance, tumor cells do not express selectins, but their respective ligands. Moreover, being the main adhesion molecules of leukocytes, the expression of several integrins, especially of the β2 subgroup, is restricted to leukocytes. In contrast to integrins, galectins are a group of adhesion receptors that leukocytes share with tumor cells. In this vein, overwhelming evidence shows that galectins are involved in extravasation [1189]. In this vein, galectin-3 expression in cancer cells was associated with a metastatic phenotype in several experimental systems [1190]. As the main link between a cell and the ECM, integrins have an essential role in the invasion process, mainly through their interactions with various ECM molecules such as collagens, laminins, fibronectin and tenascin [1191]. Mechanistically, integrin-mediated adhesion of fibronectin triggers a negative feedback signal that blocks the formation of E-cadherin mediated cell-to-cell adhesion [1192]. Dissolving E-cadherin-dependent junctions by integrin-mediated adhesion lead to separation of unparted cancer cells or groups of cancer cells from adjacent normal cells and the basement membrane below which drives the transition from carcinoma in situ to invasive cancer [1193]. In addition, the interaction between integrins and ECM enhances cell adhesion and activates cancer cell pro-survival and anti-apoptotic programs, resulting in the development of drug resistance [1194]. In a similar vein, integrin-dependent adhesion mediates leukemia cell interactions with their microenvironment. Strikingly, integrin-mediated drug resistance has been reported in T-ALL, CLL and AML [1195]. In AML, the integrin-binding glycoprotein CD98 plays a central role in chemoresistance by driving engagement of leukemia cells with their microenvironment and maintaining LSCs. Not surprisingly, Bajaj et al., suggested that CD98 inhibition should be considered for targeting both adult and pediatric leukemia [1196]. Noteworthily, glycosylation affects the functions of integrins [1197,1198,1199]. To explain further, integrins exist in a continuum of conformations between bent-closed non-ligand-bound (also termed inactive) and extended-open ligand-bound (also termed active) states [1200]. N-glycosylation positions were suggested to affect the equilibrium between these two conformers [1201]. Interestingly, galectin-3 oligomers clamp the bent-closed state to prime it for endocytic uptake, retrograde trafficking to the Golgi apparatus, and subsequent polarized secretion to the leading edge of migrating cells to enter a new functional cycle [1202]. This cycle is important for integrin-mediated functions, including cell adhesion and persistent cell migration [1203].

**The role of galectin-3 in modulating integrins/ECM glycoproteins**

GnT-5/*MGAT5* modification of *N*-glycans on integrins and other adhesion receptors influence membrane remodeling and ECM assembly [1204,1205,1206,1207,1208,1209]. It was shown that the α6β4-integrin (β4-integrin), a receptor for laminin-332 and an essential component of the hemidesmosome (an anchoring structure in the basal membrane of stratified epithelial cells), is a major carrier of *N*-glycans and is associated with poor prognosis, tumorigenesis, and metastasis. Binding of galectin-3 to β4-integrin *via* β1,6GlcNAc-branched *N*-glycans promoted β4-integrin–mediated cell motility and invasion [1210]. Moreover, overexpression of *MGAT5* leads to a substantial increase in cell migration mediated by α3β1 integrin on the laminin 5 substrate [1211]. In addition, galectin-3 interactions with GnT-5/*MGAT5*-modified *N*-glycans at the cell surface of mammary carcinoma cells stimulate α5β1-integrin activation, enhancing fibronectin fibrillogenesis and fibronectin-dependent tumor cell spreading, and motility (1212). Galectin-3 was also shown to interact directly with ECM glycoproteins such as fibronectin, collagen IV, elastin, laminin, and hensin [1213]. Intriguingly, the integrin-binding glycoprotein CD98 is a galectin-3 ligand implicated in integrin-mediated adhesion of human cancer cell lines [1214]. Furthermore, galectin-3 binding to N-cadherin contributes to destabilization of cell–cell junctions by enhancing turnover of N-cadherin and other glycoconjugates, which might favor cell migration process

[1215]. It is worth noting that the upregulation of N-cadherin (mainly exists in nerve tissue, muscle and fibroblasts) followed by the downregulation of E-cadherin (mainly exists in epithelial tissue) is the hallmark of EMT [1216]. This "cadherin switch" increases the ability of tumor cells to invade and metastasize to distant sites, which predicts poor prognosis. Therefore, EMT is considered a process in which tumor cells transform from a nonmotile epithelial phenotype to a migratory mesenchymal phenotype [1217].

**The TF-MUC1-galectin-3 axis role in metastasis**

Increased expression of the TF antigen has a big impact on promoting cancer progression and metastasis. To reiterate, the TF antigen, present in the core I structure of MUC1, is generally masked by sialic acid in normal cells but is exposed or nonsialylated in malignant and premalignant epithelia [1218,1219]. Interestingly, a striking difference was observed between interactions of galectin-1 and -3 toward the TF disaccharide (Galβ1, 3GalNAc) found in *O*-glycans [1220,1221]. Galectin-3 was found to interact with TF antigen with 100-fold higher affinity compared to galectin-1 [1222]. Not surprisingly, substantial evidence indicated that the cancer-associated TF antigen promote metastasis through binding to galectin-3 [1223]. Following the escape from primary tumor and intravasation, the first task that blood-borne neoplastic cells encounter is to survive the cell-detachment-induced apoptosis or anoikis (a type of programmed cell death that results from the loss of anchorage and detachment from ECM, which disrupts integrin ligation) and a journey through the circulation. Intriguingly, galectin-3 has been shown to overcome anoikis - a barrier to tumor metastasis- through the galectin-3-MUC1 interaction. Mechanistically, the interaction between galectin-3 and MUC1 (a natural ligand of galectin-3 that is overexpressed in cancer), *via* binding of galectin-3 to the oncofetal TF antigen on MUC1 [1224], which breaks the "protective shield" of the cell-surface MUC1 by causing MUC1 polarization, leading to exposure of smaller cell-surface adhesion molecules/ligands including CD44 [1225] and E-selectin ligands (MUC1 carry sLeA and sLeX epitopes that act as ligands for selectins) [1226]. This leads to increased cancer cell homotypic aggregation [1227] and cancer cell heterotypic cell adhesion to vascular endothelium [1228], two important steps in metastasis. Therefore, inhibition of MUC1/TF antigen-galectin-3 interactions may be a potential strategy to reduce tumor progression and metastasis. Like epithelial tumors, cancer specific MUC1 glycoforms are over-expressed on MM cells [1229]. Consequently, the TF-MUC1-galectin-3 axis (Figure-3) constitutes a novel therapeutic target in MM. Moreover, MUC1 cell surface polarization increases MUC1–EGFR association leading to increased and prolonged EGFR activation and signaling. These mechanisms might contribute to EGFR-associated tumorigenesis and cancer progression and could also influence the effectiveness of blocking the action of EGFR in patients undergoing cancer therapy [1230]. In this context, galectin-3 lattice itself was found to reduce EGFR lateral mobility and internalization, and to increase EGFR signaling [1231]. Additionally, MUC1 stimulates tumor cell release from initial tumor sites that promote metastasis [1232,1233,1234]. Furthermore, galectin-3 protects cancer cells from various forms of apoptosis *via* mainly suppressing mitochondrial apoptosis pathways [1235,1236,1237]. In adition to galectin-3-MUC1 interaction, galectin-3 protects cancer cells from anoikis by regulating their transition through the cell cycle i.e. by inducing a cell cycle arrest at an anoikis-insensitive point (late G1 phase) [1238]. Moreover, galectin-3 anti-apoptotic effect modulates cancer cell sensitivity to various chemotherapeutic agents, many of which are used in hematologic malignancies such as etoposide [1239, doxorubicin [1240] dexamethasone, and bortezomib [1241]. In addition to its anti-apoptotic functions, galectin-3 also has pro-apoptotic roles [1242]. Elevated galectin-3 levels have been shown to be prognostic for poor survival in many cancers including leukemia, lymphomas, breast cancer, and thyroid cancer. On the other hand, decreased levels of galectin-3 appear to be detrimental to patients with CLL or prostate cancer [1243,1244,1245,1246]. A possible explanation for this variance is that the localization of galectin-3 is essential to its function. In fact, the function of galectin-3 will vary depending on whether it is in the nucleus, cytoplasm, or secreted into the extracellular spaces or in the circulation [1247]. It has been demonstrated that galectin-3 is predominantly located in the cytoplasm; and in contrast to nuclear galectin-3, cytoplasmic galectin-3 is usually associated with an aggressive phenotype in cancer cells [1248].

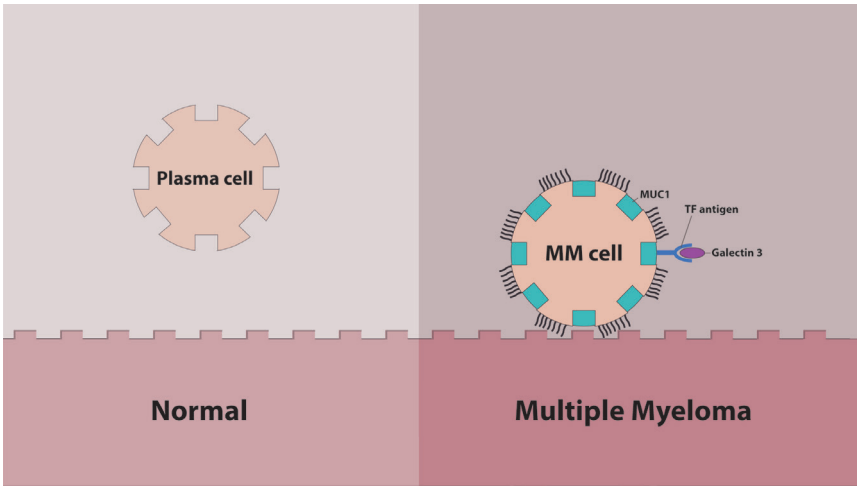


**Figure 3:** The TF-MUC1-galectin-3 axis in multiple myeloma.
The increased expression of the galectin-3-ligand TF antigen by cancer-associated MUC1, and the increased concentration of circulating galectin-3, all of which are common features in multiple myeloma (MM), promotes metastasis by induction of MUC1 polarization, exposing smaller adhesion molecules on the cell surface, including CD44, and E-selectin ligands, which increases tumor cell aggregation and favors the formation of tumor micro-emboli, preventing anoikis initiation and enhancing circulating tumor cell survival.

**Galectin-9**

Human galectin-9 is a 36-kDa protein that contains 135 amino acids and is encoded by the LGALS9 gene [1249]. Galectin-9 was identified from murine embryonic kidney and human Hodgkin's lymphoma tissues in 1997 [1250,1251]. Galectin-9 typically binds internal LacNAc units, with a preference for linear poly-LacNAc glycans [1252]. Strikingly, Gcnt2, which catalyzes I-branch (blood group I antigen) formation on glycan ligands of galectin-9 (poly-LacNAcs) attenuates galectin-9 binding [1253]. Galectin-9 can form multivalent lattices due to the different oligosaccharide-binding affinities of its two CRDs [1254]. Interestingly, its long peptide linker allows the CRDs to have rotational freedom, enhancing multimerization and lattice formation [1255]. Galectin-9 has attracted much attention because of its multiple biological functions and strong immunomodulatory effects in tumor metastasis [1256]. Not surprisingly, galectin-9 has emerged as a biomarker and therapeutic target in cancer [1257,1258]. Intriguingly, galectin-9 has conflicting roles in cancer biology, the so-called double-edged sword role [1259]. For instance, the expression of galectin-9 has been linked to tumor cell adhesion and metastasis which correlated with unfavorable prognosis in several cancers such as brain tumor [1260], pancreatic cancer [1261,1262], and AML [1263]. Recently, Hung et al., demonstrated the potential efficacy of human galectin-9 neutralizing mAbs in protecting T-cells from galectin-9-induced cell death and promoting the killing of cancer cells by T-cell *in vitro* which provide a rationale for targeting galectin-9 in cancer immunotherapy [1264]. On the other hand, galectin-9 can induce apoptosis and inhibit tumor growth of HCC [1265]. Hence, galectin-9 was proposed as a new prognostic factor with antimetastatic potential in patients with HCC [1266]. In addition, galectin-9 has also been reported to suppress tumor cell migration and metastasis in another study using highly metastatic melanoma and colon cancer cells [1267]. Overall, the loss of galectin-9 expression in many solid cancers is closely associated with metastatic progression, and treatment with recombinant galectin-9 prevents metastatic spread in various preclinical cancer models [1268]. In contrast to galectin-1 and -3, galectin-9 does not bind to glycans on CD43 or CD45 on T-cells [1269]. Surprisingly, however, galectin-9 is much more potent than galectin-1 in inducing T-cell death. It is worth mentioning that TIM-3 and CD44 have been identified as glycoprotein receptors for galectin-9 [1270]. Since CD44 is the galectin-9 receptor on neutrophils, galectin-9 was identified as a soluble mediator of neutrophil activation with pro-adhesive effects observed in cancer as well as autoimmune/inflammatory diseases [1271]. Whereas CD44 is also not required for T-cell susceptibility to galectin-9, TIM-3, expressed on T helper 1 (Th1) CD4 T-cells, was identified as an essential receptor for galectin-9-induced death of Th1 cells *in vitro* and *in vivo* [1272]. In this context, galectin-9/TIM-3 interaction is considered a major immune checkpoint pathway that can be exploited for targeting in immunotherapies [1273]. In this vein, TIM-3 and its ligand galectin-9, constitute an autocrine loop which drives the self-renewal of AML stem cells by activating the NF-κB and β-catenin pathways [1274]. Besides, human AML cells possess a secretory pathway through which TIM-3 participates in galectin-9 secretion and is also released in a free soluble form [1275]. While AML patients have a higher expression of TIM-3 on their T-cells, TIM-3 is used as an important surface marker for exhausted and dysfunctional T-cells associated with disease progression [1276,1277]. Galectin-9 also impairs NK cell cytotoxicity through association with TIM-3 in AML [1278,1279]. To sum up, the galectin-9–TIM-3 pathway help AML cells escape host immune attack by impairing the immunological activities of cytotoxic T-cells as well as NK cells [1280,1281,1282,1283]. In a similar vein, Choukrani et al., showed that recombinant galectin-9 treatment induced caspase-independent cell death in Ara-C-sensitive as well as Ara-C-resistant from both AML cell lines and primary patient-derived AML cells, including $CD34^+$ AML stem cells; however treatement excluded the healthy cord blood-derived $CD34^+$ stem cells. Intriguingly, galectin-9 was shown to potentiate the cytotoxic effect of Azacytidine in patients who are not eligible for intensive Ara-C treatment [1284]. Recently, recombinant galectin-9 has shown promising therapeutic activity in preclinical models of various hematological malignancies, including ATLL [1285], T-cell leukemia (1286), MM [1287], CML [1288], as well as Burkitt and Hodgkin lymphoma cells [1289]. In MM, galectin-9 also showed significant therapeutic activity toward primary patient-derived myeloma cells, even in tumors resistant to conventional therapeutics [1290]. Intriguingly, treatment with recombinant galectin-9 reduced the severity of GvHD in both T-cell-deplete and T-cell-replete transplanted mice [1291]. Strikingly, the main mechanism of galectin-9-mediated immunoregulation involves the galectin-9-TIM-3 axis in T-cells. However, Myeloid-Derived Suppressor Cell (MDSC) accumulation in transgenic mice with persistently high galectin-9 expression was observed in a model of lung inflammation, indicating that a potential immunosuppressive mechanism distinct from the galectin-9-TIM-3 axis might exist [1292]. Noteworthily, TIM-3, by itself, is a bona fide target for the treatment of myeloid malignancies. Targeting TIM-3 -metaphorically- kills two birds with one stone by balancing the immune system and eliminating LSCs (the principal cause of patient relapse) in AML [1293]. MBG453, or Sabatolimab™, is an anti-TIM-3 mAb that interferes with the galectin-9-TIM-3 interaction and has been demonstrated to elicit immune-boosting, anti-leukemic activity [1294]. Clinical trials are currently underway to evaluate the safety and efficacy of MBG453 combination therapy in patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS) or AML and who are not fit for intensive chemotherapy [1295]. As TIM-3 is not expressed on normal hematopoietic stem cells [1296], targeting TIM-3 with sabatolimab holds promise as a therapeutic strategy for patients with AML [1297,1298].

**I-type lectins (Siglecs)**

Siglecs are I-type lectins highly expressed on innate and adaptive immune cells including human macrophages, T-cells, B-cells, DCs, and NK cells. The Siglecs family include the conserved Siglecs (Siglec-1, Siglec-2, Siglec-4, and Siglec-15) and the rapidly evolving CD33rSiglecs, including Siglec-3 (CD33), Siglec-5, Siglec-6, Siglec-7, Siglec-8, Siglec-9, Siglec-10, Siglec-11, Siglec-14, and Siglec-16. Ligands for Siglec receptors (Sialoglycans) are broadly expressed in a variety of human tumors and in a diversity of common cancer cell lines [1299]. Most of human Siglec receptors are inhibitory in nature (excluding Siglec-11, Siglec-14, Siglec-15, Siglec-1 and Siglec-4). Inhibitory Siglecs contain ITIM and ITIM-like motifs within its intracellular domain (the cytoplasmic tail). Upon binding to complementary sialoglycans in their local milieu, engagement results in down-regulation of the immune responses, particularly innate immune responses to cancer cells, that ultimately lead to cancer progression. Mechanistically, sialoglycan-Siglec interactions have been demonstrated to contribute to an immunosuppressive TME

through the induction of a pro-tumorigenic phenotype in TAMs, inhibition of NK cell and neutrophil activation, reduced DC maturation and antigen presentation and damped T-cell responses. Strikingly, inhibitory Siglecs can thereby inhibit immune cell activation similar to PD-1 after engagement by PD-L1 [1300]. Therefore, the sialoglycan–Siglec axis is considered a novel glyco-immune checkpoint in cancer [1301,1302]. In particular, the CD33-related Siglec-7 and Siglec-9 on NK cells are of particular interest in the context of tumor immunotherapy owing to their critical roles in tumor cell immunoevasion. Analogous to classical checkpoint receptor PD-1 , Siglec-7 binds the mucin CD43 on leukemia cell surfaces and delivers an immune inhibitory signal, similar to galectins -1 and -3 [1303]. It is widely known that NK cells - a class of innate lymphoid cells - are the primary defenders against cancer precursors. Mechanistically, NK cells play a crucial role in early recognition and elimination of transformed cells that lose MHC-I expression ("missing-self recognition") or express danger ligands ("induced-self recognition") through the production of pro-inflammatory cytokines, such as IFNγ and tumor necrosis factor (TNF), and by their specialized cytolytic functions [1304,1305]. NK cells-just like $CD8^+$ T-cells-are key players in all three phases of cancer immunoediting [1306]. Recent evidence suggests that cancer-associated sialoglycans expressed by several human cancers inhibit anti-tumor immune activation by engaging Siglec-7 and Siglec-9 on NK cells [1307,1308]. Mechanistically, NK cell-mediated killing of tumor cells can be blocked in a dose-dependent manner by the interactions between tumor sialoglycans and Siglec-7 and Siglec-9 on human NK cells. Moreover, the expression of Siglec-7 and Siglec-9, on TAMs enhances cancer progression by driving macrophage polarization toward the tumor-promoting M2 phenotype [1309,1310,1311,1312,1313]. Itziar Ibarlucea-Benitez et al., showed that Siglec-7/9 blockade can significantly reduce tumor burden *in vivo* by prevention of macrophage polarization into TAM phenotype and thus reprogramming of the immune-suppressive TME [1314]. Ligands for inhibitory Siglec-7/-9 on NK cells are increased in melanoma, HCC, pancreatic cancer, colon adenocarcinoma, cervical cancer, breast cancer, NSCLC, head and neck cancer as well as hematological malignancies [1315]. There is compelling experimental and clinical evidence for the hypersialylation, often attributed to sialyltransferase upregulation leading to enhanced expression of sialoglycans in tumors, to correlate with poor prognosis and reduced survival owing to increased metastatic potential. In addition, hypersialylation plays a cytoprotective role and contributes to chemotherapy and radiotherapy resistance in several cancers. Intriguingly, the available evidence implicates hypersialylation in cellular trafficking, drug resistance and resistance to immune therapies, through modulation of the TME, in MM. In addition to the many reported sialyltransferases highly expressed in MM, O'Dwyer et al., also observed elevated levels of expression of ST3GAL4 that were associated with inferior PFS and OS in MM cells [1316]. In this vein, a landmark paper by Daly et al., provided evidence that the Siglec/Siglec ligand axis is hijacked by MM cells [1317]. Strikingly, it was shown for the first time that hypersialylation is implicated in facilitating evasion of NK cell-mediated immunosurveillance in MM through interactions of Siglec-7 with sialylated PSGL-1 (also called SELPLG), being the predominant Siglec-7 ligand on MM cells. Converesly, by using both a sialidase and sialyltransferase inhibitor, desialylation strongly enhanced NK cell–mediated cytotoxicity against MM cells. Interestingly, desialylation can uncover CD38 expression, a well-validated target in MM, and maximize NK cell-mediated ADCC in the presence of daratumumab (an anti-CD38 moAb) as well as disrupt the inhibitory Siglec-7-Siglec-7L (PSGL-1) axis, enhancing clearance of MM cells by NK cells. As PSGL-1 is highly expressed in MM biopsies as well as on MM cell lines where it regulates the homing and adhesion of MM cells to the microenvironment [1318,1319], PSGL-1 should be envisaged as a potential therapeutic target for cancer immunotherapy for MM. In addition, the glycoprotein CD43 also acts as a ligand for Siglec-7 in MM as well as leukemia (e.g., CML [1320] and lymphoma cell lines and blocking its interaction with Siglec-7 sensitizes malignant cells to immune cell lysis [1321]. It is important to note that the glycan epitope (glycotope) recognized by Siglec-7 is the disialyl core 1 O-glycan tetrasaccharide (disialyl-T) expressed predominately on CD43, CD45, and PSGL-1 counter receptors. In this context, CD43 protein is a primary determinant of Siglec-7 ligand expression on cancer cell lines. Although CD43 is expressed in all types of immune cells (except for resting B-cells), Siglec-7 binds selectively to $CD43_{disialyl\text{-}T}$ but not to other CD43 glycoforms expressed in the immune system [1322]. Therefore, targeting Siglec-7-PSGL-1 and CD43-Siglec-7 checkpoints may be potential targets for cancer therapy. Apart from Siglec-7 ligands (CD43 and PSGL-1), overexpression of the mucin genes *MUC1* and *MUC21* conferred resistance to NK cells in MM lines. In contrast, the glycosylation regulator signal peptide peptidase-like 3 (*SPPL3*) deletion facilitates NK cell evasion. *SPPL3* encodes an intramembrane protease that cleaves transmembrane glycosyltransferases such as GnT-5/*MGAT5* (that catalyze the formation of highly branched *N*-glycans and LacNAc extensions that prevent NK-mediated killing) in the Golgi apparatus [1323]. Recently, Zhuang et al., performed SPPL3 knockout in several patient-derived DLBCL cell lines (RIVA, OCI-LY1, and WSU-FSCCL) and observed a consistent increase in resistance to NK-mediated killing upon SPPL3 deletion in these cell lines. Mechanistically, the SPPL3 knockout resulted in *MGAT5* being retained inside SPPL3-deficient cells leading to an increase of complex *N*-glycans, including higher-mass glycans carrying longer poly-LacNAc extensions, which points to a shared NK evasion mechanism arising from SPPL3 deletion and the modification of cellular glycosylation status in malignant B-cells. Interestingly, they also found that *B3GNT2* deletion reduced LacNAc addition and restored SPPL3-knockout cell sensitivity to NK cells. These shreds of evidence suggest that high N-glycan branching contributes to the resistant phenotype [1324]. In this context, *B3GNT2* encodes the main glycosyltransferase that extends highly branched *N*-glycans by transfer of GlcNAc moiety in a β1,3 linkage with a terminal unsialylated galactose, preferentially on the GnT-5/*MGAT5*-generated β-1,6-linked branch in tri- and tetra-antennary *N*-glycans [1325]. Noteworthily, *B3GNT2* ranks as one of the highly amplified genes in DLBCL patients, suggesting a potential alteration in glycosylation and immune evasion [1326]. Collectively, the glycosylation regulator SPPL3, heavily glycosylated mucins, and the recently identified Siglec-7 ligands CD43 and PSGL-1 provide further evidence that glycosylation plays a crucial role in regulating NK cell-cancer interactions with potential opportunities for therapeutic targeting to enhance NK cell immunotherapy [1327]. Currently, different methods targeting the sialoglycan-Siglec axis have been already successfully tested in early clinical trials, among them antibodies are already in clinical development [1328]. Moreover, among the

15 Siglecs found in mammals, Siglec-2 (CD22) and Sigle-3 (CD33) have been already proven to be potent targets for immunotherapy. Siglec-2 is primarily expressed on the surface of mature B-cells, where it targets the binding of α2,6-linked sialic acid-containing ligands. The presence of ligands on *N*-glycans is responsible for inhibiting galectin-1 binding. This interaction is crucial for the BCR signaling on the cell membrane, followed by binding with antigen [1329]. Not surprisingly, Siglec-2 has emerged as an attractive therapeutic target in B-cell malignancies [1330,1331,1332]. After the initial development in R/R aggressive B-cell NHL, inotuzumab ozogamicin (InO), an ADC consisting of a CD22-targeting immunoglobulin G4 humanized mAb conjugated to the cytotoxic antibiotic calicheamicin, moved to CD22+ R/R B-ALL [1333]. Noteworthily, the cell surface glycoprotein CD22 is expressed in > 90% of B-ALL patients. Strikingly, InO demonstrated significant activity in R/R B-ALL in both adult and pediatric trials as either a single agent or in combination chemotherapy regimens which led to its FDA–approval for the treatment of R/R B-ALL in pediatric and adult patients [1334]. Contextually, InO showed a significantly higher remission rate compared with standard intensive chemotherapy in adults with R/R B-cell ALL in the phase 3 INO-VATE ALL trial [1335]. The post hoc subgroup analysis of of INO-VATE trial confirmed that InO remains efficacious and has a similar safety profile for R/R B-ALL in patients with a high disease burden, defined herein as bone marrow blast (BMB) >90% [1336]. The robust remission rate in the high disease burden subgroup of INO-VATE contrasts with another targeted treatment, blinatumomab, where remission rates were lower in patients with ≥50% BMB vs. <50% BMB (29 vs. 73%) [1337]. Similarly, patients with higher BMB% (≥5% vs. <5%) treated with CAR T-cell therapy experienced poorer outcomes (remission rate 75 vs. 95%, median OS 12.4 vs. 20.1 months) [1338]. In addition, new research that is attempting to expand the potential applications of InO in B-ALL, including using it in combination with chemotherapy and/or other immunotherapies, in the frontline treatment of ALL, and in treatment of measurable residual disease (MRD). Strikingly, the greatest potential of InO lies in combination therapy either in the frontline or salvage settings. Interestingly, very encouraging outcomes have been observed with InO in newly diagnosed B-ALL, whether combined with chemotherapy, blinatumomab or both [1339]. In this vein, Jabbour et al., recently showed that InO was safe and effective in eradicating MRD in patients with B-ALL in CR (the MRD conversion rate was 69%, which translated into a 2-year relapse-free survival (RFS) of 54% and a 2-year OS of 60%) [1340]. Furthermore, a phase I clinical trial (NCT03233854) tested a bispecific CAR T-cells targeting CD19/CD22 (CD19-22.BB.z-CAR) in adults with R/R B-ALL and LBCL which demonstrated safety and impressive clinical activity in B-ALL. CD19-22.BB.z-CAR T-cells were clinically active in both B-ALL, with 82% achieving an MRD− CR, and in LBCL with an objective response rates (ORR) of 62%. However, the lymphoma arm was closed in this study as the 6-month PFS in LBCL (29%, 95% CI 12–48%) in this trial was similar to tisagenlecleucel/Kymriah® (a CD19-directed CAR T-cell therapy) but enrollment is still ongoing in patients with B-ALL. Interestingly, this work provided evidence that antigen$^{-/lo}$ escape is a major pathway of resistance after CD19-CAR T-cell therapy for LBCL and quantitative antigen density in LBCL correlates with outcomes after CAR T-cell therapy [1341]. In a similar vein, Joshua and colleagues developed a novel BiTE consisting of humanized anti-CD22 and anti-CD3 single chain variable fragments demonstrating that CD22 can be utilized as as an alternate target antigen to CD19 or CD20 in a BiTE formulation for B-cell malignancies. The CD22-BiTE showed tumor growth inhibition, comparable to blinatumomab, in an established B-ALL xenograft mouse model. Interestingly, the combination of blinatumomab and CD22-BiTE yielded increased efficacy *in vivo* when compared to the single agents suggesting that this novel construct could be used as a primary, combination, or post-CD19 directed therapy [1342]. On the other hand, Siglec-3 (a myeloid cell marker) has been considered as a therapeutic target for a target on AML [1343,1344]. In a way similar to Ino, gemtuzumab ozogamicin (GO) is another ADC targeting CD33-expressing leukaemic cells (> 80% in patients with AML) that substantially improved outcomes in patients with AML [1345,1346,1347]. Noteworthily, the cytotoxic effects of both GO and InO are inversely proportional to the amount of P-gp which indicates that P-gp contributes to their clinical resistance [1348,1349,1350]. As mentioned earlier, the MDR phenotype correlates with expression of P-gp.

## Therapeutic implications

It needs to be emphasized that as a hallmark of cancer aberrant glycosylation is not just a consequence, but also a driver of a malignant phenotype. In a similar vein, aberrant glycosylation allows for the rational design of biomarker discovery research [1351]. In addition to biomarker discovery by glycomics or glycoproteomics, glycan-related vaccines, antibody therapy, or carbohydrate recognition molecules, namely, glycan-based therapeutics or glycomimetics, are promising strategies for the future. Strikingly, the specific glycan structures found on tumor cells, known as the tumor glyco-code, can alter how the immune system perceives cancer cells and can induce immune suppression [1352]. Not surprisingly, novel therapies targeting tumor-associated glycans and their biosynthesis are currently being investigated in several clinical trials [1353]. Importantly, interference with glycan–lectin interactions that are able to skew the immune system function represent a new immune checkpoint and a potential new target for cancer immunotherapy. Noteworthily, tumor cells utilize these interactions to either evade immune cell detection or inhibit the anti-tumor immune response [1354]. In this context, some of the therapeutic applications of glycobiology-targeted therapies in hematologic malignancies are outlined here:

1. Removal of 9-O-acetyl residues from Neu5Ac on the cell surface by an O-acetylesterase made ALL cells more vulnerable to vincristine and nilotinib suggesting that Neu5Ac de-O-acetylation could be used as therapy to eradicate drug-resistant ALL cells [1355].

2. Absence or therapeutic blockade of the E-selectin receptor using small molecule mimetic GMI-1271/Uproleselan effectively inhibits niche-mediated pro-survival signaling and dampens AML blast regeneration [1356]. In addition, supporting evidence showed that combination treatment with uproleselan reduced MM resistance to carfilzomib and lenalidomide, as well as AML to cytarabine, and enhanced their therapeutic effects as demonstrated by reduced tumor growth and prolonged mice survival [1357].

3. Galectin-9 has an antiproliferative effect on MM cell lines and patient-derived myeloma cells by inhibiting the JNK and p38 MAPK signaling pathways. Therefore, galectin-9 can be used as a

new therapeutic option to treat MM [1358].

4. Two labs, one run by sugar chemist and recent Nobel Prize winner Carolyn Bertozzi, PhD, and another headed by cancer expert Dean Felsher, MD, PhD discovered that the proto-oncogene MYC controls expression of the sialyltransferase ST6GALNAC4 which is necessary to make a glycan known as disialyl-T that pops up in abundance on the surface of MYC-driven cancer cells. In turn, disialyl-T functions as a "don't eat me" signal by engaging Siglec-7, thereby inhibiting the anticancer immune responses. Interestingly, the combined high expression of MYC and ST6GALNAC4 identifies patients with high-risk cancers with reduced tumor myeloid infiltration. As a result, patients with high MYC expression including DLBCL [1359], CLL [1360], BL [1361] and T-ALL [1362] may be particularly responsive to inhibition of ST6GALNAC4 activity either directly or indirectly by therapeutically targeting its product disialyl-T with an antibody or degradation with an antibody-sialidase conjugate (an antibody directs sialidase to selectively remove sialic acid from tumor cells to enable immune cells to kill the desialylated cancer cells [1363] [1364]. Interestingly, MYC was found to be translocated in 36% of patients with MM [1365] which could hold opportunities for therapeutic intervention in MM [1366].

5. The Gb3-binding lectin-CARs have demonstrated target-specific cytotoxicity against Burkitt's lymphoma-derived cell lines as well as solid tumor cells from colorectal and triple-negative breast cancer [1367]. Noteworthily, Gb3 is highly expressed by B-cells found within GCs (GC B-cells), where it is essential for the production of high-affinity antibodies [1368].

6. Significantly slower tumor progression was observed in the CD19 BiTE-sialidase treated group as compared to the CD19 BiTE treated group, demonstrating better *in vivo* anti-tumor effects of the sialidase fusion protein [1369].

7. PSGL-1 is a potential therapeutic target for MM. Immunotherapy with anti-PSGL-1 mAbs induced *in vivo* killing of MM cells (provided that complement regulatory proteins are neutralized) through apoptosis, ADCC and complement-dependent cytotoxicity (CDC) [1370].

8. Glinsky and Raz have advocated for development of MCP, a galectin-3 antagonist that acts by inhibiting galectin-3 anti-apoptotic effects [1371]. Consistent with the previous myeloma study [1372], GCS-100 (an MCP) was able to suppress both ERK phosphorylation and MCL-1 expression in AML cells. In fact, GCS-100 has proved effective in pre-clinical models of MM, lymphoma, AML, as well as solid tumors [1373,1374,1375,1376]. Considering that galectin-3 is a major regulator of Bcl-2 function, the Raz laboratory has also advocated combining anti-Bcl-2 treatment (e.g., BH3 mimetics) and therapy targeting galectin-3 (e.g., GCS-100) to improve the efficacy of anti-Bcl-2 treatment in several hematologic malignancies [1377].

9. Aasted et al., generated 4C8, a cancer-specific mAb, against tumor-associated Tn-glycosylated CD44v6. 4C8 CAR T-cells were effective against T-cell leukemia and several solid cell lines but sparing healthy keratinocytes [1378].

10. Tang et al., found that AML patients with *FLT3*/ITD or *DNMT3A* mutations had higher expression of CD44v6, in contrast to normal specimens. CD44v6 CAR T-cells eliminated CD44v6$^+$ AML cells, especially AML cells with *FLT3* or *DNMT3A* mutations while demonstrating potent anti-leukemic efficacy and safety both *in vitro* and *in vivo* [1379].

11. Vaxevanis et al., suggested for the first time the proteoglycan biglycan (BGN) as a novel prognostic biomarker and therapeutic target of sAML/MDS by its direct inhibition through BGN-specific antibodies and/or inflammasome inhibitors [1380].

12. A phase I/IIa clinical trial has been performed to study safety, efficacy and feasibility of CD44v6 CAR T-cell immunotherapy in AML and MM patients mediating a potent anti-tumor effects against primary AML and MM while sparing normal hematopoietic stem cells and CD44v6-expressing keratinocytes [1381. In addition, CD44v6-targeting nanomedicine has been explored as a promising tool for cancer therapy. This targeted nanoparticle development represents a launching point for future improvements and therapeutic and/or diagnostic opportunities [1382].

13. J. Bae et al., demonstrated increased LAG-3 expression on proliferating CD3$^+$ T-cells in MM patient Bone Marrow Mononuclear Cells (BMMCs) and peripheral blood mononuclear cells (PBMCs), as well as robust surface and intracellular expression of its ligand, galectin-3, in CD138$^+$ patient MM cells and MM cell lines. Interestingly, LAG-3/galectin-3 blockade (through LAG-3 and/or galectin-3 inhibition) can efficiently enhance the proliferation of T-cells in MM patients and functional activities of MM-specific CTL, including XBP1/CD138/CS1-targeting memory CD8$^+$ T-cells, against MM. These results identify LAG-3/ galectin-3 as an alternative mechanism of immune resistance and provide the rationale for targeting LAG-3/ galectin-3, alone and in combination with immunotherapeutic approaches, to improve patient outcome in MM [1383].

14. Layal El Halabi et al., found that LAG-3 and TIM-3 to be nearly always expressed in the TME of classical Hodgkin lymphoma (cHL). In addition, TIM-3 was detected at the surface of a third of Hodgkin/Reed-Sternberg (HRS) cells [1384]. Several preclinical cancer models showed that combining anti-PD-1 with anti-LAG-3 or anti-TIM-3 appeared to be synergistic [1385,1386,1387,1388,1389,1390,1391,1392] as well as may be a way to overcome resistance [1393]. This provides a rationale for targeting LAG-3 and/or TIM-3 in combination with anti-PD-1 antibodies in the treatment of R/R HL. Currently, a phase 3 randomized clinical trial (NCT05508867) aiming to assess the safety and tolerability as well as compare efficacy of coformulated favezelimab, MK-4280 (a humanized IgG4 LAG-3 inhibitor that inhibits the binding of LAG-3 to MHC class II) plus pembrolizumab, MK-3475 (a PD-1 inhibitor) with physician's choice chemotherapy of bendamustine or gemcitabine in patients with PD-(L)1-refractory, R/R cHL. Furthermore, a phase 1/phase 2 clinical trial (NCT03598608) aiming at evaluating the safety and efficacy of favezelimab in combination with pembrolizumab using a non-randomized study design in patients with several hematological malignancies (cHL, DLBCL and indolent NHL) is still ongoing. Results of the analysis focusing on anti-PD-1-naïve patients with R/R cHL revealed that the combination of favezelimab and pembrolizumab was associated with an ORR of 73% (22/30 patients) including 23% of Complete Response (CR) at a median follow-up of 13.5 months. The median PFS was 19 months, and the median OS was not reached. The 12-month OS rate was 96% [1394,1395]. This efficacy was also shown in the cohort of patients with R/R classical HL who failed an anti-PD-1 treatment suggesting the combination may reinduce a response in these patients. The ORR was 31% (9/29) including 7% of CR after a median follow-up of 16.5 months. The median PFS and OS were 9 months and 26 months, respectively [1396].

15. Corcoran et al., showed that genetic, pharmacological, and enzymatic approaches that remove sialic acid from N-linked glycans on CD79B lead to enhanced tumor killing by Polatuzumab Vedotin (Pola-V), an ADC directed to the CD79B subunit of the BCR, in DLBCL cell lines [1397]. Mechanistically, glycosylated residues on CD79A and CD79B create a glycan shield around the Pola-V binding site which preclude binding to its target. Therefore, these findings reveal the striking impact of epitope glycosylation, specifically a2,6 sialylation, on the binding of Pola-V to CD79B and thereby its ability to kill tumor cells and also unravelled the molecular basis of heterogeneity in response to Pola-V [1398].

16. Pang et al., demonstrated that targeting galectin-9 may hold potential value for the treatment of acute GvHD (aGvHD) after haplo-HSCT. Mechanistically, exogenous galectin-9 was found to mitigate aGvHD by restoring the Treg/Teffs (effector T-cells) balance and suppressing the PI3K/AKT/mTOR pathway. The increased Treg cells can inhibit the activation of Th1 and Th17 cells by secreting TGF-β, thus alleviating aGvHD and inducing immune tolerance [1399].

17. Interesting new research uncovered a proinflammatory stem cell niche driving myelofibrosis, through a galectin-1 signaling axis. This discovery points to galectin-1 as a promising therapeutic target with disease modifying effects (altering the inflammatory niche and reducing fibrosis) in MPNs [1400].

18. As discussed earlier, ST3GAL4 has been suggested to synthesize ligands for E-selectin, an adhesion receptor that facilitates the survival of AML stem cells within the BM niche. Interestingly, V. Krishnamoorthy et al., recently found that upregulation of ST3GAL4 in AML facilitates immune evasion by increasing the biosynthesis of ligands for the inhibitory Siglec-9. Integrated CRISPR genomic screening and clinical bioinformatic analysis identified ST3GAL4 as a potential driver of Siglec-9 ligand expression in AML. Depletion of ST3GAL4 by CRISPR-Cas9 knockout dramatically reduced the expression of Siglec-9 ligands in AML cells. Mass spectrometry analysis of cell-surface glycosylation in ST3GAL4 knockout cells revealed that Siglec-9 primarily binds N-linked sialoglycans on these cell types. In addition, this study found that ST3GAL4 knockout enhanced the sensitivity of AML cells to phagocytosis by Siglec-9-expressing macrophages. Intriguingly, this work confirms that ST3GAL4 is strongly implicated in AML pathogenesis and implies that the ST3GAL4 enzyme itself may actually be the most impactful target for the development of therapeutic inhibitors in AML [1401].

19. Intriguingly, the galectin-9–TIM-3 axis is upregulated in B-ALL, negatively correlating with clinical outcome, and galectin-9 impairs CD19-CAR T-cell function. Falgàs et al., showed that blocking the galectin-9–TIM-3 axis in B-ALL enhances the persistence and efficacy of CD19-CAR T-cells *in vivo* and ex vivo [1402]. Mechanistically, TIM-3 is commonly expressed on CAR T-cells in the context of "exhaustion," and binding of TIM-3 to galectin-9 can lead to reduced T-cell function and apoptosis [1403].

20. Substantial evidence suggests that BMSCs contribute to the progression of myeloid malignancies by remodeling the TME [1404,1405]. In this context, Feng et al., observed a significantly higher proportion of M2 TAMs in the BMSCs of MDS/AML compared to that in healthy donors. This phenomenon is associated with the aberrant glycosylated levels in leukemic stromal cells, highlighting a promising target for MDS/AML immunotherapy. Mechanistically, downregulated bisecting GlcNAc levels in BMSCs of MDS/AML patients drove TAMs polarization towards the M2 phenotype through the secretion of TGF-β1, which elevated PD-L1 expression and thereby impaired $CD8^+$ T-cell function, facilitating immune escape and the progression of MDS/AML [1406].

## CHALLENGES AND FUTURE DIRECTIONS IN IMMUNOTHERAPY: UNLOCKING NEW HORIZONS IN CANCER IMMUNOTHERAPY

Although immunotherapy has shown promising activities in several solid tumors, its effects remain suboptimal in patients with liquid tumors. For instance, despite advancements in the treatment landscape of MM, such as incorporation of the anti-CD38 mAb daratumumab, most of the patients inevitably experience relapse [1407]. In addition, the current immunotherapy platforms have already riddled with issues concerning mainly their safety profile and affordability since their inception. For instance, Kymriah® costs $475,000 per patient in the US, which is unaffordable for an ordinary family [1408]. Not surprisingly, the high demand and expensive costs associated with CAR T-cell therapy might prove unsustainable for health systems [1409]. Hence, an effective drug at an affordable price is an unmet need [1410]. On 28 November 2023, the FDA released a statement that the agency is investigating reports of T-cell malignancies, including CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T-cell immunotherapies [1411,1412,1413]. Due to the seriousness of this risk, ongoing monitoring and longitudinal surveillance remain a clinical standard in the post-CAR setting [1414]. Within this context, Elsallab et al., provided additional information on the numbers of second malignancies reported after CAR-T therapies. They found that second primary malignancies were reported in 4.3% (536 of 12394) adverse events after CAR-T therapies in the Food and Drug Administration Adverse Event Reporting System (FAERS). Strikingly, myeloid and T-cell neoplasms were disproportionately more frequent, with 208 reports of myelodysplasia and 106 reports of acute myeloid leukemias, which warrants further follow-up [1415]. Strikingly, relapse remains the major obstacle of CAR T-cell therapy leaving many hematologic malignancies inevitably fatal, and therefore new treatment strategies are imperative. Clinical evidence indicates that a large proportion of patients with B-cell malignancies suffer from relapse after CAR T-cell therapy [1416]. The initial impressive results of CAR T-cell therapy were coupled with the occurrence of relapse in approximately 30%-50% of patients after having achieved a CR [1417]. Consequently, understanding the mechanics of poor response or relapse is critical in advancing CAR T-cell therapy [1418]. Possible reasons include CAR T-cell-intrinsic qualities such as expansion capacity and T-cell exhaustion/dysfunction cell state, in addition to CAR T-cell-extrinsic factors such as antigen escape and immune suppression by the hostile BM microenvironment [1419,1420]. As T-cell dysfunction is now well established as a cause of CAR T-cell failure [1421], replacing T-cells by NK cells is expected to gain substantial momentum as an alternative therapeutic approach. Interestingly, patients infused with CAR-NK cells did not represent significant adverse events, such as CRS [1422]. However, just like CAR T-cell therapy, patients treated with CAR NK-cells also developed progressive disease despite showing initial encouraging responses [1423,1424]. In both cases, considerable

effort is still needed to replicate the success observed with CAR cell therapies in B-lymphoid malignancies in other malignancies [1425]. Furthermore, the therapeutic potential of deeper understanding of co-inhibitory B7-CD28 pathways led to the FDA approval of several ICIs for cancer immunotherapy [1426]. However, despite the marked clinical success of ICB in the treatment of several tumors, many patients do not respond, relapse, or are deemed no longer eligible for further ICB treatment [1427]. Given the dire outcomes for patients with hematologic malignancies, seeking alternative therapeutics options is a genuine demand rather than a fantasy. In this context, multiple lines of evidence suggest that TACAs are: (1) more tumor specific than protein targets; (2) expressed on tumor cell surface; (3) highly abundant; and (4) significant in tumor biology, i.e., suppressing and evading immune surveillance in the TME, altering oncogenic signaling pathways, promoting tumor survival, progression, and metastasis [1428]. In fact, glycobiology has already produced many effective drugs with validated results against several solid tumors. In parallel to solid tumors, the field of glycobiology is already replete with a host of important prognostic biomarkers and therapeutic targets for liquid tumors. Overwhelming evidence supports the huge impact of glycosylation changes in hematologic malignancies; and as such, aberrant glycosylation provides an attractive resource for immunotherapy. In particular, the repertoire of cancer-associated glycans known as TACAs expressed on liquid tumors is highly versatile and constitue a great opportunity to avail from targeted approaches. Noteworthily, glycan targeting may offer major advantages in relation to protein targeting [1429]. Since they are barely expressed on normal tissues, TACAs are truly tumor-specific antigens which indicates that targeting them offers less '*off-target*' or '*on-target off-tumor*' toxicities [1430]. Within this context, in addition to the known approaches (e.g., CAR T-cell therapy), TACAs can also be targeted by novel methods including lectins, lectibodies [1431,1432], and glycan-specific nanobodies [1433,1434]. Notably, significant advancements have been made in understanding plant and microbial lectins as therapeutic agents against various viral diseases in recent years. Among them, mannose-specific lectins have being proven as promising anti-viral agents against a variety of viruses [1435]. In this vein, I have personally proposed therapeutic lectins as a new modality of immunotherapy that can avail of the CDC-driven TACA-targeted killing of cancer cells [1436]. Supporting this hypothesis, rVAR2 represents a proof-of-principle model promoting the use of lectins against hematologic malignancies. rVAR2 is a recombinant VAR2CSA, a lectin from P. falciparum that detects an oncofetal CS structure found on many proteoglycans including syndecan-1, CD44 and Chondroitin Sulfate Proteoglycan 4 (CSPG4) that are present in a high proportion of malignant cell lines including MM and B-ALL [1437,1438]. Interestingly, CSPG4 is an established treatment target for KMT2A-R B-ALL [1439]. CS structure on CSPG4 is just one example of many immune targets that are heavily glycosylated glycoproteins in which their glycotopes can be added to the pool of TACAs. Noteworthily, neither the genome, transcriptome nor the proteome can individually predict the structural nature, distribution and dynamics of glycan chains in proteins. However, glycoproteomics attempts to bridge this gap by addressing the glycome as it appears in the proteome [1440]. Therefore, it is imperative to investigate the glycoproteomics of surface glycoproteins (e.g., CD44 variant isoforms) in order to characterize its altered glycosylation profiles and identify targetable TACAs for novel immunotherapy. In addition, glycoproteomic analysis has emerged as a promising tool for biomarker discovery and development in early detection of cancers and prediction of treatment efficacy including response to immunotherapies [1441]. Indeed, glycosylation of glycoproteins is crucial for their response to immunotherapy. Examples include CD38 in MM [1442,1443] and CD19 in B-ALL [1444], in which glycosylation changes enables resistance to daratumumab and CAR T-cells respectively. Furthermore, it has been repeatedly demonstrated that the interactions between lectins and altered/tumor-specific cell surface carbohydrates 'turns on' an immunosuppressive milieu, also known as the tumor glyco-code, which is a prominent mechanism by which tumors escape anti-tumor immune responses [1445]. Unsurprisingly, glycan-lectin interactions have uncovered an array of novel signaling pathways that mimic the known immune checkpoints CTLA-4 and PD-1 [1446]. As a matter of fact, Siglecs are mostly inhibitory receptors similar to known immune checkpoints including PD-1 or CTLA-4 that are successfully targeted with blocking antibodies for cancer immunotherapy [1447]. Consequently, disrupting these immunosuppressive glyco-immune checkpoints could serve as a blueprint to develop novel or improved cancer immunotherapeutic modalities, including T-cell therapies. In particular, the sialoglycan -Siglec, TF-MUC1-galectin-3 and galectin-9–TIM-3 axes are promising targets for checkpoint inhibitor–type intervention in hematologic malignancies. Signaling pathways that govern these pathways must also be understood to fully harness their full potential. Interestingly, these glyco-immune checkpoints can be combined with ICBs to improve their efficacy [1448]. For instance, recent evidence suggested that targeted tumor desialylation in the TME enhance tumor control by converting immunologically inert tumors into inflamed ones [1449] as well as synergize with ICB [1450]. One of the stratagies designed to desialylate the TME was through antibody conjugation to a sialidase which has shown to improve the anti-tumor immune response [1451]. In a similar vein, a very recent work goes on to show that sialic-acid removal is synergistic with BiTE treatment *in vitro* [1452]. In a similar vein, the E-selectin/ sLeX axis have been reported to regulate both hematopoietic stem, and leukemic, cell proliferative dynamics. As such, targeting E-selectin receptor/sLeX signaling pathways hold great potentials to develop effective anti-cancer regimens in the treatment of liquid tumors [1453]. In addition, the tumor glyco-code can be seen as neoantigens that represent interesting targets for therapeutic and diagnostic approaches [1454]. Intriguingly, since glycan modifications are dictated by the repertoire of glycosyltransferases and substrates responsible for their synthesis [1455], the field of glycobiology unveiled several metabolic vulnerability loops and glycosyltransferases with druggable and therapeutic potential.

## CONCLUSION

Despite that immunotherapy has shown great potential in cancer treatment, a significant proportion of patient's experience disease recurrence or resistance, owing to primary or acquired drug resistance driven by tumor immune escape. Hence, developing new strategies to overcome immune escape is the only way to enhance the response efficiency of immunotherapy. Within this context, compelling evidence suggests that aberrant glycosylation contributes to the formation of a complex "glyco-code" on the surface of tumor cells implicated in suppressing anti-tumor immune responses, which plays a crucial role in

tumor development and progression. Not surprisingly, aberrant glycosylation has emerged as a promising target for immunotherapy, ushering in a new frontier in cancer treatment: glyco-immunology. By decoding the intricate interplay between glycosylation and immunosuppression, this field holds the potential to revolutionize cancer therapeutics. Indeed, the key insights into the glycobiological landscapes of hematologic malignancies presented in this article should provide the impetus for devising novel strategies aimed at eradicating the the malignant clone as well as galvanize hematologists/oncologists to design and conduct robust clinical trials in this field. To this end, future editions of the major hematology/oncology textbooks including "The Bethesda Handbook of Clinical Hematology", "Rodak's Hematology", "Wintrobe's Clinical Hematology Book", "Nathan and Oski's Hematology of Infancy and Childhood", "Williams Manual of Hematology", and "Lanzkowsky's Manual of Pediatric Hematology and Oncology" must integrate background information on 'Glycobiology in Hematology'. As a concluding remark, this artice serves to lay the foundation for future revolution of therapeutics in hematologic oncology in the context of recent advances in glycobiological research.

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