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Glyco Code: Cancer and Immune Disorders

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Editorial

Post-translation modifications (PTMs) comprise many processes such as phosphorylation, acetylation, methylation, ubiquitination and glycosylation etc. play an important role in regulating protein function in eukaryotes [1,2]. Amongst, Glycosylation is the most common PTM that occur in all domains of life and acts as a crucial regulatory mechanism controlling many physiopathological processes. Glycosylation is a defined as an addition of carbohydrate moieties (glycans) to proteins and lipids to form glycoproteins or glycolipids respectively by the coordinated action of several enzymes in Golgi complex and endoplasm reticulum [3]. These glycans participate in several key biological events such as cell adhesion, signal transduction, protein folding, cell differentiation, host-pathogen interactions and metastasis development [4].

Several studies have shown that the molecular defects in glycan biosynthesis are identified as the main reasons for several diseases, including the cancer development and progression [5]. The fundamental function of the immune system is not only to elicit immune response against invading pathogens but also to maintain immune surveillance against the development of cancerous cells [6-8]. It is well documented that the altered glycan structures of glycoproteins and glycolipids on the surface of malignant cell have a different glycan-code than the normal healthy cells [9,10]. But it's still enigmatic how the oncogenic glycosylation affects the immune cell activity within the tumor micro environment. Understanding the glycan alterations in cancer cells can be useful in developing them as a biomarker, thus the area of research offers a new potential therapeutic opportunity.

Glycomics of Cancer

More than half of the secreted, intracellular or membrane bound proteins in humans are post-translationally modified by the covalent addition of complex oligosaccharides [11]. The two basic glycosylations i.e. N-linked (Nitrogen atom in the side chain of asparagine residue of a protein) or O-linked (hydroxyl group of serine, threonine or tyrosine residue of a protein) is classified based on which atom provides the linkage in the protein to the glycan [12]. The complex glycans conjugated to the proteins have an essential functional role, according to the US National Academy of Science report the glycans serve as an "on" and "off " switches that modulate the functions of glycoproteins. Glycan moieties of glycoproteins are associated with almost all biological processes such as cell development, differentiation, proliferation, aging and immunity.

Nearly 300 genes involved in the biosynthesis of glycans in humans, mainly two enzymes i.e. glycosyltransferase and glycosidases are responsible for the processing, assembly and turnover of glycans. Glycosyltransferases are the enzymes that build-up the monosaccharides into linear and branched glycans whereas the glycosidases catalyse the hydrolysis of oligosaccharides. In malignant transformation the expression of these genes is controlled by different mechanisms and analysis of this aberrant expression may serve as a cancer biomarkers and therapeutic tools [13]. The most common tumor associated glycans are listed below:

a) Sialylated glycans: Sialic acid is a negatively charged nine carbon monosaccharide and its expression is augmented in cancer. The most predominant form of sialic acid sugars found in humans is N-Acetylneuraminic acid.

b) Tn antigen: This antigen refers to a monosaccharide, N-acetylgalactosamine linked to the side chain of serine or threonine residue of protein by a group of enzymes called polypeptide N-acetylgalactosaminyltransferases is the first step in the O-linked glycosylation and the subsequently extended by the series of enzyme reactions. Other disaccharide structures identified in this category are sialyl Tn antigen (sialic acid addition) and galactose Tn antigen (addition of galactose over the Tn antigen).

c) Lewis antigens: Many of the glycans of this family are upregulated in cancer. The glycans of this family comprises of a disaccharide N-acetylglucosamine and galactose with one or two fucose moieties linkage.

Glycomics in Immune Disorders

Glycome is an indispensable component in the development and function of the mammalian immune system. The alteration of the basic functions of immune cells, such as differentiation, activation and apoptosis is due to the aberrant changes of immune cells glycome that leads to several immune diseases [14]. Almost all surface localized immune receptors are glycoproteins, for example the claas I and calss II major histocompatibility complex proteins (MHC class I and MHC class II), T cell and B cell receptors and co-receptors, cytokine receptors, chemokine receptors, NOD-like receptors, Toll like receptors (TLRs) and the role of the glycans on these molecules is as diverse as immune cell population. Most of the molecules involved in the process of adaptive and innate immunity (all five immunogloblins, Igs) are glycoproteins. Out of all five immunoglobulins, IgG is most extensively studied glycoproteins is an excellent example of protein function modulation by alternative glycosylation [15-18]. While the Fab region of IgG antibody is responsible for the recognition of antigens, each of the heavy chains in the Fc regions carries single covalently attached N-glycan is an essential structural component of the Fc region [19]. Lectins are proteins with glycan binding activity that were initially identified in plants and subsequently identified in all cells, microorganisms to humans. The lectin-glycan binding is a kind of molecular recognition that microorganisms use to identify and decode

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the biological information that exist on its own cellular glycome as well as the glycome of other organisms. Aberrant glycosylation responsible for the autoimmune diseases. For example, it is well established that the decreased galactosylation of IgG in rheumatoid arthritis (RA) is due to the activation of lectin complement pathway via mannose binding protein [20,21]. It has been reported that the decreased IgG galactosylation in inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE) [22,23].

Glycans are very essential for the interaction of commensal and pathogenic bacteria with the host cells. It is well known that the N- and O-glycans on the surface of pathogenic bacteria are indispensable for their motility and host interaction and thus play a key role in virulence and representing putative therapeutic targets [24]. In symbiotic bacteria homeostasis is maintained by their glycans and play a key role in the attenuation of host immune response [25]. The pathogenic bacteria that invade the multicellular animals decorate sometimes themselves with glycan structures that are similar or almost identical that are found on the host cell surfaces. These glycans form a thick coat on the surface of the pathogen and thus represents a very successful strategy for evading the host immune responses [26].

The altered glycans on the glycoproteins and glycosphingolipids on the surface of the cancer cells will be exploited by immune cells through their lectin receptors to program immune suppression and subvert key immunological defense mechanisms and contribute to early stages of invasion.

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