Blood Type Diets (BTD) and Aging: An Overview

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Abstract

It has recently been proposed that glycans, being the third alphabet of life, interact intricately with endogenous biomolecules to modulate tolerance, immune and inflammatory responses. Specifically, food glycans could impact health and be a source of inflammation and age-related diseases. These special carbohydrates are present as glycoconjugates (glycoproteins or glycolipids) in and on the surface of all the cells (glycocalyx) of all organisms or are found in free form in biological fluids. Recent advances in glyciobiology and glycochemistry have shown how glycans bind with naturally present human proteins (lectins), through protein–carbohydrate interactions (or PCI), but also how oligosaccharides can interact with other glycans, present throughout the human body (through carbohydrate–carbohydrate interactions, or CCI). Oligosaccharides present in food sources, which go beyond the definition of normal fibers, once ingested are then either absorbed in the bloodstream, where they are recognized by the immune system, or interact with the surface of GI epithelial cells, thus generating appropriate biochemical cascades that induce a tolerance or immune/inflammatory response. Because the ABO epitopes have been encountered on all human cells, not just erythrocytes and based on the different biotypology (A, AB, B, and O) impose morphic changes in the distribution of the glycans on the glycocalyx (lipid rafts and clustered saccharide patches), their CCI with food and microbe glycans will be different, thus, eliciting contrasting responses. This can explain the epidemiological data for blood type diets (BTD). Through continuous consumption of the wrong types of glycans, processes of chronic inflammation could be initiated and progress to accelerated aging. Four basic modes of action have been identified showing how glycans can trigger inflamm-aging. Since glycochemistry is a young science, further studies with newer technologies are warranted for advancement in this field.

Keywords: Glycan; Aging; Inflammation; ABO antigens; Glycotopes; Food antigens

Introduction

It is a well-established fact, now, that complex carbohydrates are ubiquitous in nature [1]. Carbohydrates are also called glycans to underline the functional diversity and complexity of their structural composition [2]. For over a century, the areas of nucleic acids, proteins and lipids have captured the attention of investigators worldwide [3]. On the other hand, carbohydrates, due to their inherent higher complexity and non-genome origin, have only more recently received increased attention through the expanding field of glycobiology [4-6].

Because of their unique chemical properties, glycans have unsurpassed structural variability, and enormous changeability beyond the simple sequence, as for proteins or nucleic acids [7]. The presence of an anomeric carbon atom, the possibility of linkage formation involving different acceptor sites and the ring size with frequent occurrence of branching and site-specific modifications allows glycans to display unique properties [8,9]. Hence, it can be stated that the proteosome and the nucleosome are no match for the glycome, as the coding capacity of the oligosaccharide language is simply orders of magnitude higher [10]. Only recently these ubiquitous molecules have been considered in nutrition and have been associated with many factors linking food components to health or disease [11]. Given the recent advances in glyciobiology and glycochemistry, it is about time that nutritional sciences incorporate such tiny sweet molecules as fundamental constituents of the nutritional environment [12].

Literature Review

Although blood type diets (BTD) have been around for a couple of decades, it has slowly gained momentum and widespread attention [13]. Since it was launched in 1996, several physicians have experimented (through empirical observations) with the diet and have found strong evidence in favor [14-17]. Nevertheless, it is reported that there’s a lack of evidence supporting the BTD hypothesis [18]. To date, only one serious mechanistic explanation, apart from the lectin hypothesis, has been put forward for BTD and involves the intervention of glycans [11]. Their presence in food and their particular biochemistry make them exceptionally prone to interact with human biomolecules and elicit and modulate immune and/or inflammatory responses [11,19-22]. Ultimately, these processes of inflammation and immune tolerance could be regarded as possible underlying initiators of aging and age-related diseases [23,24]. Inflamm-aging (aging from inflammation) is deemed the long-term result of chronic stimulation of the innate immune system [25]. In order to understand how glycans molecular biology and biochemistry influence the process of aging and disease, a cursory overview of their occurrence, antigenicity and immune signaling potential is required.

Glycocalyx and signaling mechanism

The cell surface is literally coated with carbohydrates in the form of glycoproteins, with oligosaccharides (sugar residues), proteoglycans, with polysaccharides, and glycolipids (as glycoconjugates) [26,27]. This layer is called the glycocalyx and is responsible for a vast number of biological functions [28-30]. Some of the most important roles include:
PRRs are receptors that recognize a wide variety of external pathogen-associated molecular patterns (PAMPs) [47]. PRR also react to the biological roles of glycans and their impact on the immune system [43,44], and modulating roles in many biological processes [42,45]. Several of such GBPs function as pattern recognition receptors (PRRs) [43]. PRRs are receptors that recognize a wide variety of external pathogen-associated molecular patterns (PAMPs) [47]. PRR also react to endogenous molecules like damage associated molecular patterns (DAMPs), closely linked to inflammation [48]. Activation of membrane-bound or intracellular PRRs by special exogenous and internal determinants initiate signaling events linked to innate immune responses [49]. C-type lectin (CTL) receptors (CLRs) are among the most efficient PRRs and interact with glycan structures on microorganisms leading to adaptive immune response [50].

Another phenomenon known as 'lipid raft', has a central role in this signaling scenario [49,51]. Lipid rafts are essentially the compartmentalization in time and space of lipid and protein cargo on the plasma membrane of cells [52]. The cell membrane is stuffed also with sphingolipids and glycosphingolipids (GSL) forming special microdomains [53]. Both glycolipids, glycoproteins and GPI proteins can reorganize (or self-associate) themselves spatially on the cell surface in these microdomains [54]. The reorganization in lipid rafts occurs through protein-carbohydrate interactions (PCI) or carbohydrate-carbohydrate interactions (CCI) to form glycolipid-enriched membrane microdomains of submicron length [31,55,56]. Many proteins with raft affinity, all heavily glycosylated have the ability to laterally segregate in fluctuating nanoscale assemblies (membrane subcompartmentalization) of sphingolipid, cholesterol, and proteins [57,58]. Multivalent binding between carbohydrates and proteins increases the avidity of cell signaling, molecular recognition and inflammations [59].

Lipid rafts, consisting of clusters of structural proteins, enzymes, and signaling receptors, regulate several biological functions, especially signaling events [60]. This has been confirmed by other studies suggesting that such rafts could play an important role in many cellular processes including membrane trafficking, cytoskeletal organization, and pathogen entry [61-63]. Moreover, galectin-4 or -8, can bind to and cross-link multivalent glycoproteins and glycolipids of lipid rafts, leading to formation of micro domains and lattices that initiate signal specific pathways [64,65]. The formation of these lipid raft assemblies are known to be responsible for initiating many signal transduction pathways, including those for immune cell activation [36]. Finally, the (epithelial) glycoalyx has emerged as an important participant in modulating inflammation, infection and allergic processes [39].

**Food glycans and antigens**

**Food antigens:** Dietary antigens or allergens (substances present in food) are known to elicit immunologic reactions generally defined under the category of food hypersensitivity (FHS) [66]. Among the many types of reactions to food components, dietary cross-reactive antigen epitopes have often been associated with food allergies and food intolerances [67]. In literature, epitopes are implicitly assumed to exclusively consist of amino acids, but glycan epitopes and classical hapten are important IgE-binding epitopes [68].

A hypothesis that the carbohydrate structures are another potential source of immunological cross-reaction between different plant allergens was proposed in the 1980s [69,70]. Since then, many food glycans (as xeno-glycans) were isolated, identified and structurally characterised [71,72], called cross-reactive carbohydrate determinants (CCD) [73]. CCDs generally have vast structural variability consisting of oligomannosidic hybrid or complex type structures [74,75]. These CCDs have been shown to have immunomodulatory weak allergic and/or non-allergic immunogenic properties, either as free (unlinked) glycan or on (glyco)protein allergens [70,76-78]. Some may also cause false-positive allergologic tests [75]. Identifying the number, structure, and function of glycans in cellular biology is a truly daunting task [28]. Glycans are present on a myriad of nuclear and cytoplasmic proteins [29]. Furthermore, they are endowed with diverse and complicated structures, typical of oligosaccharides (chains of monosaccharides between 3 and 20 sugar units in length) [76]. Dissimilarly to proteins or nucleic acids, which are linear, the glycosidic linkage in oligosaccharides have multiple attach points on the sugar ring, thus allowing both linear and branched structures (called antennae) [7]. The majority of bi-, tri-, and tetra-antennary glycans found in nature have diverse sugar residues linked to the terminal N-acetylgalactosamine (GlcNAc) giving rise to distinct glycan determinants [79].

The main carbohydrates included in human diet are polysaccharides in the form of starches, with variable chain length, monosaccharides and disaccharides (sucrose and lactose) [80]. There are other non-starch carbohydrates, normally called dietary fibres, that do not possess either α or α glycosidic bonds and are hence not hydolysable by the human digestive enzymes [1,4,6,81]. Indeed, non-digestible plant fibers can be divided into insoluble (cellulose, hemicellulose and lignin) and soluble (gums and pectins) fibers [82]. These can be metabolized only by the microbiota in the cecum and colon [83]. Further types of fibre include prebiotics, such as inulin and oligofructose (also called fructooligosaccharides (FOS)) galactooligosaccharides (GOS), and the human milk oligosaccharides (HMO) [84,85]. These special carbohydrates, too, can manifest properties not unlike those displayed by the food glycans previously discussed [11].

**ABO epitopes:** Most interestingly, many food antigens seem to be carbohydrate moieties similar to the histo-blood group antigens (HBGA). Human HBGA are glycan structures and carbohydrate epitopes present on glycoproteins and glycolipids of human cells [86]. HBGAs are classified into four groups (type 1, 2, 3 and 4), depending on the binding position (α or β) of sequential carbohydrate moieties [87]. Several studies [72,88,89] have found HBGA like glycans on glycoproteins and glycolipids in diverse food sources such as oysters, clams, fruits and vegetables. Recently researchers have also found...
The ABO blood group is intimately linked to another blood group of carbohydrate origin: the Lewis blood type [94]. Serologically, Lewis status is defined by the expression of two main antigens: Lea and Leb antigens [95]. Four possible Lewis phenotypes, although only three are commonly encountered in adults: Le(a-b-), Le(a+b-), and Le(a-b-). Lewis glycans are also important in the distinction of humans into two categories based on secretor and non-secretor status [94]. The HBGAs and ABO moieties have a wide tissue distribution in human cells [96]. In addition to their expression on the surface of red blood cells, the ABO and Lewis antigens are highly expressed on the surface of epithelial cells of the gastrointestinal (GI), bronchopulmonary, and urogenital tracts [88]. The expression of ABO antigens is also found on lymphocytes, platelets, endothelial cells and most epithelial cells [97,98]. Moreover, they are found in the saliva in several other biological tissues, in human milk (also as free oligosaccharides), and in general on the mucosal epithelium of the GI tract [76,89,99-103].

The other two carbohydrate antigen systems closely linked to both ABH and Lewis are Li and the globo series (P antigens), often found on glycolipids [41]. ABH antigens on red blood cells can modulate cellular interactions without being a direct ligand themselves, but by stabilizing other carbohydrates on the fluid cell surface in clusters (called “clustered saccharide patches”) [104]. Depending on the ABO blood type, the ABH antigens could interact through CCI or PCI with other glycans making them more (or less) accessible to relevant GBPs. The clustering of these closely spaced oligosaccharides, forced into an unexpected conformation, favors a high-affinity recognition needed for correct GBP binding to the glycans [105]. The stabilizing effect of these clusters demonstrated that the HBGAs can effectively modulate CCI involving other glycans (α2-3-linked Sias and α2-6-linked Sias), without being directly involved or being the primary target of CBPs [106]. Hence, glycan diversity together with special spatial conformation (unique clustered saccharide patches facilitated by ABH antigens) can be differentially recognized by GBPs, showing binding specificity [107].

Glycan Reactions

Lectins: Glycans, as highly structurally variable biomolecules can be selectively and with high affinity bound to special proteins, called lectins, present ubiquitously and abundantly in all phyla [7,108]. Although lectins (GBPs) recognize glycans with high affinity, nonetheless glycans display also multivalency as a feature by which their density and spatial organization can modulate the binding [109]. This effect, known as glycoside cluster effect, provides a mechanism for enhancing the overall affinity and selectivity of glycan recognition by lectin [110].

Several GBP (or carbohydrate-binding proteins, CBP, namely lectins) are present in nature and have been recovered in diverse food sources, being widely distributed among plants and animals [111]. Lectins are known to be anti-nutritional factors and to cause intestinal disorders [112]. The original mechanism to explain the workings of BTD was based on the presence of lectins in foods [113]. These CBPs are generally very resistant to heat and digestion, and have been recovered in active form throughout the colon and in the faeces [114,115]. CBPs are so selective that they are capable of recognizing just one to four monosaccharides organized in a special arrangement, called motif [116]. Lectins also showed polyclonal behaviour displaying the ability to bind to various glycoforms [117].

The binding of lectins is inhibited by most high-density polyvalent oligosaccharides-containing glycoproteins and their cryptoforms, masked by similar sugar residues such as blood group determinants or sialic acids [117]. Dietary lectins act as PRRs which bind to specific epitopes on surface glycoproteins (or glycolipids) on the glycoalyx of several cell types [118]. Quite a few hundred plant lectins have been identified so far, with various classification systems being proposed [119]. Some toxic effect of lectins can be attributed to the partial resistance to proteolysis in vivo [113]. But this explanation may not be only valid for local (GI) effects, but also for systemic effects as lectins can induce IgE-mediated and IgG-mediated reactions [112]. Although some lectins are known to resist degradation in the alimentary canal and crossover to the circulatory system, they are normally not expected, as proteins, to be absorbed as is [120]. Anyhow, there is a lack of depth of the mechanistic complexity needed to entertain the many biochemical and biological phenomena (inflammatory and immunologic reaction) that result from food consumption.

Glycans: An innovative mechanism is required as both central and supplementary to the already existing one. Food glycans (like all glycans) have special biochemical properties that allow them to manifest molecular mimicry (structurally similar though with chemically different features) with HBGAs [108]. Molecular mimicry is the phenomenon in which glycans with various structures and different moieties can appear to be identical or nearly identical to those found on their host cell surfaces [12]. The mechanism considers molecular mimicry as a fundamental property of glycans. Nevertheless, the following mechanism for generation of immune and inflammatory responses is an incomplete summary of all the possible interactions of food glycans with the human biochemical network. Four principal modes of action (MOA) have been identified.

The starting point is the ingestion of oligosaccharides with food. The oligomeric sugar moieties present unbound or bound on the glycoconjugates of the various food items are not degraded during digestion [69,84]. Once the undigested carbohydrates arrive intact at the level of the intestinal mucosa, they can either

1) Interact with the human lectins, such as galectin-4 or -8, present in the GI tract [121,122], or

2) React with glycans of glycoconjugates of various types on the cell membranes of the enterocytes [117], or

3) Be processed differentially by the gut microflora resulting in (a) Production of useful short-chain fatty acids (SCFA), which have beneficial effects [123], (b) Variation of the composition of the gut microbiota (positively or negatively), which will consequently influence inflammation [124].

4) Be absorbed into the internal milieu by diffusion or pinocytosis where they (a) Are presented to the APCs (antigen-presenting cells), such as dendritic cells, which will present the glycan for the generation of specific anti-glycan antibodies (AGA) [34,125], (b) Interact with the complement proteins through the lectin pathway.
Either one of these distinct MOA (1, 2, 3 and 4) will elicit or modulate an immune, tolerance or inflammatory response [35,44,126]. It is also likely that all of these MOA can occur at the same time and for each glycan (depending on the concentration and food kinetics).

Moreover, all of these MOA are modulated by HBGAs, as the principal glycoform ubiquitously present in humans. The HBGAs can interfere in the binding of endogenous lectins to antigens, so that ABO blood group can differentiate individuals and their reactivity towards any glycan or lectin [104,106]. The presence of a particular blood group glycan can modify the glycan reactivity of cell surface glycoconjugates towards human GBPs (PRRs) or towards GBPs of animal, vegetable (food) or microbial origin [107]. Therefore, the HBGAs epitopes of glycans on glycoproteins/glycolipids generate specific recognition epitopes [106]. The formation of multivalent interactions between glycoproteins/glycolipids and clustered surface glycans is favored in lipid rafts [36]. This contributes to special plasma membrane architecture and peculiar cellular properties, typical of each ABO phenotype [127].

These ABO-mediated changes in membrane topology can explain the several pathophysiologic differences between various blood groups [128]. ABO blood type has been linked to a number of diseases, including cancer and musculoskeletal diseases [92]. For example, blood group A was confirmed by several studies to be associated with elevated risk of gastric cancer, while blood group O with lower risk of pancreatic cancer [129]. These differences may be due to the presence of different ABO glycans. As a consequence, specific PCI or CCI with ABO glycoptopes are primarily responsible for mechanisms of self or non-self-discrimination of our innate and adaptive immune system [130]. Xeno-determinants can finally be recognised as self or non-self-depending fundamentally on the resemblance to ABO glycoforms.

The MOA 1 and 2, involving the interaction between food glycans and human lectins and glycoconjugates, can occur also on other cells once they are passing the intestinal barrier. As glycoconjugates are abundant in food items, the density and concentration of these glycans reaches a considerable amount. There is increasing evidence that even low concentrations of these glycans are enough to reach signaling threshold and initiate numerous biological processes [29].

MOA 1: The undigested oligoglycans (for example HBGAs-like moieties found in food, xenoantigens) form high affinity PCI with soluble (galectins) or membrane-bound human lectins (PRRs) [90,131]. The interaction will impose morphodynamic changes to the transmembrane proteins in the lipid rafts and evoke a biochemical response [132]. Food glycans can interact with mono-, di- or polyvalent human lectins, such as ABO specific GBPs, through PCI, which may be multivalent to further increase the affinity by several orders of magnitude or CCI [7,114,133]. Galectin-4 or -8, may bind to and cross-link multivalent glycoproteins and glycolipids on the cell surface in appropriately formed lipid rafts, leading to formation of microdomains and lattices that initiate signal specific pathways [64,134]. High affinity ligands to selectins, antibodies, and other types of GBPs [105,135,136], are favored by the presence uncommon conformations of glycans in HBGAs enhanced clustered saccharide patches. Such GBPs (sigslecs and galectins) play critical roles in diverse cellular functions such as cell adhesion, signal transduction and immune response [137]. Galectins for example have been established as important regulators of innate and cell-mediated immune homeostasis, inflammation, malignancy, and autoimmune disease [138].

MOA 2: After the first putative multivalent CCI was hypothesized, several studies demonstrated the existence, ubiquity, polyvalent self-interaction/recognition and strength through multimerization or glycocide cluster effect of such interactions [31,61,101,134,139-148]. In this MOA, the binding occurs with a high-affinity PCI and with low affinity CCI [149]. Once PCI or CCI between glycans and surface receptors are established, the formation of special cross-linking between GBPs and glycoproteins, called lattices, may be favored or impeded depending on the particular functional and spatial conformation of the membrane lipid rafts [60].

Lipid rafts are glycolipid enriched domains that function as a signaling compartment in the plasma membrane [63]. Several glycoproteins in these lipid micro domains display clear signal modulated interaction (glycosylation dependent signal transduction) by the glycans of glycolipids, via ultralow affinity but multivalent CCI [31,53,61,150]. The nanoscale heterogeneity of the lipid rafts is functionalized to larger levels by lipid- and/or protein-mediated activation events (e.g., multivalent ligand binding of glycans between glycolipids and glycoproteins) [33]. The discrimination between self and nonself (on the basis of glycan determinants) can be accomplished by AGAs and GBPs of the innate immune system [79]. But this depends on what is recognized as self therefore essentially on what resembles the ubiquitous HBGA [11].

MOA 3: This MOA has been amply documented and reviewed elsewhere and will be just briskly discussed [11,124]. The importance of the intestinal microflora in health cannot be overstated [151]. As it is known that dietary fibers allows for a more diversified gut microbiota which is beneficial for the host, glycans are hardly ever deemed important or spelled out. Of course, they could not have been considered as they were practically unknown to the nutritional community [152].

MOA 3a: Briefly, the structural and chemical variability of glycans is so great that a vast gene pool is required to encode for enzymes capable of degrading the diverse glycans. SCFAs have been linked to a vast array of beneficial effects. An association between cellular metabolism (a major energy source for intestinal cells), SCFAs, and transcriptional regulation (with consequential immune modulation) has recently been established [153].

MOA 3b: Microbes are known to adhere to biological surfaces, including the surface of human cells, through PCI and CCI [154]. Since the main glycan structure in the human body is the HBGA glycoform, microbes have high affinity to each individual’s ABO glycohenotype. Indeed, recent findings strongly suggest HBGA are an important factor modulating the intestinal microbial composition [11,94]. There is hence an alignment between the host ABO phenotype and the HBGA expressing bacteria (microbiome) [155]. Actually, human gut microbiota degrades both dietary and host glycans with the use of carbohydrate active enzymes (CAZymes) [156]. Those that are better suited to attach to a particular ABO phenotype will have the advantage to better feed on host glycans for carbon and energy [94,157].

Diet (in the form of the types of glycans present in foods) shapes gut microbes and affects their composition and function, impacting host-microbe interactions [11,158]. The ingestion of the wrong glycans may favour pathogens, or incorrectly ABO-aligned microorganisms, thus resulting in dysbiosis (with deleterious effects) [159]. Dysbiosis will negatively affect health.
MOA 4a: Although there is a myriad of AGA present in human serum, their generation and function are not well understood [125]. Normally, healthy humans harbor sets of AGA to blood group-, xeno-(heterophil), and infection-related glycotopes [160]. If, after presentation by the appropriate APC, an AGA recognizes a presented food glycan to be molecularly similar to a non-self (xeno) antigen, the AGA will react and elicit an immune response. CCDS have been observed between environmental and food allergens through high levels of IgE AGA [161]. For example, there are circulating AGA in healthy humans against N-glycoly neuraminic acid (Neu5Gc) and galactose alpha-1,3-galactose (α-gal), glycans present in dairy products and red meats [162].

MOA 4b: A further intriguing possibility not mentioned before is the interaction with the complement proteins (thus, directly with the innate immune system). The complement is a complex network of plasma proteins, present in the blood, but also in other body fluids, and is an integral part of the innate immune system [163]. The lectin pathway is one of the three modes of activation of the complement and proceeds through pattern recognition of glycans by serine protease lectins [164]. The lectin pathway uses mannose-binding lectin (MBL), ficolins (ficolin-1, -2 and -3) as well as collectin-10 and -11 (all lectins), as initiator molecules to recognize glycans DAMPs and PAMPs [165]. Fucolins and collectins act as PRRs forming complexes with MBL-associated serine proteases (MASPs) to initiate complement activation and display different and diverse specificities in their binding to ligand (glycans) [166]. Given that diverse glycan can exhibit molecular mimicry to resemble host glycans, it is chemically feasible that these AGA will react and elicit an immune response. CCDs have been confirmed

Notably, an association between the increased inflammatory processes is not meant to substitute the previously verified food glycan structures responsible for inflammatory and immunogenic responses [43,44]. It has been shown that food glycans can cause inflammation or immune-mediated responses based on ABO typology, as recommended by the BTD [34,59]. Given the multifaceted biochemical activities of the ubiquitous glycans, their chemistry and biology, following BTD may help reduce the sources of inflammation [11,176]. As a consequence of continuous ingestion of non ABO aligned glycans, chronic inflammation could develop by any of the mentioned MOA and persist leading to accelerated aging [169].

Because of the various specificities between lectins and the myriad different glycans (interactions between proteins and glycolipid complexes glycolipids and glycolipids, and glycolipids and other carbohydrate complexes), it is not astonishing that the role of food glycans has been missed until now [135,144]. The dearth of information concerning glycans and their presence in food is due essentially to the lack of access to glycans, the poor throughput of traditional assays and the challenges of profiling of AGA [125]. Studies in this field are poised to accelerate greatly due to the availability of high throughput and high-content technologies such as the multiplex glycan bead array (MGBA) [137]. As we progress through technical advances (biophysical approaches), we will be able to create new methods to distinguish subtle differences of microdomains and thus find new PCI and CCI between glycosyl epitopes on glycoproteins and glycolipids [61].

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Competing Interests

The authors declare no competing interests.

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Page 9


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