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ABO Blood Type-Food Relationship: The Mechanism of Interaction between Food and Human Glycans

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Abstract

A recent scientific review of literature has highlighted the importance of novel actors in nutritional science. Among these glycans have come to the forefront due to recent advances in glycobiology and glycochemistry. Moreover, the epidemiologic, diagnostic (case reports and case series) and literature (expert opinions) data regarding blood type diets (BTD) have been closely associated with glycans. Indeed the presence of oligoglycans in all food sources has been confirmed. These special carbohydrates are present in the form of glycoconjugates (glycoproteins or glycolipids) in and on the surface of all the cells (glycocalyx) of all organisms that we eat. During digestion they remain intact through the GI tract as we lack the enzymatic repertoire of the human body to unbind their particular linkages. The oligoglycans, which should not be confused with normal fibres, are then either absorbed in the bloodstream, where they are recognized by the immune system, or interact with the surface of GI epithelial cells. The result is that through protein-carbohydrate interactions (PCI) or through carbohydrate-carbohydrate interactions (CCI), dietary glycans can generate 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), ABO antigens impose morphic changes in the spatial distribution of the glycans on the glycocalyx (lipid rafts and clustered saccharide patches). Dietary glycans can hence interact with human lectins and glycoproteins through PCI and CCI in and ABO dependent manner, thus, eliciting contrasting responses. Glycobiology and glycochemistry have paved the way to understand the biochemical interactions between glycans and human lectins on different ABO type cell glycocalyx.

Keywords: Glycan; ABO Blood Group; Clustered Saccharide Patches; ABO Antigens; Glycotopes; Food Antigens; Glycobiology; Lipid Rafts

Abbreviations

ABH: A, B, O (or H) and AB Blood Type; ABO: A, B, O and AB Blood Type; APC: Antigen-Presenting Cells; CBP: Carbohydrate Binding Proteins; CCD: Cross-Reactive Carbohydrate Determinants; CCI: Carbohydrate-Carbohydrate Interactions; CFG: Consortium of Functional Glycomics; CRD: Carbohydrate-Recognizing Domains; ECM: Extracellular Matrix; EGFR: Epithelial Growth Factor Receptor; FHS: Food Hypersensitivity; FOS: Fructooligosaccharides; GAG: Glycosaminoglycans; GBP: Glycan-Binding Proteins; GEM: Glycolipid-Enriched Membrane; GOS: Galactooligosaccharides; GPI: Glycosylphosphatidylinositol; GSL: Glycoshingolipids; HBGA: Histo-Blood Group Antigens; HMO: Human Milk Oligosaccharides; IgX: Immunoglobulin A, E, G, and M; Le: Lewis Blood Type; PCI: Protein-Carbohydrate Interactions; PG: Proteoglycan; PPI: Protein-Protein Interactions; PRR: Pattern Recognition Receptors; Sias: Sialic Acids.

Introduction

Historically and traditionally, nutritional sciences have concentrated on the major classes of macronutrients and micronutrients to define food composition, quality and human nutritional requirements [1]. The carbohydrates class of macronutrients is generally divided into simple (short chains), complex (long chains of essentially glucose) and fibers (tough or not easily digestible sugars) [2]. Most of the attention concerning fibers (either soluble or insoluble

non digestible carbohydrates) has been on their principal role as bulking agents in laxation the regularization of intestinal transit and as food for our gut microbiota [3].

But recently, in the last 30 or 40 years, new sciences have emerged (glycobiology, glycomics and glycochemistry), which have profoundly changed our view of the role of small or long chains of non-digestible carbohydrates, called glycans, in cellular biology [4].

On account of the vast literature accumulated in the last decades concerning these new sciences [5-7], a new paradigm has emerged where food glycans may contribute extensively to our health. On this regard, a recent article has been published highlighting the interactions between food glycans and endogenous lectins [8].

Even more interestingly, it has been hinted that glycans are linked to the histo-blood group antigens (HBGA) so intimately that this phenomenon may explain the success of blood type diets (BTD). The BTD essentially correlates together one's blood phenotype and the kind of food that one should eat [9]. As it was first proposed by D'Adamo in 1996, eating foods that are compatible with one's blood type will have beneficial effects on the body which are not limited to reducing body weight [9,10].

Around the world the BTD has been met with mixed reactions by the general public and researchers or scientists, Some have experimented successfully with it [11,12], while others have criticized its results, depending on the outcome they measured [13]. Whatever the case, there is a fundamental mechanism that links BTD with health effects that has recently been uncovered: the ubiquitous glycans.

This brief review shall elucidate such mechanism with state-of-the-art scientific and literature knowledge.

Glycan Interactions

Glycans

Glycans are carbohydrate structures composed of various saccharide molecules [14]. Particularly, it is important to consider the structure of glycans. Essentially, glycans encompass all forms of carbohydrates but their multifaceted branching and linkage type make them quite ambiguous to define [15]. Glycans that are under contention here are oligosaccharides in the form of N- and O-linked glycans, and free (unbound) of similar structure.

If we do not consider the most abundant biopolymers in nature (cellulose, chitin and glycosaminoglycans [GAG]), we are left with N-glycans, O-glycans, and glycosphingolipids [16]. While the major sources of carbohydrates in nature are dimers or other higher polymers of glucose (sucrose, trehalose and starches) with α-glycosidic linkages [17,18], glycans are oligomers of different monosaccharides, often linked with β-glycosidic bonds [19].

Glycans are stereochemically-complex biomolecules [20]. Because of their unique chemical properties, glycans have unsurpassed structural variability and changeability beyond their simple linear sequence [21]. The frequent occurrences of branching and site-specific modifications [22,23], allow to behave biochemically in several different ways [24]. Apart from heterogeneity, another extraordinary property of glycans is their multivalency. Multivalency is the capacity of multiple glycans to enhance binding affinity and specificity with their relevant ligands [25]. The effect of glycan-specific multivalency is fundamental to understand the important roles glycoconjugates play in the innate immune response, adhesion, or receptor-mediated signal transduction events [26]. Polyvalency requires a special spatial distribution of glycans to interact with their ligands and is studied by glycomimetics [27]. Glycomimetics allows for the planning and synthesis of glycan mimicking molecules for therapeutic purposes [28]. In figure 1 the highly variable linkage points of galactose sugar residue are shown.

Figure 1: Galactose (Gal) [PubChem CID: 6036].

Carbohydrates can be divided into digestible and indigestible carbohydrates [29]. Indigestible carbohydrates, or non-digestible carbohydrates (NDC) include crude fiber, nonstarch polysac-

charide (NSP), soluble dietary fiber (SDF), insoluble dietary fiber (IDF), and resistant starch (RS) [30]. Sometimes, indigestible carbohydrates are equated to dietary fiber (DF). In this view, DF components are non-starch polysaccharides (NSP) and RS [31]. The main carbohydrates included in human diet are starches. RS are known to resist digestion in the upper GI tract [32]. RS are complex carbohydrates and polymers of glucose known to modify the composition of gut microbiota [33]. DF do not possess either α [1,4] or α [1,6] glycosidic bonds between glucose moieties and are hence not hydolysable by the human digestive enzymes [34]. DF or NDC can be metabolized only by the microbiota in the cecum and colon [35]. There are many types of DF but all are essentially carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes [36].

Glycans have in common with DF the non-hydrolizability of their glycosidic bonds. Indeed, glycans cannot be degraded by α-amylases (human digestion enzymes) [37]. This occurs both because of β- and α-glycosidic bonds with non-glucose sugar residues. Given the limited amount of glycoside hydrolases (GHs) and polysaccharide lyases (PLs) encoded by human genome, DF and glycans are not digestible [38]. Human GHs comprise enzymes capable of hydrolysing only, starch, lactose, maltose/trehalose (as dimers or trimers of glucose) and possibly chitin [39]. In figure 2, the differences between DF and glycans are visually reported.

Figure 2: Fibres and glycan antigens (graphing tool used is GlyTouCan Builder).

An example of the many different linkage points on a hexose sugar: a total of ten possible bonds.

The first three CFG notated structures represent starch (amylopectin, because of the branching, although the branching occurs every 20-30 residues of glucose [17], cellulose (linear like amylose but with β-glycosidic bonds) and galactooligosaccharide (GOS), respectively; while the last one is a N-glycan (more precisely a syalylLewis X terminal on a N-core glycan type II (all generated with GlyTouCan Builder, available at https://glytoucan.org/Structures/graphical, and notation taken from the Consortium of Functional Glycomics, available at www.functionalglycomics.org). The starch and fiber molecules are obviously longer in length [16] but have been shortened for easier display.

Lectins

Glycans are recognized by glycan-binding proteins (GBPs), also called lectins [40]. Lectins play a pivotal role in many different aspects of the physiology (as they are naturally present in the human body), including the immune defence [41]. This is accomplished through their ability to decipher glycan-containing information into a myriad of cellular responses [42].

Lectins are carbohydrate-specific reagents and biological recognition molecules [43]. Lectins are ubiquitous (in nature) carbohydrate binding proteins (CBP) [44]. GBPs may contain multiple carbohydrate-binding sites (or domains, CBD, that is, are di- or polyvalent) [45,46]. GBPs preferentially recognize (through their carbohydrate-recognizing domains [CRD]) carbohydrate complexes protruding from glycolipids and glycoproteins, or present on the ECM, binding to them with low affinity protein: carbohydrate interactions (PCI, usually in the mM range) [47]. The CBPs on GBPs typically accommodate glycan ligand motifs made up to a tetrasaccharide in size [19].

As shown in figure 3, many glycans with different structural motifs can still react with high affinity with human lectins. In table 1, some of the antigens on the glycan array that have been evidenced as high affinity ligands, are listed with the IUPAC nomenclature to define their molecular composition.

Graphical representation of the results of a lectin-glycan binding test using a glycan array (PA_v5). As evident, many glycans linked to the glycan array react strongly (high affinity) with Galectin-3, a few of which are structurally reported in Table 1. All glycans, with PCI signal above 250, are considered as having high affinity.

A lectin-glycan binding test (Glycan-GBP Interaction Core (H) Data) using a glycan array (PA_v5) was performed on a human GBP

Description of the glycan epitope	Signal	SEM(PA)
Galb1-4GlcNAcb1-3Galb1-4GlcNAcb1-3Galb1-4GlcNAcb?#Sp0	637.8807	32.587845
GlcNAcb1-3Galb1-4GlcNAcb1-3Galb1-4GlcNAcb#Sp0	626.43225	41.02542
Fuca1-2Galb1-4GlcNAcb1-3Galb1-4GlcNAcb1-3Galb1-4Gl cNAcb#Sp0	623.521	27.160454
Gala1-3(Fuca1-2)Galb1-4GlcNAcb#-Sp0	585.3492	22.520658
Fuca1-2(GalNAca1-3)Galb1-4GlcNAcb1-3Galb1-4GlcNAcb 1-3Galb1-4GlcNAcb?#sp0	503.503	18.691166
Fuca1-3(Fuca1-2(GalNAca1-3)Galb1-4)GlcNAcb1-3GalNA c??#sp14	464.44864	14.128436
GlcNAcb1-3Galb1-4GlcNAcb1-3Galb1-4GlcNAcb1-3GalNAc a?#sp14	397.36057	23.452572

Table 1: Primary Screen Data extract for human Galectin-3 micro array (cfg_rRequest_2564).

Figure 3: Galectin-3 glycan binding specificities (taken from CFG website: cfg_rRequest_2564).

molecule (Galectin-3), according to protocol cfgPTC_242 (and publicly available at http://www.functionalglycomics.org). The table represents some of the high affinity ligands (with signal greater than 250) for the human protein galectin-3, showing different glycans have similar binding strengths. #Sp indicates the linkage point of the glycan on the microarray. The diversity of the first two or three sugar residues of each glycan should be noted, including the various glycosidic linkages (a1-3 or b1-4) between each saccharide: notwithstanding this heterogeneity (indeed microheterogeneity [48] all glycans react strongly with the given lectin.

Glycan sites

Every cell's surface is literally coated with carbohydrates in the form of glycoproteins, with oligosaccharides (sugar residues), proteoglycans, with polysaccharides, and glycolipids (as one of the two main forms of glycoconjugates) [49]. This structure is called the glycocalyx and is responsible for a vast number of biological functions [50]. Among the various functions are cellular and self or non-self-recognition, to signalling or immune regulation and homeostasis [48].

Moreover, the outer layer glycocalyx interacts with the extracellular matrix (ECM) [51,52]. The ECM is a meshwork of fibres composed primarily of glycosaminoglycans (GAGs, such as heparin, heparan sulphates, chondroitin sulphates and hyaluronan) and proteoglycans (PG, such as, syndecans and glypicans, among many) [53,54]. With this plethora of interconnections, the ECM has many yet undiscovered properties of inter- and intracellular signalling regulation and functions [55,56].

There is evidence for a myriad of roles for lectin-carbohydrate interactions [44]. Important functions include intracellular signalling pathways that regulate the immune response [57,58], and modulating roles in many different biological processes [59]. Overall, these roles suggest that lectins and sugars mediate their effects through non-redundant pathways [60]. Moreover, multivalent binding between carbohydrate and proteins increases the avidity of cell signalling, molecular recognition and inflammations [61].

Furthermore, cell membranes are starred with glycoshingolipids (GSL), which maintain their fluidity and freedom of movement [62-64]. Consequently, glycans, glycolipids and GPI (glycosylphosphatidylinositol) proteins are free to move and reorganize spatially on the membrane [65]. GSL can reorganize (or self-associate) themselves spatially on the cell surface through protein-carbohydrate interactions (PCI) or carbohydrate-carbohydrate interactions (CCI) to form 'lipid rafts' [66]. Lipid rafts are indeed are glycolipid-enriched membrane microdomains of submicron length [67]. Many proteins with raft affinity are all heavily glycosylated [24]. These proteins can laterally segregate in fluctuating nanoscale assemblies (membrane subcompartmentalization) of sphingolipid, cholesterol, and proteins [68,69].

Lipid rafts, although fiercely contested [62], consist of clusters of structural proteins, enzymes, and signalling receptors, among other protein types, regulate several biological functions [70].

Events such as lateral diffusion of membrane proteins and lipids, adherence to the extracellular matrix [71], and signalling events are just a few of the many different biological roles covered by lipid rafts [72]. Such rafts could play an important role in many cellular processes including in the immune system [73]. These signalling platforms are essential to immune-mediated signal transduction, membrane trafficking, cytoskeletal organization, and pathogen entry [74,75].

An example of a lipid raft in formation is shown in figure 4.

Figure 4: Formation of a Lipid Raft [8].

The formation of a lipid raft is effected by the presence of glycans that interact with other carbohydrate moieties on glycolipids and glycoproteins. Glycoproteins move and coalesce into microdomains where they are able to interact differentially with other glycoproteins or glycolipids based on the particular HBGA epitopes that are constitutionally present.

Moreover, special immune lectins, galectins, may bind to and cross-link multivalent glycoproteins and glycolipids on the cell surface in appropriately formed lipid rafts [76]. Galectins therefore are not evenly distributed within the glycocalyx but are gathered in patches [77]. This phenomenon may lead to formation of stable microdomains and lattices that initiate signal specific pathways [78,79].

The formation of these lipid raft assemblies is known to be responsible for initiating many signal transduction pathways, including those for immune cell activation [80]. Finally, the glycocalyx and lipid rafts have emerged as an important participant in modulating inflammation, infection and other immune or allergic processes [73,81-83].

ABO epitopes

The characteristics of glycans as just discussed in intimately linked to the ABO blood group system. This is because the ABO group determinants are glycans [84]. The ABO blood group is the most important blood group system in transfusion and transplantation medicine [85,86]. The A, B, O blood group systems were first described by Karl Landsteiner in 1900 and the AB blood group was later described by Von Decastallo and Sturli in 1902 [87]. As glycans, the ABO epitopes star glycoconjugates on and inside the cell membrane. Indeed, the human ABO blood group antigens, are complex terminal glycan structures present on glycolipids and glycoproteins [88]. ABO phenotype glycans are not found just on red blood cells but occur also on both cell surfaces and plasma protein [89]. Blood group antigens are alloantigens in humans, and are present not just in blood or plasma, but also on epithelial cells [87]. Furthermore, ABO glycotopes are found expressed on glycolipids, glycoproteins, and mucins of the GI tract [90]. Actually, they are expressed on cell surface GSL or glycoproteins of a variety of other human cells and tissues (e.g. bronchopulmonary, skin and urogenital epithelial cells, neurons and vascular endothelium), and in various body fluids and secretions [86,91-95]. Such expression is also dependent on secretor status of the individual [96].

The ABO blood group system comprises 4 blood groups: O (or H), A, B and AB [87]. Three variant alleles (A, B, and O or H) of a single gene on chromosome region 9q34.2, the ABO gene, determine a person's blood type by encoding two glycosyltransferases (GT) with different substrate specificities [97]. The ABO gene is located on chromosome 9 and has three alleles consisting of 7 exones distributed over 18 kb of genomic DNA [98]. Blood group A and B GT (ATs and BTs), encoded by ABO gene (A and B are codominant alleles, while O is recessive), transfer an N-acetyl-d-galactosamine (GalNAc) and a d-galactose (Gal) to the same acceptor substrate H substance [94,99]. The acceptor substrate (H antigen: Fuc alpha 1–2 galactose) remains without further modification because the transferase encoded by the O allele is non-functional [100]. Hence, the ABH antigens are not primary gene products but they are the enzymatic reaction products of GT enzymes [101]. There is also a very rare genetic polymorphism, named Hh, allowing for a lack of H antigen: these individuals are known as hh or Oh or Bombay type [102].

The ABO system results from polymorphism of the terminal ends of complex carbohydrate structures (type 1 or lacto [Galβ1-3GlcNAc] and type 2 or neolacto [Galβ1-4GlcNAc] core chains) of glycoproteins and glycolipids [86,91], as shown in figure 5.

Figure 5: Blood group antigen type I [developed with GlyTouCan Builder].

The Type I glycan unit structure, as shown here and in subsequent figures, is exemplified by β1-3 glycosidic bonds, different with respect to type II chains (LacNAc) which form β1-4 glycosidic linkages with a terminal GlcNAc [36].

These are likely to explain the many studies on associations between ABO blood group and various types of disease from neoplastic to cardiovascular disorders [95,103]. Such diseases include several cancer types [86,104,105], peripheral artery disease [106], thrombotic vascular disease [93], coronary heart disease [107], peptic and duodenal ulcers [108], among a wide array of other human diseases [94].

Many more studies highlighted the possible influence of the ABO blood group on the severity of several infections, including but not limited to:

- Schistosomiasis or bilharzia [109],
- Malaria [110],
- Rotavirus type A, B and C [111],
- Dengue virus [112],
- Urinary tract infection [113].

These associations have been given scientific validation through extensive research in infectious disease, tumor immunology, and membrane chemistry [101]. Furthermore, it has been known for quite some time the existence of a modulatory role of ABO blood group antigens on several inflammatory and adhesion molecules [104], receptor ligand interactions [110]. Indeed, a close link has been found between ABO antigens and systemic inflammation response modulating inflammatory markers, including tumor necrosis factor-alpha (TNF-α) and soluble intercellular adhesion molecule-1 (sICAM-1) [103].

Well-documented association between the distribution of ABO blood group antigens and plasma Von Willebrand factor (VWF) and coagulation factor VIII (FVIII) levels have been recognized [92,104]. This may result from the influence of ABO on the life-span of vWF due to ABO-modified N- and O-glycans on the vWF protein [107]. Indeed, plasma levels of vWF are approximately 25% to30% lower in group O subjects than in non-O individuals [93].

Although the exact mechanisms of the reported associations between blood group antigens and disease, are yet to be fully elucidated what is currently known provides some intriguing clues [101]. Nevertheless, the ABO blood types remain important self-antigens with vast implications in immune tolerance [114].

Histo Blood Group Antigens

The ABO blood group is intimately linked to another blood group of carbohydrate origin: the Lewis (Le/le) blood type [115]. The H/h, ABO and Lewis epitopes form the human HBGA [116,117]. The secretor phenotype (the ability to secrete A, B and H antigens into body fluids, like sweat, semen and also saliva) is determined by the fucosyltransferase 2 enzyme (FUT2), encoded by Se/se gene [105,118]. Serologically, Lewis status (Le/le) is defined by the expression of two main antigens as a result of the activity of the FUT3 enzyme: Le^a and Le^b in a type I chain and Lex and Le y in a type 2 chain [119]. Therefore, the following Lewis phenotypes are possible: the non secretor Le(a+b-) [or Le^a, Le and se/se], the secret or Le(a-b+) [or Le^b, Le and either Se/Se or Se/se] and the Lewis negative Le(a-b-) [le and Se/Se, se/se or Se/se] [101,120]. An individual can be a secretor (Se) or a nonsecretor (se) independently to its ABO or Lewis blood classification [121]. FUT2 is the key enzyme to initiate the secret or pathway [117]. Figure 6 shows a few Lewis antigens and their similarities with ABH: the additional fucose in α1-4 (in type 1 chains) or α1-3 (in type 2 chains) linked to GlcNAc, distinguishes the Lewis from ABO antigens.

Figure 6: Similitude between Lewis and ABH Blood group antigens.

All of the above antigen are Lewis determinants (from left to right) [122]: first line includes Lewis Y (structurally similar to H antigen but with the GlcNAc fucosylated in α1-3), B Lewis Y (similar to the B determinant); second line Lewis X (precursor of Lewis Y), A Lewis Y (similar to A antigen), third line Lewis A (precursor of Lewis B), B Lewis B (similar to B antigen), fourth line Lewis B (similar to H antigen with the additional fucosyl group on the GlcNAc residue), and A Lewis A (similar to A antigen). First two lines are Type 2 chains, last two lines are Type 1 chains.

Indeed, apart from red blood cells, the ABO and Lewis glycotopes (HBGA) are highly expressed on platelets, leukocytes, plasma proteins and on the surface of epithelial cells of the gastrointestinal [123], bronchopulmonary, and urogenital tracts and bodily secretions [101,124].

HBGAs are bound to glycolipids (GSL [123]) and glycoproteins alike [124].

HBGA are recognized and bound by microorganisms such as

- Vibrio cholerae, Pseudomonas aeruginosa and Escherichia coli [125],
- Human norovirus [117],
- Rotavirus [126],
- Lagovirus [127],
- Candida albicans [124],
- Helicobacter pylori [128]
- Agents causing other infectious diseases [129].

There are of course other blood group systems identified for a total of 32 [113]. But the only other carbohydrate antigen systems (also closely linked to ABH and Lewis) are the Forssman and the globo series (P antigens, I or Li, and Globoside) [101]. All others are non-carbohydrate-based antigens, i.e., enzymes or proteins [130]. These other five blood glycan antigen are linked essentially only to glycolipids especially GSL and have rare polymorphism [131]. The most common phenotypes are P1 and P2, always include the P antigen (Gb4 or Globoside) and paragloboside which can both be extended to manifest ABO glycans [132]. The Forssman glycolipid synthases (FSs), isogloboside 3 synthases, and α1,3-galactosyltransferases of the α1,3-Gal (NAc) transferase family are encoded by closely ABO-related *GBGT1, A3GALT2,* and *GGTA1* genes, respectively [99]. All these antigens, being found on GSL, can be further elongated to form ABO like terminals which may be fundamental for lipid raft formation [122,131,133].

ABH antigens can modulate cellular interactions without being a direct ligand themselves [134]. ABO glycotopes can stabilize other glycans on the fluid cell surface in clusters (called "clustered saccharide patches", as closely spaced oligosaccharides) thereby making them more (or less) accessible to relevant GBPs [135]. The stabilizing effect of these clusters is exerted by ABH blood group antigens through CCI with other glycans, forced into unusual conformations, without being directly involved or being the primary target of GBPs [136]. Hence, diverse glycans can differentially be recognized by GBPs given the special spatial conformation (clustered saccharide patches) facilitated by ABH determinants [137].

Food and microbiota

Causative agents such as haptens (non-immunogenic compounds that form active complexes with an immunogenic carrier) are deemed as one of the most important risk factors related to the impact of food on the body [138]. In literature, epitopes and hap-

tens are always implicitly assumed to exclusively consist of amino acids, but glycan epitopes and classical haptens are important antibody binding epitopes [139-142].

Carbohydrate structures of various plant foods are source of immunological cross-reaction between allergens [143,144]. Most are in the form of glycoconjugate N-linked carbohydrates [106], called cross-reactive carbohydrate determinants (CCD) [145,146]. Others have oligomannosidic, hybrid or complex type structures, and display immunomodulatory, very weak allergic [103] or non-allergenic immunogenic properties [147,148]. These glycans can either be in free (unlinked) form [108] or be present on glycoconjugates such as (glyco)protein allergens [142,149].

Moreover, most food antigens possess carbohydrate moieties similar to HBGA [150,151]. HBGA are known to be displayed on glycoproteins and glycolipids in diverse food sources such as oysters, clams, fruits and vegetables, including lettuce [152-154]. It is also likely that glycans similar but not identical to HBGA, herewith called HBGA-like, may display phisico-chemical and biological properties akin to HBGA [155-157]. Since ABO specific antibodies are present in humans [114,158], it is also highly likely that HBGA-like epitopes in food may trigger unspecified immune responses.

ABO and Lewis (HBGA) epitopes expressed in the GI tract actually shape the composition of gut microbiota [159]. Being expressed on intestinal epithelial cells (IECs), the ABO glycans are potential receptors for non-pathogenic and pathogenic microorganisms influencing immune responses [95]. Virus also can differentially recognize HBGA displayed on IECs and on mucins in secretor individuals [160]. Human gut microbiota has developed elaborate, variable and sophisticated systems for the sensing, capture and utilisation of host and dietary glycans [2]. Indeed host and dietary glycans serve as food source for intestinal bacteria [161]. Some gut bacteria can take up only a narrow range of glycan species, whereas others can digest many different complex glycans [162]. This occurs because of the specificity of the GHs and PLs produced by each bacteria's genome [163]. Hence, survival of microbiota members from diverse genera depends on their ability to degrade host and dietary glycans that cannot be metabolised by the host [164]. Host glycobiology therefore affects gut microbial composition as microbes being adapted to use HBGAs differentially as a nutrient [165,166]. As earlier introduced, non-digestible complex polysaccharides and dietary glycans are key determinants of microbial populations in the colon [167]. Consequently, elaborate interactions form between dietary glycans, the host, and gut microbes that vary broadly in the types of glycans intestinal bacteria are capable of metabolizing [168].

The human gut microbiota is so important to health and disease that is sometimes referred to as an 'organ' as it performs functions analogous to systemic tissues [2]. The commensal bacteria play relevant roles in host physiology and the imbalances in its composition, referred to as dysbiosis, have been linked to certain disease conditions [160]. Altered gut microbiota ("dysbiosis"), often containing enteropathogens, triggers a subclinical constellation of intestinal pathologies from inflammation to increased risk of lifelong co-morbidities [169]. A symbiotic gut microbiota may be important in determining cardiovascular disease risk [170]. Indeed, our microbiota has been linked to intestinal health, immune function, and to complex disease phenotypes such as obesity and insulin resistance [171].

The same strategies of cell-adhesion are also used by pathogens like trans-species O-GalNAc glycosylation of the parasite's proteins [172]. Infectious agents can bind host glycans with their lipopolysaccharide surface glycans through CCI [173]. Pathogenic invasion of the host's enteric environment may then contribute to continuous dysbiosis, which leads to a cycle of increased risk in cognitive impairment, type 2 diabetes, and cardiovascular diseases [169]. This underlines important role of commensal bacteria in the gut barrier integrity (tight junctions), by modulating inflammation and metabolic functions [174]. Gut dysbiosis and altered intestinal barrier integrity may be further to anxiety and depressive disorders [175].

Hence, the human gut microbiota plays a central role in glycobiology and in the influence of glycans on health and innumerable diseases.

The mechanism

Since the presence of glycans on proteins is believed to fine-tune the function of the protein [130], ABO distinctive antigens can easily be foundational in modulating the glycoconjugate's function.

A first theoretical framework of BTD was based on the beneficial or detrimental effects of lectins in foods, based on one's ABO type [9,10].

The original mechanism for the ABO-food relationship focused on the presence of lectins in foods, being widely distributed in

plants [176]. These are generally very resistant to heat and digestion [177]. Dietary lectins act as GBP which identify to specific epitopes on surface glycoproteins (or glycolipids) on the glycocalyx of several cell types including erythrocytes or lymphocytes [178].

Several GBPs are present in nature and have been recovered in diverse food sources, and are widely distributed among plants and animals [179].

There are several reasons why the classical mechanism of ABO-food interaction has been proposed as being originated from food lectins [180].

1. Many lectins present in the diet resist heat and digestion, at least partially [47, 181] (and remain in active form throughout the colon being recovered in the faeces of animals and humans [182-185];
2. These lectins can resolve various glycoforms with different degrees of avidity, through the standard PCI [122, 186,187];
3. The lectin showed polyvalent behaviour (the glycoside cluster effect, both multiantennary or simple and high-density polyvalent or complex) [188,189];
4. The binding of lectins is inhibited by most high-density polyvalent oligosaccharides-containing glycoproteins and their cryptoforms, masked by similar sugar residues such as HBGA or sialic acids [119].

While this explanation is capable of explaining local enteric inflammation and toxicity [178,183], it is nevertheless incomplete. Since lectins are proteins, it can be quickly advanced the critique that proteins are digested, even incompletely, thus loosing their glycan binding capacity.

A novel mechanism is required.

The interaction

The novel mechanism proposed involves the presence and action of oligomeric sugar moieties present on the glycoconjugates of the various food items [8]. Given the incommensurable intricacy of the immune system, the present is an incomplete, fragmentary and imperfect exposition of the evidenced pathways of dietary glycan interactions.

These special oligoglycans, free or as glycoconjugates inside and on the surface of all the cells of all foodstuffs remain intact through the GI tract [143]. Since we lack the enzymatic repertoire to unbind their particular linkages [164,190], they cross the whole GI tract up to the colon, if not uptaken. Indeed, humans enzymes are capable of degrading only a few glycosidic linkages present in a subset of carbohydrates, the digestible carbohydrates [34]. The oligoglycans should not be confused with normal fibres although they share the same type of beta glycosidic bonds [191]. These NDC can then be broken down through colonic bacterial fermentation to form beneficial short chain fatty acids (SCFA) [35].

And/or NDC/glycans are then either cross the intestinal barrier through tight junctions (TJ) [174] or come in contact intact (undigested) with intraepithelial T cells (IETs) or dendritic cells (DC) [192]. Materials can pass through the luminal side of the intestinal barrier either through cell membranes of IECs or the transcellular and paracellular spaces between them (TJ) [193]. Permselective, active transport of nutrients across the TJ is regulated by inflammation or SCFA produced by beneficial bacteria [194]. Thus, glycans enter the bloodstream, as much larger molecules can in dysbiotic or inflammatory conditions [195-197]. Once in the blood (through the portal vein [198]) bypassing TJs [175], they can be recognized by lectins of the immune system (galectins, selectins etc.) [42, 135,199,200]. On the one hand, IETs have appropriate receptors that recognize glycans and generate responses to such antigens [201]. Responses include the production of highly specific immunoglobulin A (IgA) antibodies against bacterial glycans [202]. Moreover, commensal microbes, through SCFA, can shape the mucosal immune system by regulating several types of T cells [203]. The gut normally produces gram quantities of IgA, which is presumed to protect the gut from pathogen attack [204]. IgAs have a remarkable capacity to recognise and bind several glycan motifs [205]. On the other hand, antigen presenting cells (APCs) such as DCs are capable of recognizing these antigens and initiated immunologic or immune tolerance reactions [144,148,206]. APCs possess lectin receptors which are potent antigen-uptake receptors with specificity for glycan structures [207]. Once glycans are recognized by these glycan-binding receptors on DCs, modulation of interferons and other cytokines occur to initiate immune responses [208]. Owing to their small size and to the sharing behaviour of mutualistic bacteria, glycans could be accessed by IECs and IETs [209]. This phenomenon is known to occur with xenoglycans (glycans that are extraneous to humans) being metabolically incorporated into human cells [210].

And/or glycans can interact with the surface of IECs, through PCI and CCI [173, 189], that is with glycans of glycoconjugates and

with polylactosamine-containing glycans, abundant at the ECM [211].

And/or oligoglycans can interact with the human lectins, such as galectins [42], soluble, immobilized on the ECM, and/or bound to the cell membranes of IECs or macrophages [212,213]. Galectins can trigger distinct signaling programs and modulating immune cell activation, differentiation, recruitment and survival and inflammation [42, 214]. Interestingly, there may be links between galectins, IgA and T cells for the maintenance of gut homeostasis [215]. Galectins are thus considered pleiotropic factors as they not only provide innate immunity with an arsenal against bacterial molecular mimicry, but are also regulators of a wide variety of biological processes [216]. Altogether, galectins function as glycan self/non-self recognition receptors and be effector factors in innate immunity, leading to glycan immune tolerance reactions [211,217].

Overall, these actions generate appropriate biochemical cascades that induce a tolerance or immune/inflammatory response, through various known mechanisms [58,122,218-221]. By keeping both the innate and the adaptive immunity challenged with dietary glycans, a continuous state of inflammation is perpetrated [214,222]. Dietary glycans may act as CCD, bringing about Ig mediated immune responses [223,224]. Continuous uptake of wrong dietary glycans may initiate chronic inflammation [225].

To this multifaceted picture (though still partial and piecemeal), ABO blood typology should now be added. Since the ABO epitopes have been encountered on all human cells, the different biotypology (A, AB, B, and O) impose morphic changes in the spatial distribution of the glycans on the glycocalyx [134,136]. Given their stereochemistry, glycans may form highly specialised and selective interactions that can play key roles in a wide variety of biological processes [20,173]. The resulting ABO-guided lipid rafts and clustered saccharide patches will interact differently through their CCI with food glycans, thus, eliciting contrasting responses [137,226]. Integrins are reorganized in these patches altering their activation state and influencing not only their ability to interact with ECM ligands but also their synergistic downstream signaling [52]. Glycobiology and glycochemistry have paved the way to understand the biochemical interactions between glycans and human lectins on different ABO type cell glycocalyx.

The restricted presentation of membrane-associated glycans is due to orientational constraints imposed on the glycolipid through its lateral interactions with other membrane lipids and proteins [123].

In sum, there is bountiful evidence that food glycans can interact consistently and in a preordained manner with endogenous lectins [8].

Food glycans (like all glycans) have special biochemical properties that allow them to manifest molecular mimicry (display of glycan motifs resembling host glycans [216]), with HBGA [227-229]. Dietary glycans can after ingestion interact with mono-, di- or polyvalent human lectins, such as ABO specific GBPs, through PCI or CCI [40,230].

Since galectins may bind to and cross-link with multivalent glycoproteins on the ECM [231], and glycoproteins and/or glycolipids on the cell surface in appropriately formed lipid rafts, leading to formation of microdomains, lattices or clustered arrays, dietary HBGA-like glycans may then evoke an inflammatory response [211,232,233].

Nevertheless, the result is the same: dietary glycans can cross the intestine barrier into the blood stream, as evidenced by food cross-reactivity and carbohydrate antibodies found in the blood [148,200,234,235].

Moreover, HBGA characteristics of the host (formerly ABO, but also Le/le and Se/se) influence microbiota composition [128]. The symbiotic relationship between ABO-differentiated microbiomes and the host regulate different homeostatic balances in these distinct individuals who require personalized interventions [159].

Wrong gut microbiota (dysbiosis) caused by ingestion of wrong HBGA glycans for that individual can alter the permeability of TJ and lead to unwarranted crossing of immunogenic materials triggering several disorders [8, 174].

This newly proposed mechanism is not meant to substitute the previously confirmed ABO-food interaction (food lectins binding to human glycoconjugates) but to be complementary to it and extend it.

Conclusions

As stated in a recent extensive review on glycobiology [48], nearly every disease process (mostly involving disordered inflammation and immunity), that affects humans and other animals, pertain to glycans.

It is not astonishing that glycans have emerged as central players in nutrition and health. Nor is it astounding that the role of dietary glycans, either free or linked to glycoconjugates, has been missed until now, due to their unmatched complexity. It is not enough to point to lectins as a possible mechanism for BTD. Only the ubiquitous presence, resiliency and uniquely varied biochemistry of glycans brought to the forefront by recent advances in glycobiology can aid explain BTD impact on society [8].

Science is homing into the definition of the exact mechanism for several food hypersensitivities and slowly it will be possible to isolate the specific food glycan structures. Moreover, the pathophysiology of dietary glycans responsible for CCI with HBGA and PCI with human lectins, is meant to be expanded and improved upon with newer technologies. Nevertheless, given the multiple systems involved in glycobiology, a more interdisciplinary approach is needed.

Dietary glycans can hence cause inflammation or immune-mediated responses based on ABO, Lewis and secretor typology and this explains the nature of BTD. It is also acknowledged that this alone is incapable of completely explaining all the varied responses to food (food hypersensitivities) that differentiates the blood type A from the O, the B or the AB [236-238]. Although this is definitely a good starting point.

As we progress through technical advances (biophysical approaches and combinatorial glycoarrays [239]), 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 [240]. The ultimate goal may be to identify the glycan motifs in food components responsible for eliciting ABO- or HBGA-differentiated immune and inflammatory responses.

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Ethics approval and consent to participate

Not applicable.

Consent to Publish

Not applicable.

Availability of Data and Materials

Not applicable. All materials are publicly available at the referenced online databases

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