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Recent Advances in Nutritional Sciences: An Overview of Glycans and miRNAs

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Abstract

There are many nutritional substances that humans consume on a daily basis: water, carbohydrates lipids and proteins are main biochemical components of food. But others in a smaller amount are vitamins minerals and enzymes. At a possibly lesser quantity are glycans and miRNAs. The presence of oligoglycans in all food sources has been an established fact for many years. These special carbohydrates are present as glycoconjugates (glycoproteins or glycolipids) in and on the surface of all the cells (glycocalyx) of all organisms that we eat and remain intact through the GI tract as we lack the enzymatic repertoire of the human body to unbind their particular β-linkages. Glycans bind to naturally present human lectins (through protein-carbohydrate interactions), but also with other human glycans (through carbohydrate-carbohydrate interactions, or CCI). Moreover, these glycans, like fibres, are digested by the gut microbiota that resides within the intestine. As our biochemistry shapes the composition of the microbiome, so does the composition of glycans and foods that we consume, triggering biological responses. miRNAs are small, single-stranded, 19- to 23- nucleotide-long RNA molecules and affect the stability of messenger RNA (mRNA) influencing protein synthesis. miRNAs are also present in foods and act on both the microbial composition in our gut and may be absorbed by the walls of the GI tract, demonstrating resistance to food processing and enzymatic attack. Though still a topic of controversy, these small, noncoding RNAs that control gene expression may directly enter into the circulating miRNA population of dietary exogenous miRNAs. It can hence be possible to identify a relationship between glycans and miRNAs in food on one side, microbiota composition on the other and the resultant health status of the host (immune system), on the third side.

Keywords: Glycan; miRNA; Microbiome; Glycotopes; Food antigens; Glycobiology, ABO blood group

Introduction

Modern science has amply discussed and explained the nutritional requirement of macronutrients and micronutrients [1].

The diet generally provides three macronutrients [2], carbohydrates, proteins and fats [3], and three micronutrients (vitamins, minerals and water) [4], which are essential for life [5]. These are absorbed in the gastrointestinal tract (GIT) after being processed by human and eventually microbic enzymes [6].

There are, nevertheless, other classes of bioactive compounds that have been recently studied, namely glycans and microRNA (miRNA or miR). In reality, glycans are carbohydrates (specifically, oligosaccharides, another group of carbohydrates), which have been studied for their special antioxidant and immunostimulating properties [7]. But, almost unbeknown to the nutritional research community is that oligosaccharides are ubiquitous [8,9], especially in the form of glycoconjugates [10]: either protein-bound [11] or lipid-bound [12]. In a similar manner, miRNA, a group of small non-coding RNA molecules that regulate genes at the post-transcriptional level [13], are found in animal and plant based foods [14]. Although mixed results have been obtained from studies on cross-kingdom transfer of exogenous miRNAs (exomiRs) in humans [15,16], many reports suggest exomiRs pass through the gastrointestinal tract and are found in human serum regulating the expression of endogenous mRNA [17].

These two particular bioactive compounds, because of their diverse structure and functions, can have enormous effects on health. A thorough review of current and past scientific literature has been performed on the advances of both fields and the results are presented, along with recommendations for future research.

Glycans and miRNAs

Glycans are not just fibers

According to the National Institute of Health [18], dietary fiber is defined as nondigestible carbohydrates while functional fibers are isolated, nondigestible carbohydrates with shown beneficial physiological effects in humans. Total fiber is the sum of dietary fiber and functional fiber [19]. In general, fibers and/or some types of resistant starches (RS) cannot be digested enzymatically by humans [20].

Dietary fibers are classified in a variety of ways, depending on the origin of the fiber, the molecular composition and the functional effects (viscosity, fermentability and solubility) [21].

Most beneficial effects reflect their laxative effect [22]. As just mentioned, all fibers are not hydrolized by the human digestive enzymes [23]. We, humans, do not have the enzymatic capability to degrade complex nonstarch polysaccharides - dietary fiber [6,24-26]. Our digestive capabilities are extremely reduced and are essentially limited to starch, sucrose, and lactose [27-29].

Undigested dietary carbohydrates include polysaccharides (including cellulose, hemicellulose, xylan, and pectin [30]) as well as

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some undigested starch [31]. And hence they are not absorbed in the small intestine (upper GIT), unlike most starches, having the function of increasing stools bulk [26,32], whereby the regularity effect.

RS are essentially long glucose chains linked with α-D-(1-4) and α-D-(1-6) glycosidic linkages, but are also hardly accessible to amylases [33,34]. In this sense, RS are similar to normal glucose based starches: α-D-(1-4) glycosidic bonds for amylose, a linear polysaccharide, and both α-D-(1-4) and α-D-(1-6) for branched amylopectin [35]. RS interspersed within amylose and amylopectin, rendering them more inaccessible to human hydrolases [36]. In the end, RS exhibit a level of slow digestibility (up to the large intestine), which manifests as a slow release of glucose [34].

Dietary fibers are thus very important for health [6,26].

Moreover, dietary fibers have other beneficial effects such as appetite control and energy intake through fermentation and production of short chain fatty acids (SCFA) by gut bacteria [37].

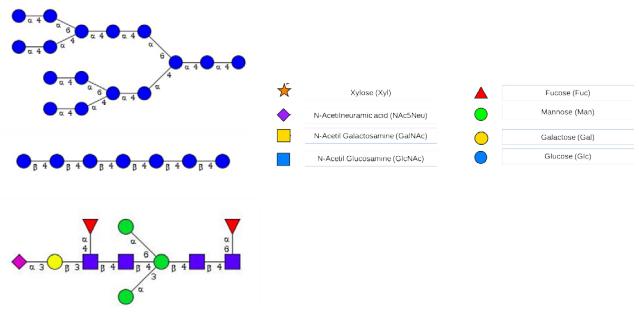
Less fermentable fibers tend to increase fecal weight to a greater degree than more fermentable fibers [38].

But, functional fibers are also composed of small oligosaccharides [32]. Nevertheless, no nutritional study has reviewed those carbohydrates that resist digestion in the small intestine (fibers, according to the 2009 CA [39] and are present in all food sources. Glycans, are one of four principal components of the cell [40].

These carbohydrates have different structural composition with respect to standard insoluble [41], soluble [42], prebiotic homopolysaccharides [43], which constitute most of the known fibers. Chemically, backbone of these indigestible glycans is composed of sugar residues linked together by β-1,4-glycosidic bonds [30].

Figure 1 shows the difference between starch, fibres and widespread glycan antigens (mostly, branched N-linked [44-46] and O-linked oligosaccharides [47] from glycoconjugates [48].

For an in-depth review of glycoconjugates and glycans, reference is made to an entire journal series, Glycoconjugates, and to arguably the most important textbook on the topic: Essentials of Glycobiology [49]. This extensive analysis of the scientific literature included the multiplicity of functions, the intrinsic diversity (microheterogeneity [50]) and ubiquitousness (including protein site occupancy [51] with O- and N-glycosylation [52]) of these sugar antigens and will be briefly and partially introduced.



Note: The first structure represents a branched starch (glucose) with its α1-4 and 1-6 glycosidic linkages. The second represents indigestible cellulose (glucose) with its β1-4 glycosidic bond. The third structure is a cartoon representation of a simple (linear) glycan with many linkage types between several different saccharide residues. On the right, a simplified version of the explanation of which monosaccharides the cartoon geometric figures represent.

Figure 1: Structural differences between starches, fibers and glycans.

Glycans are ubiquitous

Glycans are ubiquitous in nature [53,54]. The cell surface is literally coated with carbohydrates in the form of glycoproteins, with oligosaccharides (sugar residues), proteoglycans [43,55-57], polysaccharides, and glycolipids (as glycoconjugates) [58-60]. This little-known part of the cell is called the glycocalyx [61-63]. The glycocalyx is responsible for a vast number of biological functions from ion exchange, to cellular recognition, cell adhesion and development [64,65], from protein folding and activity [66], to regulation of signalling, or immune regulation [67], self or non-self-recognition [68], and homeostasis [69,70].

The cell surface interacts with the extracellular matrix (ECM [56,71,72]), also made up of glycans [73-77], apart from proteins.

Glycoconjugates are widely present in animal [78], as well as plant [79-83] and microbial [84-87] structural and functional systems [88]. Many of the plant glycan antigens are on the cell wall [89,90]. So is the bacterial cell wall [84,91], as it is surrounded by peptidoglycans [92] and lipopolysaccharides [93].

More than 50% of all proteins in eukaryotes are known to be glycosylated [46]. Nearly all human secreted and cell surface proteins are co- and post-translationally modified by glycans [40,65]. The different protein glycoforms depend on glycan site-specific microheterogeneity [94] and influence the physical, rheological [95], chemical and biological [96,97] properties of proteins, though having similar molecular weights.

Asparagine (N)-linked glycosylation is the most widespread form of modification found in secreted glycoproteins of all eukaryotes and some prokaryotes [45]. It is closely followed by O-glycosylation as a major form of protein glycosylation at the serine/threonine residues [98].

Given the diverse and complicated structures of the oligosaccharides (multiple branched chains of monosaccharides between 3 and 20 sugar units in length) [99], a standard symbolic representation system has been devised [49].

The presence and importance of glycans in human milk cannot be underestimated [100]. Human milk oligosaccharides (HMO) [101] are a family of unconjugated, structurally diverse and complex glycans that are very abundant in human milk [102-105].

Thus, conjugates of carbohydrates are ubiquitous in nature [78]. Glycans are reactive chemical species

Glycans are recognized by glycan-binding proteins (GBPs) [53,106], or lectins, which play a pivotal role in many different aspects of the physiology [40], including the immune defence [107]. Thus, glycans react with lectins and bind to them.

Lectins are carbohydrate-specific reagents and biological recognition molecules [108,109]. Lectins, too, are ubiquitous (in nature) [110, 111], as carbohydrate binding proteins [60]. They are found abundantly in both plants [112] and animals [113], and in bacteria [114]. Lectins have specific carbohydrate-binding sites (or domains, CBD) [115], and that preferentially recognize with low affinity (protein-carbohydrate interactions, or PCI, usually in the mM range) [113,116]. Lectins are thus perfectly suitable as decoders for carbohydrate-encoded information [117].

Lectin-glycan interactions are involved in a myriad different biological processes [118,119], including intracellular signalling pathways that regulate the immune response [120,121]. Glycans are so reactive that lectins will also bind to carbohydrate chains on glycolipids and proteoglycans or interact with polysaccharides and free sugars [122].

Many classification systems for lectins are based on morphology and interaction [123]. Given the heterogenicity of structures and specificities of GBPs [119], recently, the number of lectin families has jumped from 10 by the end of the 20th century to 50 [124].

There are many lectins that have specific immune functions [125], namely

1. Galectins [126,127] also called S-type lectins,
2. C-type lectins (like DC-SIGNs and Dectin 1 [128-130]),
3. Siglecs [131,132], a major subfamily of I-type lectins [133]
4. I-type lectins [134] (among which intercellular adhesion molecule-1 (ICAM-1) [135-137], neural cell adhesion molecules (NCAM) [138,139], and some clusters of differentiation (CDs) [140], are the major examples), and
5. Selectins [141-143].

The complementarity between glycans and lectins has been defined as the third alphabet of life [138,144]. An alphabet capable of transmitting maximum information in a minimum of space [145].

Moreover, glycans are known to allow proteins to reorganize (or self-associate) themselves spatially on the cell surface through PCI or carbohydrate-carbohydrate interactions (CCI) [64,83] to form 'lipid rafts' [58,59,146,147]. These microdomains, or clusters of glycoproteins (lectins) [148] and glycolipids, once formed, regulate several biological functions [149-152], including immune reactions [116,153].

Figure 2 is a schematic representation of the formation of lipid rafts on the glycocalyx, as special microdomains [154].

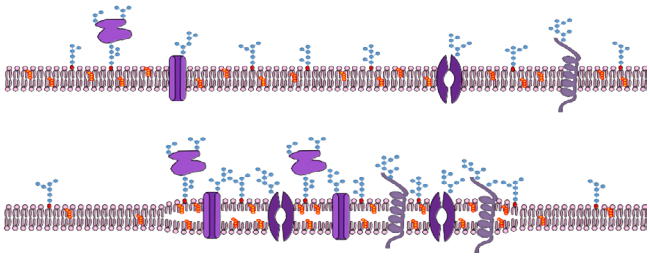
The biologically significant CCI have lower affinities with respect to PCI [156] but are still powerful enough to participate in cellular processes [157-159]. This occurs thanks to simultaneous multivalent noncovalent interactions with the appropriate saccharide or amino acid moieties [54,157].

A hypothesis that the carbohydrate structures are another potential source of antigenicity (food antigens) was proposed in the 1980s [160,161]. The glycans on different plant and animal protein allergens were then found to possess properties of immunological cross-reactivity [162]. Many food glycans (especially from plants) were isolated and structurally identified [163,164]. These glycans were called cross-reactive carbohydrate determinants (CCD) [165,166].

Many CCDs have been characterised as N-glycans [167,168], having weak allergic [169] or non-allergenic immunomodulatory properties (Table 1) [170].

miRNA are ubiquitously small and reactive

MicroRNA (miRNA or miR) are small, single-stranded, 19- to 23-nucleotide-long RNA molecules and affect the stability of messenger RNA (mRNA) thus influencing protein synthesis [171]. miRNA are small non-coding RNA (ncRNA) molecules that are not translated into proteins [172]. Various proteins are involved in the process of reduction of ncRNAs to miRNAs [173]. miRNAs regulate gene expression by silencing genes through translational repression and/or messenger RNA (mRNA) destabilization [174,175]. Since binding to mRNA is not homologous [176], a single miRNA could potentially regulate hundreds of genes [177]. Although small RNA molecules are classified into two other types, small interfering RNAs (siRNAs) and Piwi-interacting RNAs (piRNAs) based on different characteristics and origins [178,179], we shall refer to miR for all of them, for simplicity.



Note: The two sections of a cell membrane represent the before and during the lipid raft event. Glycans are shown as small blue hexagons on the top of proteins or lipids (the phospholipids of the bilayer membrane). Depending on the type of glycans (ABO) the creation of the lipid raft will change slightly in architecture [155], allowing certain proteins to become closer and thus be able to recognize foreign matter differentially.

Figure 2: Lipid raft enacted by ABO glycans.

Several studies have demonstrated that bioactive food components can affect miRNA expression and transport through the bloodstream through exosomes, and thus their pathways, in many diseases, including cancer [180]. Exosomes are 40-100 nano-sized vescicles present in various biologic fluids and are known to contain miRNAs [181].

It has recently been discovered that small RNAs are present in human gut and regulate homeostasis by targeting chromatin and transcripts [182].

miRNA, as a class of small, noncoding RNAs that control gene expression of almost every cell process, by targeting mRNA, have been shown to be not only modulated by these dietary bioactive compounds [183], but also be present in the diet. miR have been detected and classified in cow's milk and colostrum [184], mammalian milk [185,186], human breast milk [187]. miR are present in plants [188,189].

There are several recent studies suggesting that plant miRNA may be absorbed by cells of the mammalian epithelial wall from food and are packaged into appropriate microvescicles where they are protected from degradation and delivered into the bloodstream [190].

Small RNA molecules can be attacked and broken down by special enzymatic machineries called nucleases/nucleotidases [191-193]. Nonetheless, miRNAs are able to withstand RNAse and other extreme conditions [194] indeed, small strands of RNA (siRNA and miRNA) are able to be absorbed by the walls of the intestinal barrier intact, demonstrating resistance to food processing and to enzymatic attacks [195,196].

The absorption of exomiRs in plant food has been a topic of controversy in past years [197,198]. The dietary delivery of miRNAs in humans is at least feasible [199], and several researchers recently found plant exogenous miRs in human samples [16,200]. Indeed, orally delivered therapeutic RNA strands, called short interfering RNA (siRNA) has been demonstrated *in vivo* [201].

miR, as small endogenous RNAs that pair to sites in mRNAs to

Function/Effect	Glycans[1]	MIR
Immune modulatory	HMO with PRRs (lectins)	In milk or foods
Self/non-self recognition	glycans from microbe or diet with human receptors (lipid rafts)	-
Regulation of signalling	On free and cell glycoconjugates (lipid rafts)	Microbiome-GIT interaction
Protein folding	On cell surface proteins (lipid rafts)	-
Homeostasis	glycans from microbe or diet with human receptors	Food MIR modify epigenetics
Cross-communication with ECM	On free and cell glycoconjugates	
Cell to cell communication	On cell surface glycoconjugates (lipid rafts)	MIR from one cell acts on another

[1]Glycans react with lectins through PCI/CCI.

Table 1: Interaction of glycans and MIRs with health.

direct post-transcriptional repression, are predicted to regulate up to 60% of human protein-coding genes [202,203]. The mechanism of action involves

Being similar to methylation, miR are involved in epigenetic regulation of protein synthesis [172]. miR are involved in homeostasis as well as disease progression [204].

Health Impact

The relationship between diet, the gut microbiota, microbial activity, and gut physiology is quite complex [39]. Many studies have been completed to model the impact of the microbiota on human health [205-207] and homeostasis [208]. Other studies have linked interactions between the immune system and the gut to several metabolic diseases [206,209,210]. A pattern seems to emerge in which several environmental factors are linked together and trigger disease or health [211]. A recent relationship has emerged between diet, microbiota and health status [212].

All these factors and triggers must be explained somehow by fundamental interactions between the gut, the diet and the microbiome. This can be aided by considering the impact of glycans and miRNAs. Table 1 shows this interaction which will be explained in the next subsections.

The Gut and the immune system

The gastrointestinal tract is the body's foremost tissue boundary, interacting with nutrients, exogenous compounds and gut microflora [213]. The gut-associated lymphoid tissue (GALT) is expectedly the largest immune organ in the body [214].

The intestinal surface is covered by a single cell lining of intestinal epithelial cells (IEC) [215,216], and a mucus layer [98,217]. The gut secretes intestinal mucins [182], like MUC2 [98], the major colonic mucin, which is a large protein extensively O-glycosylated [211].

Many other cell types make up the GI mucosa [191,218-224], among these are dendritic cells (DCs) [225], that sample commensals and antigens and interact with lymphocytes: B and T cells [226,227].

The innate immune system is the first line of host defence of both humans and animals and is present in the gut [224]. The function of the innate immune is to recognize pathogen-associated molecular patterns (PAMPs) or microbial-associated molecular patterns (MAMPs) [228], using a variety of host receptors called pattern recognition receptors (PRRs) [229,230]. Interestingly, many of the PRRs are lectins [120,122] and interact with foreign or endogenous glycans.

PRRs are involved in antigen capture, presentation, and activation of immune [208,231] and inflammatory responses [230,232-234].

After the mucus [235], the IECs have a significant role in limiting exposure to commensal microbes by producing antimicrobial molecules [236]. Many of these are lectins [228,237-241].

Most of these immune-related effects are triggered by the commensal microbiota [242] to maintain a state of equilibrium between defence against pathogens and tolerance to resident microbes [243].

Gut microbiota

In the distal part of our digestive tract resides the human intestinal microbiome, a complex and dense ecosystem of bacteria [6,241]. The gut microbiota is, in fact, a vast mutualistic and symbiotic collection of diverse microbes [24,208,215,216,236,244-246], providing the host with a broad range of functions in exchange for a stable environment [24]. This mutualism [205], or cooperative partnership [241,247] and centred around diet [248]. This strategic symbiotic/commensal relationship of the human holobiont [249] is enacted in two ways [250].

Firstly, the microbiome can degrade otherwise indigestible components (glycans) of our diet [251-253] and transform these plant and animal-derived glycans into SCFA [26,250,254-258], which serve as multifaceted nutrients for colonocytes with health benefits [24,252,259-263].

Secondly, the gut provides a plethora of glycan substrates (glycoconjugates like chondroitin or heparin or mucin) that are utilized by the microbes for growth [250,264-268].

The microbiota shifts rapidly in response to dietary changes in fiber (glycan specificity or glycan preference [269]) or macronutrient content [23].

Moreover, it is known that the gut microbiota shapes aspects of host metabolism and immune function [24,270-274], is implicated in several disease states [252,275-277], and influences myriad of other biological activities [278], such as host-energy balance [206,208,254,279] and colonization resistance [211,246].

Many studies have evaluated the effects of different compositions of bacteria [280-285], causing dysbiosis [276], a disruption in the host's nutrition [286] and immunity [287] (or inflammation [173,232] and other diseases [276]), as opposed to normobiosis [288].

The innate immune system also shapes the commensal microbial communities [271], through multiple lectins, PRRs, [208,289,290], as regulators of intestinal microbiota for homeostasis [291]. The resident microbiota utilizes molecular mimicry [292] as a tolerance mechanism, whereby bacteria display surface molecules (glycans) that resemble those of the host's surface to render them immunologically inert [293]. Glycoconjugates like lipopolysaccharides, peptidoglycans [279], lipoteicoic acid [294,295], and other microbial polysaccharides have been identified cell-to-cell contact [205,274,296,297], mediated by both PCI and CCI [298].

By their part, the commensal microbes have an immunomodulatory effect on the host [242,243,299]. The capsular polysaccharide (CP)

as shown in Figure 3, have both protective functions for the bacteria [300,301] and immunologic potential (contributing to virulence) [302,303]. Other CPs or immunomodulatory glycans [304] activate yet further molecular pathways for host immune responses [305-309].

Overall, these mechanisms allow a complex interplay between the bacterial flora and the host, mediated by glycans.

Gut-microbiome-diet interaction

It is known that imbalances in gut microbial populations can be managed through diet [310,311]. Diet impacts microbial ecology [311], through differences in glycan metabolic activities [312,313]. This depends on the microbiome's differential expression of a number of carbohydrate-active enzymes (CAZymes) [27,28,314], capable of targeting a wide range of complex glycans [28,263,315-318]. Glycans are thus differentially consumed by the gut microbiota [94,263,319].

Many glycan substrates in foods differ in quantity and quality [252] and can greatly impact microbial composition [253,257,283,314,320-332] and activity [31,311,323,329,330,333-337].

Although these depend on the initial genetic composition of an individual [287,335,338].

Host chemical features, which are genetically encoded (e.g., mucin chemotypes), are primary determinants of the normal microbiota [313]. Such factors are also nutrient sources for the microbiome [26,256,257,339].

Several studies have demonstrated this interaction [340-342]. The two types are: GIT glycans-microbe lectins and gut lectins-microbe glycans.

The first type of interaction occurs between receptors of microbes (lectins) and glycans of the gut. Microorganisms have been known to be susceptible to histo-blood group antigens (HBGA) [343-347] and ABO determinants (glycans) [348-351] since the 1980s [352,353], and these are present along the entire GI tract [354]. Microbes include *H. pylori* [265,355-357], cholera [358-360] and rotavirus [361,362].

The second type of interaction between microbe glycans (foremostly, HBGA) and human lectins has also been recognized [130,293,363-368].

Irrespective as to which type of interaction, micro-organisms have been conclusively shown to bind differentially to glycans on host cells or mucins [40,63,358,369-371], including ABO [298,320,372,373].

The ABO blood group is one of the genetically determined host factors modulating the composition [374,375] (differences in proportion and profiles [375]) and function of the human intestinal microbiota, through glycan-glycan cross-talks [69].

One example of food item to consider is human milk. This food contains HMOs [376-378], which are essentially sialylated and α1–2, α1–3, α1–4 fucosylated glycans [105,379,380]. The presence of β1-3, β1-4 and β1-6 glycosidic linkages [377] make them a selective food source for both the microbiome and the host [102,381-383].

HMOs have been shown to cross the epithelial barrier [384,385], and to circulate in the blood [379,386], before being excreted in the urines [387], or to pass directly through the GIT into the faeces [388]. HMOs can bind to cell surface receptors of IECs and leucocytes and thus modulate neonatal immunity [103]. Thus, HMOs, similarly to other food-derived oligosaccharides [389], seem to have direct and indirect effects on the mucosal and systemic immune function of the consumer [381,390-403].

Milk also contains high expression levels of miR [404]. Whether these miRNAs can affect the human commensal microbes may be suspected but is currently unknown. But, biologically meaningful amounts of miRNA, present in cow's milk, are absorbed during consumption [405] and circulate in the blood [196]. Quite a few studies have found miR present in cow's milk and human milk [406]. These milk miRs have been linked to various immunoregulatory roles on target genes among mammals [404,407].

Studies have linked microbes with differential expression of caecal miR signature and thereby with regulation of the intestinal barrier function [173] and immune response [172,177,408,409]. As an epigenetic factor of regulation, miR may be controlled by microbiota through SCFA production [410].

Finally, human endogenous miR excreted by IECs, and called faecal miRNA, are known to shape intestinal commensal microbes [411,412]. It has been shown that IEC's miRNAs are absorbed by the microbiota [413] and modulate the gene transcripts affecting bacterial growth [414]. This is part of the complex regulatory networks of host pathogen interaction [202]. Exosomal miRNAs are released for the regulation of bacterial gene expression [415].

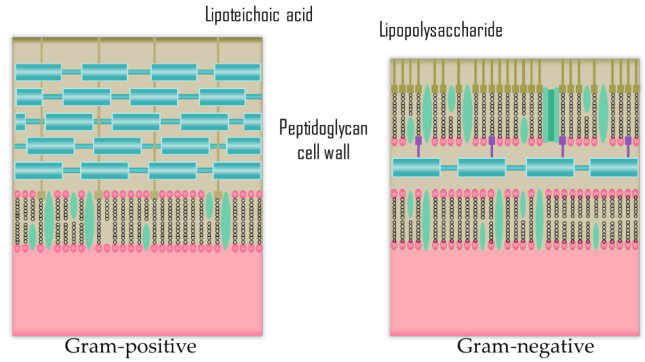
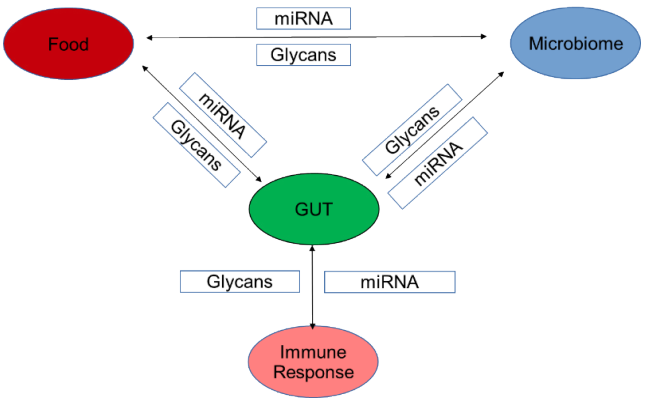


Figure 3: Glycoconjugates of external capsule/membrane of microbes.



Note: Three-way interaction of food, GI microbial communities and GI tract. Firstly, food shapes the commensal microbiota in the gut by defining which microorganism will thrive and which won't. Secondly, human gut will modulate the composition of the intestinal microbiota. Finally, glycans and miRNAs from both food and commensal bacteria can be pass through the GI tract walls and interact with the immune system.

Figure 4: Interaction among food, microbiome and gut.

Impact of food on health: the triple relationship

An interplay between diet, microbes and the gut as herewith briefly outlined has already been noticed [416]. This is not a unique intuition, as it copies very closely what has already been described [271]. The novelty is the outlook given to glycans and MIRs.

Figure 4 summarizes the previous sections.

Briefly, Figure 4 explains how

1. Food interacts with both the commensal microbiome and the gut to control immune responses and consequently health
2. Food modulates the composition of the microbiome (3.3), which affects immunity (3.2)
3. Food directly influences immune responses through glycans (2.2) and miR (2.3), by acting on the gut linen and on the GALT
4. The gut also influences the microbiome through glycans and miR (3.3), and
5. Commensal bacteria modulate gut development and homeostasis and immunity (3.1).

So, since the gut microbiota can be altered upon feeding of specific glycans and MIRs (from food) that promote the selective growth of one or more microbial genus (era)/species depending on the glycanic alignment with the gut, this confers health benefits to the host [288,416]. But, food (glycans) must be aligned with the genetic makeup (glycans) of an individual for the benefits to be maximised, otherwise there may be an opposite effect: an immune or inflammatory reaction. The afore-represented relationship could be called the health triangle, as diet can modulate health maintenance and disease prevention [417], through the various known mechanisms [214,228,418-423] with the help of glycans and MIRs.

Therefore, environmental factors within the intestines (e.g., glycans and MIRs from diet and microbiota) may influence innate immunity to cause chronic inflammation [211,342,424,425].

A holistic perspective

One last variable to input in therefore mentioned equation is the typology of glycans that constellate the glycocalyx of practically every human cell. Without exception, the most important glycotope system of the human body is the HBGA system (ABO and Lewis), given its ubiquitous tissue distribution in humans [175,426-434], free or bound to the ECM [116]. HBGA (Lewis rather than ABO) are also present on oligosaccharides abundant in human milk [101,379].

Particularly, the ABO epitopes have been shown to be fundamental in the characterization of the different possible biochemical cascades originating in self or non-self (inflammatory and/or immunologic) reactions [62]. Moreover, since glycans on proteins and lipids can slightly modify the glycoconjugate's shape and functionality [70,155], HBGA can contribute to special spatial plasma membrane architecture [435], allowing for peculiar cellular properties [436]. These special clusters, or lipid rafts, have been shown to form differentially in the presence of ABO antigens [155,437]. Figure 2 shows schematically an such event where the terminal of glycans can be substituted with HBGAs.

Hence, it is noticeable how HBGAs contribute to each individual glycophenotype [99], with subsequent dissimilar events following consumption of the same food items as outlined in section 3.4.

In this context, the advent of Blood-Type Diets (BTD) [438], after it was first proposed by P. J. D'Adamo in 1996 [439], becomes now theoretically admissible. Clinically, other practitioners followed the nutritional indications of the BTD [440-442], such as Italian physician P. Mozzi [443], with success. Although little academic attention was given to BTD due to lack of both suitable experimental clinical data [444,445], an initial primary mechanism was proposed involving dietary lectins [446], and their potential biological activity [112,447].

Since HBGA-like glycans have been found in food items [448], and because microbes bear HBGA-like substances (outside the cell surface) [449], recognition events triggered by PCI or CCI with endogenous lectins are the norm. This cascades in an alignment of food items and microbiota with the genetic constitution of an individual (gut linen) based on an ABO glycophenotype. The mechanistic explanation of BTDs (through PCI or CCI) becomes therefore straightforward and highly probable. This is one genetic way in which microbial communities in the gut can be highly individual and influence health [306].

Conclusions and Future Research

As has been amply documented, there is a multifaceted and intricate relationship between food, microbiota and the gut [450]. This relationship is heralded by glycans and miRs. We are currently just starting to appreciate the complexities of these relationships on a totally new level: that of glycans and small ncRNAs.

This is not to say that proteins, fatty acids and DNA or other substances present in food should not also be included in this health triangle. On the contrary, these macronutrients should indeed be included to gain a full picture of nutritional epigenomics [451] and nutritional immunology. The main scope of this work was to underline two outliers, which have too often been neglected.

As newer technologies become available to analyse these two different molecules, many new questions can be answered. Chiefly important are profiling of glycans and exomiR in food items. Due to their size and difficulties in the isolation process, this has evaded for so long a time.

Once the glycans and exomiRs are identified, their kinetics should be closely studied. Independent analysis of each glycan or miR should follow the principles of pharmacokinetics. Quali-quantitative absorption of the substance from food items is the first step in the study of its bioavailability. Tissue distribution and relative metabolism or interaction is the next step of the study. The endpoint is to discover how these molecules influence health. A task requiring an in-depth description of the biochemical pathways that involve cross-talks between these and other macro- and micro-nutrients.

In ultimate analysis, the complexity of human glycans (especially HBGA), their presence in the animal, vegetable and microbial world and their relative reactivity with the ubiquitous lectins cannot be set aside any longer. As we are gaining access to new strategies for study of glycomics, the primary differentiation in responses to foods between distinct ABO blood individuals will become easier to understand. Chief among these strategies is the possibility of full structural characterization of oligosaccharides in their unique glycoforms and their absolute quantitation in foods. As we have just scratched the surface of glycans and miRs, the next step is to appraise their vast networks of biological functionalities.

A task that, in by itself, may well take several decades to complete.

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