Opinion

Infection's Sweet Tooth: How Glycans Mediate Infection and Disease Susceptibility

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Glycans form a highly variable constituent of our mucosal surfaces and profoundly affect our susceptibility to infection and disease. The diversity and importance of these surface glycans can be seen in individuals who lack a functional copy of the fucosyltransferase gene, *FUT2*. Representing around one-fifth of the population, these individuals have an altered susceptibility to many bacterial and viral infections and diseases. The mediation of host–pathogen interactions by mucosal glycans, such as those added by FUT2, is poorly understood. We highlight, with specific examples, important mechanisms by which host glycans influence infection dynamics, including by: acting as pathogen receptors (or receptor-decoys), promoting microbial stability, altering the physical characteristics of mucus, and acting as immunological markers. We argue that the effect glycans have on infection dynamics has profound implications for many aspects of healthcare and policy, including clinical management, outbreak control, and vaccination policy.

Mucus Glycans: More Than Just Decoration

Mucosal infections account for over one-tenth of deaths globally, and are a major source of morbidity [1]. These are predominately infections of the respiratory tract, gastrointestinal tract, and genitourinary tract. With these sites exposed to external sources, encounters with microbial pathogens are unavoidable; however, the likelihood that an interaction will result in an infection varies substantially between individuals [2]. The ability to predict the outcome of exposure remains a central challenge in modern medicine.[i]

The extent to which mucosal surfaces influence the risk of infection is complex and remains poorly understood. Often, these mucosae are oversimplified as mere physical barriers; however, their molecular composition, consisting of intricate **glycan** structures (see Glossary) on secreted proteins and lipids, provides many additional immunological functions [3,4]. The large diversity of glycans that can be displayed by mucosal surfaces are determined both by inherited variation [5] and transcriptional regulation within epithelial cells [6]. Importantly, interindividual variation in the types of glycan present on mucosal surfaces is a major contributor to differences in susceptibility to a variety of infections [3,5,7,8]. Indeed, the contribution of mucosal glycans to infection susceptibility has gained much recent interest, owing to studies that have provided mechanistic insight into their function [9–11].

Mucosal constituents that are decorated with glycans are formed through a process mediated by a diverse family of **glycosyltransferase** enzymes, mostly acting in a template-independent manner [12]. **FUT2** encodes an α(1,2)-fucosyltransferase that is expressed in mucosal tissues

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Mucosal surfaces form a major interface between us and the external environment. These surfaces are decorated by complex sugar moieties that profoundly affect its function. Individual variation in these mucosal sugars contributes to overall infection and disease susceptibility within the population.

Recent mechanistic studies involving mouse models have revealed how the *FUT2* gene mediates host–bacterial interactions, via its effect on mucosal surfaces. There is now a need to further characterise the role of mucosal sugars in bacterial and viral infection dynamics. We describe several mechanisms that highlight the importance of mucosal sugars in host defence and their contribution to disease susceptibility.

Variation in glycans within the population may play a crucial, yet underappreciated, role in viral-infection susceptibility, with the potential to inform clinical management.

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by multiple epithelial cell types. *FUT2* facilitates the attachment of the L-fucose monosaccharide to specific O-linked glycan chains, producing α(1,2)-fucosylated glycans [5,8]. This resulting α(1,2)-fucosylated glycan is a highly versatile structure and can be further modified to form one of a number of clinically important glycans, including the A and B histo-blood group antigens on mucosal surfaces [5,8]. Mucosal histo-blood groups are analogous to those found on erythrocytes, although only those secreted by mucosal surfaces are dependent on *FUT2*. For example, an individual who has an A blood type will express A-type glycans on erythrocytes, but will only express A-type glycans on mucosal surfaces if they have a functional *FUT2* [5]. After the glycosylation process, α(1,2)-fucosylated proteins and lipids are either secreted from mucosal epithelium into the lumen directly, or are anchored to the apical cell surface membrane. Because *FUT2* controls the nature of the various α(1,2)-fucosylated glycans secreted by mucosal surfaces, it was termed the 'secretor' gene, although it does not regulate secretion *per se* [5].

As α(1,2)-fucosylated glycans act as important precursors for a range of mucosal glycans, the high frequency of nonsense SNPs within the *FUT2* gene in humans [13] is perhaps surprising. In fact, approximately one-fifth of the global population harbour two nonfunctional alleles and are therefore unable to express α(1,2)-fucosylated glycans on mucosal surfaces [7,13]. While individuals with a functional *FUT2* allele are termed 'secretors', those with loss-of-function mutations are termed '**nonsecretors**'. Interestingly, the frequency of nonsecretors varies substantially with ethnicity [7,13], with a range of SNPs found to confer this nonsecretor phenotype. However, the widespread distribution of these traits indicates a conserved selective advantage for nonsecretors under certain circumstances [14] (Box 1). In addition to an absence of α(1,2)-fucosylated glycans in mucosal secretions, including the absence of histo-blood group antigens, nonsecretors also display increased levels of sialylated glycans in mucosal secretions [15], presumably as a result of reduced glycosyltransferase competition.

A clue as to why these loss-of-function mutations are carried at such a high frequency, and an illustration more generally of the importance of surface glycans to infection susceptibility, is the major differences in rates of bacterial- and viral-mediated diseases between secretors and nonsecretors (Table 1, Key Table). A large number of studies have now reported significantly higher rates of viral infection in secretors, including life-threatening infections caused by HIV, influenza, and norovirus [16–21]. At the same time, secretors appear to be at a reduced risk of infections caused by bacterial pathogens, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Salmonella enterica* serovar Typhimurium [9,11,22–24]. This dichotomy in susceptibility also extends to chronic multifactorial diseases, such as chronic pancreatitis [25], and diseases of altered immune regulation, such as asthma [26,27], type 1 diabetes [28], and psoriasis [29]. It is important to note that while all of the studies listed in Table 1 reported significant associations between secretor status and disease, sample sizes and effect sizes vary.

Glossary

FUT2: the gene encoding an α(1,2)-fucosyltransferase expressed in epithelial cells of multiple mucosal tissues. This enzyme catalyses the addition of L-fucose to the terminal galactose of a glycan in an α1,2 confirmation. This α(1,2)-fucosylated glycan is termed the H antigen.

Glycan: a polymer of covalently linked sugar monomers.

Glycosyltransferase: enzymes that catalyse the transfer of a sugar monomer from a donor to an acceptor substrate molecule, forming a glycan. A diverse range of glycosyltransferases exist, each with a particular specificity for sugar monomers and glycosidic linkage.

Microbiota: all commensal, symbiotic, and pathogenic microorganisms sharing a defined niche.

Natural antibodies (NAbs): immunoglobulins that are produced independently of T cell selection. NAbs generally have a weaker affinity, with lower specificity, compared to T cell-dependent immunoglobulins.

Nonsecretor: an individual who has two loss-of-function mutations in the *FUT2* gene and therefore fails to express α(1,2)-fucosylated glycans in mucosal secreted and cell-surface glycoproteins and glycolipids.

Box 1. *FUT2* SNPs and Historical Infections

Multiple SNPs, found in the *FUT2* coding region, confer loss, or hindered function. The most common nonsense SNP in Caucasian, African, and central Asian populations is a G→A substitution at base pair 428 (rs601338); however, the most common in east Asian populations is an A→T substitution at base pair 385 (rs1047781) [7,13]. Both SNPs occur at similar frequencies in their respective populations, with estimates dating the emergence of the 428G→A mutation to at least 1.87 million years ago and the 385A→T mutation to at least 256 000 years ago [72]. The age and frequency of these mutations suggest that they are maintained in the gene pool by balancing selection, where both secretor and nonsecretor variants provide selective advantage. Available evidence suggests that differential resistance to infection is the driver of this balancing selection [14], although identification of the causative infective agent is speculative. However, this phenomenon has been observed outside of the human population, where infection-driven selection of glycosyltransferase variants was reported in a study of rabbit populations, where those with endemic rabbit haemorrhagic disease virus had glycosyltransferase SNPs at higher frequencies compared to populations without endemic virus [73].

Key Table

Table 1. Secretor Status Profoundly Influences Infection and Disease Susceptibility[a]

Infection	Secretors more susceptible	Nonsecretors more susceptible	Refs
Norovirus (GII.4)	✓		[21,74]
Rotavirus (VP8)	✓		[36–38]
Influenza A virus	✓		[19]
Rhinovirus	✓		[19]
Echovirus	✓		[19]
RSV	✓		[19]
HIV	✓		[16–18]
Helicobacter pylori	✓		[24,75,76]
Candida albicans		✓	[77,78]
Streptococcus pneumoniae		✓	[22]
Neisseria meningitidis		✓	[22]
Haemophilus influenzae		✓	[23]
Salmonella enterica serovar Typhimurium[b]		✓	[11]
Citrobacter rodentium[b]		✓	[9]
Campylobacter jejuni		✓	[41,42]
Urinary tract infection		✓	[79,80]
Bacteraemia (after haematopoietic stem cell transplantation)		✓	[81]
Disease	Secretors more susceptible	Nonsecretors more susceptible	Refs
Non-CF bronchiectasis severity[c]	✓		[67]
Asthma severity	✓		[82]
Graft-versus-host disease	✓		[81]
Intestinal-type gastric cancer		✓	[83]
Primary sclerosing cholangitis		✓	[84]
Crohn's disease		✓	[53,85]
Celiac disease		✓	[86]
Asthma		✓	[26,27]
Type 1 diabetes		✓	[28]
High plasma vitamin B12		✓	[87–89]
Chronic pancreatitis		✓	[25]
Psoriasis		✓	[29]
Acute uncomplicated pyelonephritis		✓	[90]
Behçet's disease		✓	[91]

[a]Secretor phenotype is associated with increased susceptibility to viral infections and respiratory disease severity, but with decreased susceptibility to bacterial infections and a diverse range of chronic inflammatory diseases.
[b]Demonstrated in *Fut2*$^{-/-}$ mice with no human epidemiological evidence.
[c]Abbreviation: CF, cystic fibrosis.

Despite the well-described associations between *FUT2* and other mucosal glycosyltransferases, and a diversity of infections and diseases, our understanding of the mechanisms behind these relationships remains poor. Infection and pathogenesis are complex processes, with mucosal glycans likely influencing susceptibility through both direct and indirect mechanisms.

### Sticking Around: FUT2 and Pathogen Adherence

α(1,2)-fucosylated glycans influence infection susceptibility directly, through facilitating pathogen adherence. As has been reviewed in detail [30–32], multiple bacteria encode specific receptors that bind to host α(1,2)-fucosylated glycans for pathogen adherence. A well characterised example of this is in *Helicobacter pylori*, facilitated by the BabA adhesin. BabA has a specificity for the 'Lewis b' α(1,2)-fucosylated mucosal glycan, therefore BabA-expressing *H. pylori* is more readily able to adhere to the gastric mucosa and colonize the stomachs of secretor individuals [33] (Figure 1A). *BabA*-encoding *H. pylori* and subsequent infection susceptibility is something of an exception, as this is the only bacterial species listed in Table 1 where susceptibility is increased in secretors (due to the specificity of BabA towards α(1,2)-fucosylated glycans). Two viruses have analogous receptors, norovirus (specifically strain GII.4) [34,35] and rotavirus (specifically strains containing spike protein VP8) [36,37]. Both of these viruses encode different adhesins, specific to α(1,2)-fucosylated glycans. The absence of these glycans in nonsecretors therefore confers high levels of resistance [20,21,38] (Figure 1A).

More complex *FUT2*-dependent pathogen adherence pathways have also been characterised, based on glycan location. Glycosylated proteins and lipids are abundant in the gastrointestinal tract, either anchored to the cell surface, secreted into the lumen, or taken in through ingestion. Therefore, infection susceptibility, where pathogens adhere to glycans, depends on the location and anchoring of the glycan. Glycans that are not attached to the epithelium can, in fact, reduce infection susceptibility by acting as receptor decoys. For example, the cell surface mucin, MUC1, carries Lewis-b glycans and is shed from the surface of gastric epithelial cells acting as a releasable decoy to limit adhesion by BabA-expressing *H. pylori* to other cell surface Lewis-b-expressing molecules [39]. As a separate example, maternal secretor status affects glycosylation of glycoproteins in milk [40], and consequently maternal secretors reduce their infants' susceptibility to *Campylobacter jejuni* diarrhoea [41]. This has been attributed to *C. jejuni* binding to α(1,2)-fucosylated milk glycans [42], which act as a receptor decoy in the infant, sequestering the pathogen away from the epithelium (Figure 1B). As these examples demonstrate, the dynamics of how glycan-mediated adherence (either membrane-bound or luminal) ultimately confers susceptibility or resistance to infection is complex.

Commensal Influence: *FUT2* and the Microbiota

In addition to influencing pathogen adherence, *FUT2* has been shown to also affect infection susceptibility indirectly. For example, murine studies have shown that the presence of *Fut2* reduces susceptibility to *S. Typhimurium, Enterococcus faecalis* and *Citrobacter rodentium* infection through the effect of α(1,2)-fucosylated glycans on the commensal gut **microbiota** [9–11] (Figure 1C). Even small changes to microbiota composition can alter nutrient availability, profoundly affecting the ability of bacterial pathogens to colonise the gut [43]. Beyond such 'colonisation resistance', murine studies have also shown that *Fut2*-dependent fucosylated glycans are an important endogenous nutrient for commensal microbes, facilitating rapid host recovery following periods of stress caused by intestinal infection or inflammation [9]. These findings are supported by *in silico* analyses of microbial structure stability using microbiota data from *Fut2* knock-out mice [44].

By contrast, a large study in healthy adult humans reported no difference in faecal microbiota composition between secretors and nonsecretors [45], contradicting previous, positive
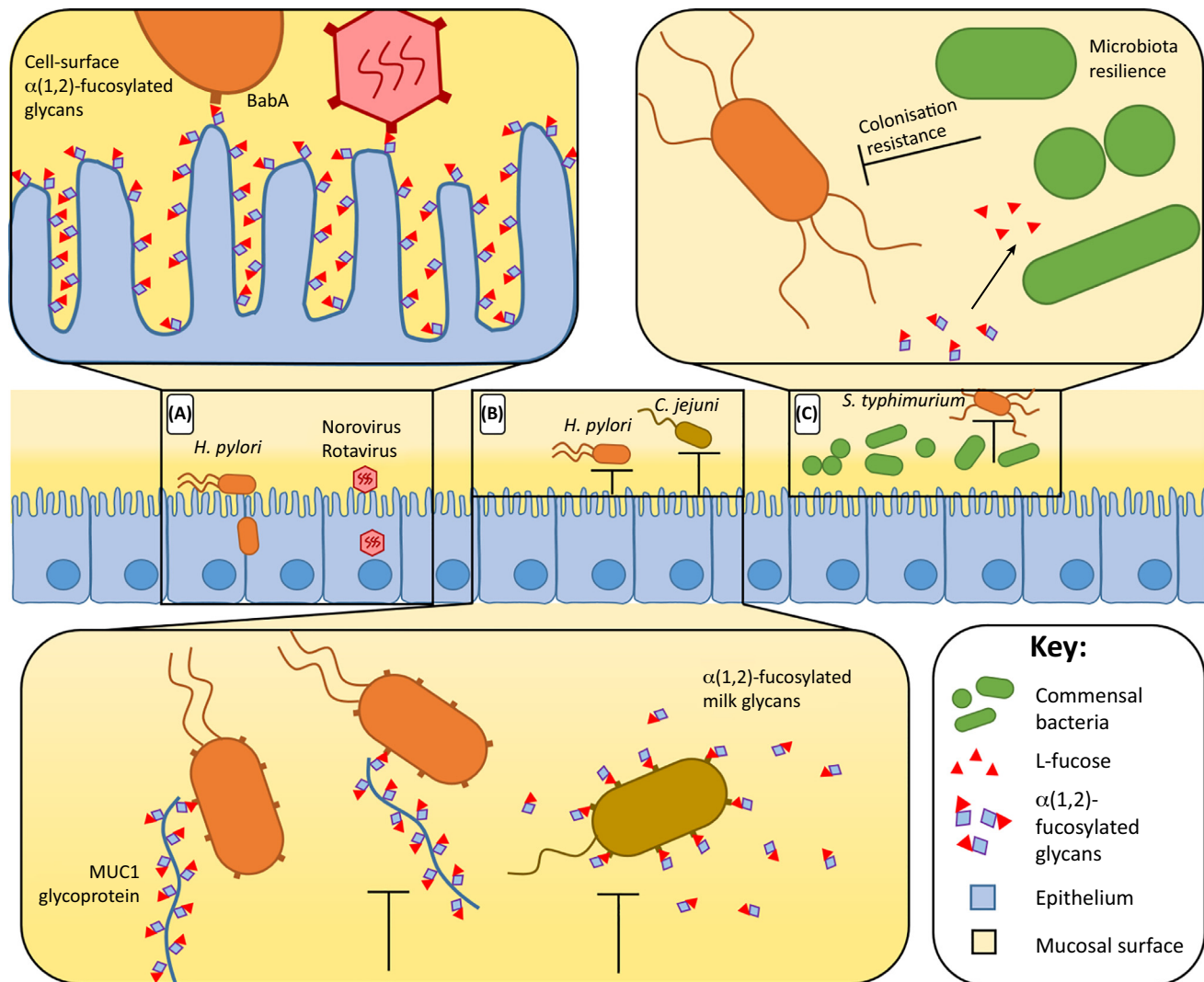
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Figure 1. α(1,2)-Fucosylated Glycans Affect Infection Susceptibility. (A) Adhering to membrane-bound α(1,2)-fucosylated glycans facilitates pathogen infection. (B) Adhering to luminal α(1,2)-fucosylated glycans can act as a receptor decoy, reducing infection susceptibility. MUC1 glycoprotein is membrane bound, however, detaches from the epithelium following pathogen binding. (C) Commensal microbes can utilise α(1,2)-fucosylated glycans, occupying a niche space and hindering pathogen colonisation. Abbreviations: *H. pylori*, *Helicobacter pylori*; *C. jejuni*, *Campylobacter jejuni*; *S. typhimurium*, *Salmonella enterica* serovar Typhimurium.

associations from a smaller cohort analysing mucosal microbiota from biopsies [46]. The use of intestinal mucosal biopsies in the smaller cohort study, where a greater host genotype effect may be expected [47], may explain this discrepancy [44].

Differences in microbiota composition and resilience may also explain the numerous diseases associated with secretor status (as detailed in Table 1). Many of these conditions (including asthma, Crohn's disease, celiac disease, and psoriasis) are associated with intestinal micro-biota composition [48–50]. If secretor status can influence gut microbiology, it is reasonable to suggest that secretor status may contribute to microbiota-related disease susceptibility among predisposed individuals, as discussed elsewhere [8,30,31,46,51–53]. However, given the numerous confounding environmental exposures in human populations, large cohort studies

with detailed metadata are required to determine the contribution of secretor status to these complex, multifactorial diseases.

## Sugar Structures: Glycans Influencing Mucus Barrier Function

The physical barrier properties of mucus define its primary function, as governed by its viscosity, permeability, and rheology [3,4]. Mucins, the major proteins that make up the mucus layer, are comprised of 70% glycans by mass [4]. Small variations in the molecular composition of mucin glycans can therefore impact the overall physical properties of mucus. While α(1,2)-fucosylated mucins constitute a large proportion of secretor mucus, interestingly, nonsecretors display higher levels of sialylated mucins [15]. Sialic acid, like fucose is often added as a terminal saccharide and has different properties to fucose.

At a molecular level, sialylated terminal glycans have a larger polar surface compared to fucose [54,55]. The higher electronegative change in sialylated mucins has therefore been proposed to increase both mucus hydration and electronegative repulsion, compared to fucosylated mucins [54,55]. Particularly in the airways, mucus hydration is an important characteristic for mucociliary clearance [4,54]. Well-described examples of impaired clearance are evident in diseases such as chronic obstructive pulmonary disease and cystic fibrosis [4]. While this requires experimental validation, higher sialic acid levels in nonsecretor airways may affect mucus clearance mechanisms. Such a difference might explain the observed findings of a study in which infection by influenza virus, respiratory syncytial virus (RSV), rhinovirus, and echovirus were all lower in nonsecretors [19]. It is interesting to speculate that altered mucus characteristics in nonsecretors may contribute to this reduced susceptibility to viral infection.

Anti-sugar Antibodies: Host Antibodies Recognise Nonself Glycans

A major contributor to mucosal immunity is the detection and neutralisation of pathogens by secreted antibodies [56,57] – particularly **natural antibodies** (**NAbs**), which are generated in a T cell-independent way and have broad-spectrum activity against a diversity of antigens [57]. A subset of NAbs have an affinity towards glycans, recognising those specific to bacteria, but also to glycans found naturally within the human population. For example, the A and B histo-blood group antigens elicit strong NAb-specific immune responses in noncompatible individuals, best known as the primary cause of blood transfusion reactions [58]. An interesting research question is whether these same A and B antigens decorate viral particles and affect viral transmission between histo-incompatible hosts.

By definition, viral replication is reliant on host-cell machinery, which includes glycosylation by host glycosyltransferases. Many viruses also utilize host membranes for encapsulation. Several studies have demonstrated that viruses shed from epithelial cells displaying A or B glycans also display these glycans. Specifically, cell lines infected with HIV-1 [59] or measles virus [60] were found to produce viral particles coated in their specific blood group glycan (as depicted in Figure 2). While these studies were performed *in vitro* using transformed cell lines, they support a logical conclusion; viruses from a cell expressing particular glycosyltransferases carry a host-glycan fingerprint of this parent cell. Addition of anti-histo blood group NAbs was found to bind to these viruses and elicit antibody-mediated inactivation [59,60]. Further studies have investigated NAb-mediated viral neutralisation using other, analogous glycan structures, showing supporting results [61,62]. However, it is unlikely that nonsecretors develop NAbs with specificity to secretor glycans, as α(1,2)-fucosylated glycans exist in nonmucosal sites, which are not reliant on *FUT2*. Secretor status may however affect a virus's ability to evade host antibody defences. As FUT2 mediates the display of ABO histo-blood group antigens in mucosal secretions, viruses that come from a nonsecretor would not display blood group antigens
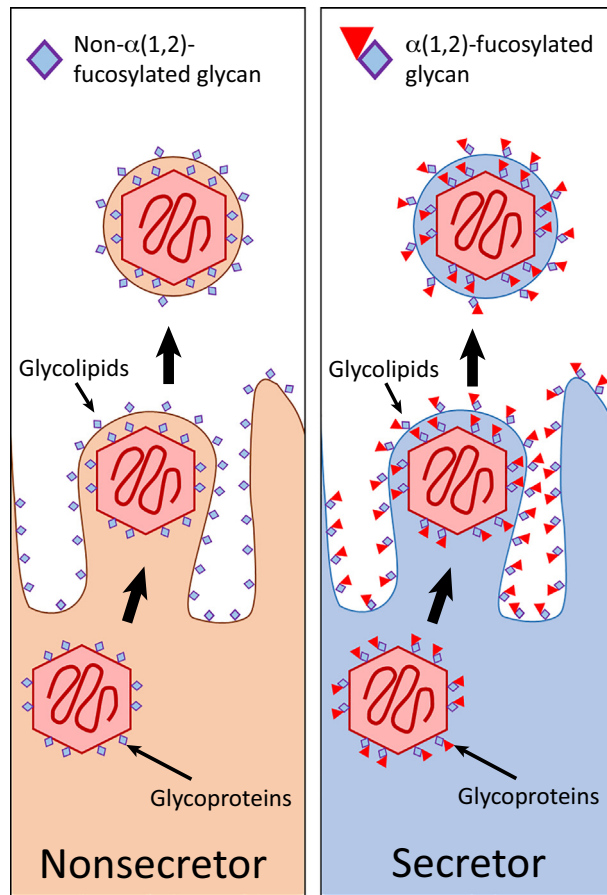
Figure 2. Viruses Are Decorated in Host Glycans. Viral replication requires the use of host cell machinery, including host glycosyltransferases. Underlying genetic factors (such as *FUT2* SNPs) affect glycosylation of shed viruses. Viral glycoproteins and glycolipids (for enveloped viruses) differ between viruses shed from secretor and nonsecretor cells.

and hence would not be affected by anti-histo blood group NAbs. Further infection models are required to elucidate the contribution of viral glycosylation to infection dynamics.

Using Glycosyltransferase Characteristics to Inform Policy and Practice

The majority of studies discussed have been observational, with stratification by glycosylation status revealing differences in infection or disease susceptibility. Information on the underlying mechanisms surrounding the contribution of glycosyltransferases remains very limited (see Outstanding Questions). However, it is becoming apparent that common SNPs in genes such as *FUT2* have clinically important predictive capabilities. We are now entering an era in which whole-genome sequencing is becoming increasingly common in both research (for large cohort studies) and at an individual level (as a predictive tool for risk susceptibility). These growing data repositories provide an opportunity to explore effects of glycosylation variability on risks of infection and disease susceptibility at a population-level, as well as at an individual level.

Glycosylation status might, for example, be informative at a population level during infection outbreaks, where identifying at-risk individuals is vital for effective control management and global security. For example, a retrospective analysis of 45 people exposed to severe acute respiratory syndrome (SARS) virus in a Hong Kong hospital in 2003 found that individuals who did not express

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A or B histo-blood group glycans had reduced frequency of infection (odds ratio 0.18), supporting the NAb-anti-viral hypothesis [63]. Developing stratification strategies based on glycosylation compatibility could therefore inform and reduce infection spread. At an individual level, identification of common genetic infection and disease risk factors, such as *FUT2* SNPs, could inform and direct an individual's behaviour to minimise infection and disease risk, particularly when linked to other risk factors. Further, with the apparent link between glycan variation and antibody repertoire [5,8], individual glycosylation status may inform patient stratification in clinical settings such as predicting vaccine efficacy and progression of chronic diseases.

A major growing clinical concern is the global increase in prevalence of chronic diseases caused by a diverse range of complex lifestyle, genetic, and environmental factors. Respiratory- and gastrointestinal-associated diseases often have a direct microbial component, and many other seemingly unrelated chronic diseases are also associated with our interactions with microbes, including type 2 diabetes [64], asthma [65], and rheumatoid arthritis [66], to name but a few. Secretor status is associated not only with susceptibility to many of these chronic diseases, but also their progression and severity. This relationship could inform the stratification of patient populations and the prediction of adverse events. For example, stratification of patients with noncystic fibrosis bronchiectasis by secretor status identified that chronic airway infection, lung function, and pulmonary exacerbation frequency were higher in secretor individuals [67].

The frequency of allergic diseases is also increasing rapidly, particularly in developed countries [68]. Early-life antibiotic exposure or a dysregulated microbiota has been linked with allergen sensitisation [65]. Maternal secretor status is linked with infant microbiota composition [44,69], and nonsecretors are more susceptible to asthma [26], psoriasis [29], and early-life IgE-associated eczema [70]. While it is essential that we better understand how the influence of glycan fucosylation on the microbiome contributes to the development of these conditions, such relationships might also present opportunities for novel therapeutic strategies. For example, might breast milk, supplemented with α(1,2)-fucose, reduce allergic disease susceptibility in at-risk infants? Oral supplementation with α(1,2)-fucose has been shown to be well tolerated and shift the intestinal microbiota in healthy adults [71], highlighting its safety and efficacy as a potential prebiotic.

Concluding Remarks

We are now in the era where data repositories are available that combine genomic sequence data with clinical metadata from large cohorts [13]. The effect of genetic variation in genes that mediate mucosal glycosylation, such as SNPs in *FUT2,* increases our understanding of immunology at a population level, and creates opportunities to implement effective precision medicine. Testing glycan-mediated mechanisms of infection and disease susceptibility is now warranted to assess their inclusion in clinical and policy practices. Ultimately, precision medicine requires an integrated decision-making model that encompasses extrinsic factors, including diet, mental and physical health, the microbiome, and intrinsic factors, such as human genetics and subsequent phenotypes. While testing population-level variability remains challenging [2], a better understanding of the factors by which glycans mediate disease susceptibility offers the potential to significantly improve clinical outcomes.

Resources

[i]www.cdc.gov/amd/

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