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The role of the blood group-related glycosyltransferases *FUT2* and *B4GALNT2* in susceptibility to infectious disease

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ABSTRACT

The glycosylation profile of the gastrointestinal tract is an important factor mediating host-microbe interactions. Variation in these glycan structures is often mediated by blood group-related glycosyltransferases, and can lead to wide-ranging differences in susceptibility to both infectious- as well as chronic disease. In this review, we focus on the interplay between host glycosylation, the intestinal microbiota and susceptibility to gastrointestinal pathogens based on studies of two exemplary blood group-related glycosyltransferases that are conserved between mice and humans, namely *FUT2* and *B4GALNT2*. We highlight that differences in susceptibility can arise due to both changes in direct interactions, such as bacterial adhesion, as well as indirect effects mediated by the intestinal microbiota. Although a large body of experimental work exists for direct interactions between host and pathogen, determining the more complex and variable mechanisms underlying three-way interactions involving the intestinal microbiota will be the subject of much-needed future research.

1. Introduction

The vast majority of proteins and lipids in the human body are glycosylated, *i.e.* possess covalently attached sugars, and referred to as glycoproteins and glycolipids. Glycosylation is a co- or post-translational, enzyme-directed modification of glycan structures, and it is involved in a plethora of physiological and pathological processes including aging (Dall'Olio et al., 2013), cancer (Pinho and Reis, 2015), inflammatory diseases (Larsson et al., 2011) and infectious diseases (Moran et al., 2011). In the gastrointestinal tract (GIT), transmembrane glycoproteins (mucins) constitute the glycocalyx protecting the mucosal surfaces, while secreted mucins form mucus layers (Corfield et al., 2001). Notably, most of the 346 histo-blood group antigens described to date are carbohydrates, glycoproteins, or glycolipids (Storry et al., 2016). Originally discovered on the surface of erythrocytes (Landsteiner, 1900), blood group antigens are also expressed in most epithelial tissues and were found in bodily secretions, such as saliva, urine, feces, and milk (Ravn and Dabelsteen, 2000).

The histo-blood group system ABO (H) and the structurally related Lewis histo-blood group are the major human alloantigen systems. ABH and Lewis antigens decorate the terminal structures of various glycans, including O- or N-glycoproteins, mucins, as well as the glycolipids of the lacto, globo and ganglio series and lactosylceramide (Marionneau et al., 2001). ABH and Lewis antigens are synthesized by a number of different glycosyltransferases acting in a successive manner. For example, addition of an α1,2-linked fucose to disaccharide precursors creates the Lewis^b and H antigens. Subsequent attachment of N-acetylgalactosamine (GalNAc) or galactose (Gal) residues to H antigen structures creates A or B antigens, respectively (Table 1). These antigens are present in GIT epithelia, in nasal epithelium and in trachea, as well as in the lower genito-urinary tract, and in bodily secretions.

Due to their location in tissues that serve important barrier functions, histo-blood group antigens can mediate important first interactions with microbes (Koropatkin et al., 2012). Accordingly, these structures are frequently involved in the evolutionary arms race between host and pathogen, as evidenced by striking signatures of natural selection at the DNA sequence level (Saitou and Yamamoto, 1997; Fumagalli et al., 2009; Linnenbrink et al., 2011). Variation at histo-blood group genes can influence host-pathogen interactions in at least three ways: either directly by affecting bacterial adhesion and invasion, indirectly *via*

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Table 1
Structures of histo-blood antigens.

Histo-blood antigens	Structure
Blood group H (O)	
H-1 antigen	Fucα1-2Galβ1-3GlcNAcβ-
H-2 antigen	Fucα1-2Galβ1-4GlcNAcβ-
H-3 antigen	Fucα1-2Galβ1-3GalNAcβ-
Blood group A	Fucα1-2(-GalNAcα1-3)Galβ-
Blood group B	Fucα1-2(-Galα1-3)Galβ-
Lewis^{a}	Galβ1-3(-Fucα1-4)GlcNAcβ-
Lewis^{b}	Fucα1-2Galβ1-3(-Fucα1-4)GlcNAcβ-
Sialyl-Lewis^{a}	Neu5Acα2-3Galβ1-3(-Fucα1-4)GlcNAcβ-
Lewis^{x}	Galβ1-4(-Fucα1-3)GlcNAcβ-
Lewis^{y}	Fucα1-2Galβ1-4(-Fucα1-3)GlcNAcβ-
Sialyl-Lewis^{x}	Neu5Acα2-3Galβ1-4(-Fucα1-3)GlcNAcβ-
Core structure Sd^{a}/Cad	GalNAcβ1-4(Neu5Acα2-3)Galβ-R
Sd^{a} antigen	GalNAcβ1-4(Neu5Acα2-3)Galβ1-4GlcNAcβ1-3Gal
Cad antigen (glycophorin A)	GalNAcβ1-4(Neu5Acα2-3)Galβ1-3(Neu5Acα2-6)GalNAc-Ser/Thr
Cad antigen (glycolipid sialylparagloboside)	GalNAcβ1-4(Neu5Acα2-3)Galβ1-4GlcNAcβ1-3Galβ1-4Glc-ceramide

modification of gut microbiota composition or as a nutrient source. Excellent recent reviews emphasize an importance of mucosal glycans in bacterial adhesion and bacteria-mucus interactions (Formosa-Dague et al., 2018; Josenhans et al., 2020; Juge, 2019). In this review, we discuss the roles of mucosal *Fut2* and *B4galnt2* histo-blood group-related glycans in susceptibility to microbial infections. We focus on two general modes of action: (i) direct interactions with glycan structures and (ii) indirect effects that may be mediated by the endogenous microbiota.

2. FUT2

In humans, the *FUT2* gene (Chr19q13.33, termed the "secretor gene") encoding the α-2-fucosyltransferase enzyme is expressed in mucosal tissues by several epithelial cell types (Fig. 1). This enzyme facilitates the transfer of L-fucose (Fuc) residues from the GDP-Fuc precursor to Gal in an α(1,2)-linkage, and thus generates the terminal glycan epitope Fucα1-2-Galβ-R (Kelly et al., 1995, p. 2). In individuals with a functional FUT2 (so-called "secretors"), α(1,2)-fucosylated and poly-fucosylated proteins and lipids are secreted into the gut lumen and also found in abundance on the apical side of the mucosal epithelium (Björk et al., 1987). In mucosal tissues, *FUT2*-dependent, α(1,2)-fucosylated glycans are required to form the ABH and most of the Lewis histo-blood group antigens (Table 1).

The *FUT2* gene displays a high degree of polymorphism in functional- *versus* non-functional alleles, which varies according to geography (Ferrer-Admetlla et al., 2009). Along with two commonly found functional *FUT2* alleles (Se and Se^{357}), more than 20 different single nucleotide polymorphisms (SNPs) within the *FUT2* gene have been discovered in different populations (Soejima et al., 2012). It is estimated that around 20 % of humans are homozygous for FUT2-inactivating nonsense mutations, and are thus "non-secretors" (Koda et al., 2001). In non-secretor individuals, α(1,2)-fucosylated Lewis^{b} and Lewis^{y} antigens, as well as all ABH antigens are not produced in mucosal tissues or in bodily secretions (Henry et al., 1995). The frequencies of secretor and non-secretor phenotypes appear to be similar in different human populations (Ferrer-Admetlla et al., 2009). Multiple studies highlighted important roles of the secretor status in various diseases: *e.g.*, secretors were shown to be more susceptible to graft-*versus*-host disease (Rayes

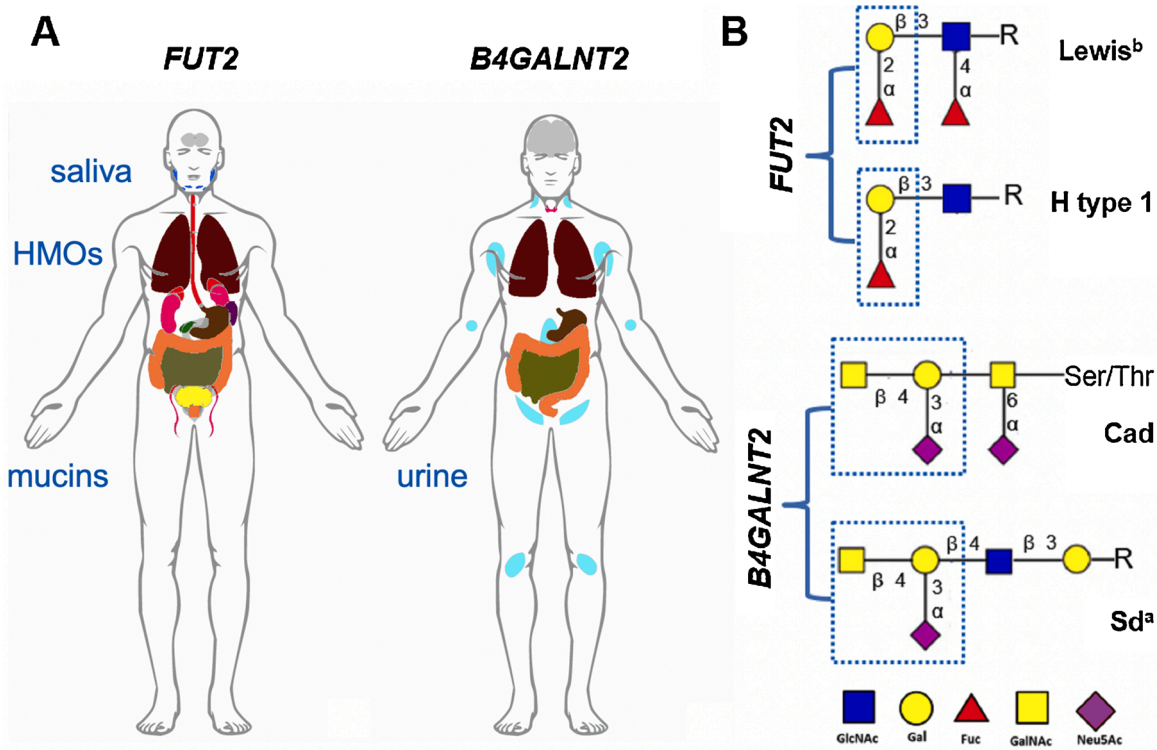

Fig. 1. *Tissue distribution and the representative structures of B4GALNT2- and FUT2-dependent antigens.* **A**, Tissues with high levels of either *B4GALNT2* or *FUT2* gene expression are depicted. Additionally, bodily secretions containing aforementioned antigens are indicated. HMOs – human milk oligosaccharides. Anatomograms are adopted from the EMBL Expression Atlas (Papatheodorou et al., 2020). **B**, Examples of *B4GALNT2*- and *FUT2*-dependent antigen structures. The FUT2 enzyme governs the transfer of fucose (red triangle) residues to galactose (yellow circle) in an α(1,2)-linkage, thus producing the terminal epitope Fucα2-Galβ-R (Kelly et al., 1995). Subsequent activity of the FUT3 enzyme creates Lewis^{b} antigen. Different glycosyltransferases can further decorate H-antigen with GalNAc- or Gal-residues which creates A or B blood group antigens. The B4GALNT2 enzyme catalyzes the transfer of GalNAc (yellow square) to the sialylated glycans containing Neu5Acα2-3) Galβ motif which facilitates the synthesis of Sda and Cad antigens (Piller et al., 1986) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

et al., 2016), asthma exacerbation (Innes et al., 2011), and non-CF bronchiectasis (Taylor et al., 2017). In contrast, non-secretors have higher risks to develop primary sclerosing cholangitis (Folseraas et al., 2012), intestinal-type gastric cancer (Duell et al., 2015), Crohn's disease (McGovern et al., 2010), and type 1 diabetes (Smyth et al., 2011). Importantly, infectious disease also differs according to secretor status. For example, an increased incidence of infections with *Neisseria meningitidis, Streptococcus pneumonia* (Blackwell et al., 1986a), and *Haemophilus influenza* (Blackwell et al., 1986b) is reported in non-secretors, whereas non-secretors are protected from norovirus (Lindesmith et al., 2003). In addition, it was shown that *Fut2*-deficient mice are more resistant to vaginal *Candida albicans* infection (Hurd and Domino, 2004).

3. B4GALNT2

In 1967, a new antigen termed Sd^a (or Sid) was discovered on the membrane of erythrocytes by two independent groups (Macvie et al., 1967; Renton et al., 1967). Subsequent studies demonstrated that approximately 90 % of humans express the Sd^a antigen not only on red blood cells, but also in bodily secretions – with the highest concentration detected in urine (Morton et al., 1970) (see also Fig. 1). While expression levels of Sd^a antigen vary considerably between individuals, genetic polymorphisms are not described (Zhao et al., 2018). It was shown that GalNAc-binding lectins agglutinate the Sd^a antigen and its more reactive form, the Cad antigen (Tollefsen and Kornfeld, 1983). While the Sd^a/Cad antigens and the blood group A antigen both contain GalNAc and Gal, they are, in fact, structurally different (Table 1).

Serafini-Cessi and colleagues described the Sd^a synthase isolated from guinea pig kidneys: β1,4-*N*-acetylgalactosaminyl transferase 2 enzyme, which catalyzes the transfer of GalNAc from UDP-GalNAc to the sialylated N-linked chains of Tamm-Horsfall-like glycoprotein (Serafini-Cessi et al., 1986). Accordingly, a human analogue recognizing (Neu5Acα2-3)Galβ groups as acceptors and facilitating the synthesis of Sd^a/Cad antigens was identified (Piller et al., 1986). It was shown that the human *B4GALNT2* gene (Chr17q21.33), initially discovered in the colon carcinoma Caco-2 cell line, has two different isoforms: a short and a long isoform with an extended cytoplasmic domain (Lo Presti et al., 2003; Montiel et al., 2003). The major short *B4GALNT2* transcript variant and the corresponding protein were found to be mostly expressed in normal, but not in cancerous, epithelial colonic cells and also in healthy colon and stomach (Groux-Degroote et al., 2014). *B4GALNT2* is down-regulated in colo-rectal cancers and associated with increased metastasis (Dall'Olio et al., 2013). Introduction of Sd^a antigen in gastrointestinal cancer cells inhibited their metastatic potential and resulted in a total loss of cell-surface sialyl-$Lewis^x$ and sialyl-$Lewis^a$ antigens (Kawamura et al., 2005). Indeed, because the Sd^a and sialyl-Lewis antigens share a common α2,3-sialylated type 2 structure (Table 1), it was suggested that their biosynthesis is mutually exclusive (Pucci et al., 2020).

The gene encoding murine Sd^a synthase *B4galnt2* was cloned and characterized; cDNA predicted a type 2 transmembrane protein of a topology similar to other Golgi-glycosyltransferases (Smith and Lowe, 1994). Mohlke and colleagues discovered a novel *Mvwf1* ("Modifier of von Willebrand Factor-1") allele in the RIIIS/J inbred mouse strain which has reduced levels of von Willebrand factor (VWF) antigen in plasma and a prolonged bleeding time (Mohlke et al., 1996). Subsequent studies identified RIIIS/J-like *B4galnt2* alleles, conferring a unique tissue-specific switch in *B4galnt2* expression from intestinal epithelium to vascular endothelium, in multiple wild-derived mouse strains (Johnsen et al., 2008), as well as in wild mice (Johnsen et al., 2009). The expression of *B4galnt2* in murine blood vessels causes aberrant VWF glycosylation and enhances VWF clearance from the circulation, which results in a phenotype that closely resembles von Willebrand disease, a human bleeding disorder (Mohlke et al., 1999). Nevertheless, it appears that *B4galnt2* allelic polymorphisms have been maintained for at least 2.8 million years in the mouse lineage, suggesting that a loss of *B4galnt2* expression in the gut- and/or gain in blood vessels might be important for host-pathogen interactions (Linnenbrink et al., 2011; Vallier et al., 2017).

4. Direct interaction (glycan-mediated pathogen adhesion)

Carbohydrate-containing structures (glycans) have many important roles for the interaction between bacterial pathogens and their hosts. These interactions mediate bacterial adhesion, invasion, and immune evasion. Furthermore, glycans can serve as a source of nutrients or as ligands for bacterial toxins. Secretory and membrane-bound glycans also protect the host from pathogenic and opportunistic microorganisms. As previously mentioned, the blood group-related glycosyltransferases FUT2/Fut2 and B4GALNT2/B4galnt2 can influence susceptibility to various pathogens. Interestingly, while some pathogens can clearly benefit from the host expression of these genes, FUT2- and B4GALNT2-dependent glycosylation can also be detrimental to other pathogens. In this section we will discuss the role of *Fut2* and *B4galnt2*-dependent glycans for the direct interaction with individual bacterial and viral pathogens.

4.1. *Salmonella enterica*

S. enterica is a common human pathogen and constitutes a major disease burden worldwide. It can have several primary clinical manifestations from gastroenteritis to typhoid fever depending on the infecting serovar (Gal-Mor et al., 2014), and uses host glycans in the mucus and on the cell surface to adhere to and invade host cells (Taylor et al., 2018). This facultative anaerobic, Gram-negative bacterium is an intracellular pathogen that uses its virulence factors including fimbriae/pili, flagella and type 3 secretion systems (T3SS), encoded by *Salmonella* pathogenicity island (SPI)-1 and SPI-2, to infect host cells (Ibarra and Steele-Mortimer, 2009). Fimbriae as one of the adhesive structures present on the bacterial surface are important for the initial attachment to host cell surfaces. Depending on the serotype, *Salmonella* has up to 20 fimbrial adhesins (Wagner and Hensel, 2011; Yue et al., 2012). The *std* fimbrial operon encodes the π-class Std fimbriae, which bind terminal α(1,2)-fucose residues (Chessa et al., 2009). *Fut2*-deficient mice were shown to be more susceptible to *Salmonella* infection at an early time point post infection (Goto et al., 2014; Suwandi et al., 2019). In contrast, *Fut2*-deficient mice displayed a substantial reduction in bacterial colonization and inflammation after long-term *Salmonella* infection (Suwandi et al., 2019; Weening et al., 2005). It is hypothesized that at day one after infection, α(1,2)-fucose-containing glycans in epithelial cells and secreted mucus may prevent *Salmonella* infection, although the exact mechanism is not clear (Goto et al., 2016). At later time points of infection, the presence of α(1,2)-fucose-containing glycans present in the intestine of *Fut2*-proficient mice can be exploited by *Salmonella*. Furthermore, we and others also demonstrated that bacteria expressing *std* fimbriae exhibited increased adhesion to human cell lines and murine intestinal organoids when terminal α(1,2)-fucose was present (Chessa et al., 2009; Suwandi et al., 2019). Taken together, both *in vivo* and *in vitro* results demonstrate that *Salmonella* can exploit host fucosylation in the intestine using its Std fimbriae.

Less is known how *B4galnt2* expression influences the direct interaction of *Salmonella* with intestinal epithelial cells. Invasion assays showed that knockdown of *B4galnt2* expression significantly decreased *Salmonella* invasion compared to *B4galnt2*-expressing cells (Rausch et al., 2015). Although *Salmonella* does not seem to directly bind to *B4galnt2*-dependent GalNAc residues *in vitro* (Giannasca et al., 1996), the overall glycan profile might also change in the cells not expressing *B4galnt2* in addition to the lack of Sd^a antigen (Dall'Olio et al., 2014; Groux-Degroote et al., 2014), and thus impair *Salmonella* invasion. Overexpression of the *B4galnt2* gene in MDCK cells convert α2,3-sialic acid receptors into Sd^a-like epitopes, which might influence the susceptibility of *Salmonella* infection (Wong et al., 2019). However, a direct

link between *B4galnt2* expression and *Salmonella* susceptibility still remains elusive and needs further study.

4.2. Escherichia coli

E. coli is a Gram-negative, facultative anaerobic and rod-shaped bacterium. It is a commensal bacterium of the gastrointestinal tract, but there are also pathogenic *E. coli* strains that cause a variety of diseases. At least six different pathogenic *E. coli* strains cause enteric disease, whereas others cause extra-intestinal infections such as urinary tract infection and meningitis (Kaper et al., 2004). Enterotoxigenic *E. coli* (ETEC) is a leading cause of infectious diarrhea in the developing world, particularly in young children. These pathogens are also a major cause of traveller's diarrhea in endemic areas (Black, 1990). In a clinical study, it was demonstrated that children with a *FUT2* non-secretor status are more likely to have symptomatic ETEC infection in comparison to those with secretor status (Mottram et al., 2018).

ETEC, like commensal and other pathogenic *E. coli*, has adherence factors including fimbrial and non-fimbrial adhesins that are important for attachment to the host surface. This bacterium encodes at least 23 distinct fimbriae (named colonization factors, CFs) (Torres et al., 2005). Interestingly, it was reported that children with a *FUT2* non-secretor status are more likely to be infected by ETEC expressing the colonization factor antigen I (CFA/I) and other ETEC CF family fimbriae (Ahmed et al., 2009). Mottram and colleagues demonstrated that CfaB, the major subunit of ETEC CFA/I fimbriae and of another four related ETEC fimbriae, increases binding incre to Chinese Hamster Ovary (CHO)-K1 cell line expressing Lewis^{a} (mimicking *FUT2* non-secretor status) compared to cells carrying Lewis^{b} antigens (*FUT2* secretor status) or wild-type CHO-K1 cells. Furthermore, the authors performed an *in-silico* analysis, which predicted the potential structural binding region between Lewis^{a} and CfaB of CFA/I and related fimbriae (Mottram et al., 2018). In addition to ETEC, a clinical study showed that in women, Lewis blood-group non-secretor status is associated with an increased frequency of recurrent urinary tract infections caused by uropathogenic *E. coli* (UPEC) (Sheinfeld et al., 1989). In another study, UPEC strain R45 expressing both P and F adhesins was shown to bind to glycosphingolipids extracted from vaginal epithelial cells from non-secretors, but not from secretors (Stapleton et al., 1992). Taken together, these studies indicate that the expression of *Fut2* plays an important role in protecting the host against pathogenic *E. coli* infection.

Less is known about a possible role of *B4galnt2* glycans on *E. coli* interaction with the host. There is no evidence for direct binding of *E. coli* to *B4galnt2* glycans. In contrast, *B4galnt2* mediated modification of Tamm-Horsfall glycoprotein may even protect against *E. coli* infections by masking its receptor by blocking its binding sites in the large intestine and kidney (Serafini-Cessi et al., 2005).

4.3. Helicobacter pylori

H. pylori is one the most common human infectious agents and causes chronic infection of the human stomach. This Gram-negative and flagellated bacterium is considered as the main cause of ulcers and gastric cancer (Marshall and Warren, 1984; Warren and Marshall, 1983). This microaerophilic bacterium is often found within the mucus that covers the gastric epithelium. *H. pylori* attaches to gastric epithelial cells which is important in establishing persistent colonization and induction of gastric inflammation (Celli et al., 2009; Hessey et al., 1990; Schreiber et al., 2004). The best-characterized *H. pylori* adhesin is the blood group antigen-binding adhesin (BabA) that binds to ABO(H)/Lewis^{b} blood group antigens located on the surface of gastric epithelial cells and mucins (Borén et al., 1993; Ilver et al., 1998; Nell et al., 2014). In the Lewis^{b} blood group, the *FUT2* gene adds a fucose molecule in α(1, 2)-linkage onto a galactose residue. *FUT2*-deficient individuals are unable to synthesize ABO(H)/Lewis^{b} antigens, but can express Lewis^{a} antigens due to the action of FUT3 (Bergstrom and Xia, 2013). *Fut2*-deficient mice are characterized by a significantly decreased degree of α1,2-fucosylation, and hence Lewis^{b} antigen expression in the stomach. Interestingly, this change impairs gastric mucosal binding of *H. pylori* BabA adhesion in epithelial cells and mucus (Magalhães et al., 2016, 2009). Thus, *H. pylori* is able to exploit *Fut2*-dependent host glycans using its BabA adhesin.

Similar to the situation in *E. coli*, there is no evidence for direct binding of *H. pylori* to *B4galnt2* glycans. However, *H. pylori* binds to sialic acid *via* its adhesin SabA (Mahdavi et al., 2002). It would be interesting to clarify whether *B4GALNT2* expression in the stomach could reduce *H. pylori* attachment through the masking of sialylated residues.

4.4. Viruses

Glycans also contribute to viral infection, serving as entry receptors for virions. Clinical studies revealed an association between secretor status and multiple respiratory viral diseases, *e.g.*, those caused by influenza virus A and B, rhinoviruses, respiratory syncytial virus and echoviruses (Raza et al., 1991). In addition, several studies also showed an association between non-secretor status and a reduced risk for HIV-1 infection (Ali et al., 2000; Chanzu et al., 2015; Kindberg et al., 2006).

Recently, a CRISPR activation screen identified that *B4galnt2* overexpression can inhibit influenza A virus infection (Heaton et al., 2017). *B4galnt2* overexpression modifies sialic acid-containing glycans, which can be used by influenza A viruses as a receptor, recognized by the viral glycoprotein hemagglutinin. The same study also showed that *B4galnt2* overexpression prevented infection with several avian influenza virus strains tested, including H5, H9, and H7 subtypes. Another study also demonstrated that overexpression of *B4galnt2* in MDCK cells modified surface α2,3-sialyllactose receptors, which lead to a decreased binding and invasion capability of influenza viruses with α2,3-receptor (Wong et al., 2019). Thus, expression of *B4galnt2* can inhibit influenza A virus infection through the modification of sialic-acid containing glycans, which are important for viral attachment.

Human noroviruses, previously known as Norwalk virus, are one of the common causes of gastroenteritis in children and adults worldwide (Lopman et al., 2016). These single stranded RNA viruses belong to the Caliciviridae family and are transmitted *via* the fecal-oral route, including consumption of contaminated food or water and direct person to person contact (Robilotti et al., 2015). Human norovirus is classified into at least five genogroups (GI-GV), which are further subdivided into genotypes. GII.4 is the predominant human norovirus that causes the majority of gastroenteritis outbreaks (Robilotti et al., 2015). Several studies showed that the susceptibility to norovirus infection is mediated by *FUT2,* whereby non-secretors are resistant to several norovirus genotypes, including GII.4 (Currier et al., 2015; Lindesmith et al., 2003; Lopman et al., 2015; Nordgren et al., 2013). Histo-blood group antigens (HBGAs), influenced by *FUT2* gene, are cell attachment factors for norovirus and important for a productive norovirus infection. Crystallography studies revealed that α(1,2)-fucose-containing H- and A-type HBGA and Lewis antigens are important binding sites for a majority of human noroviruses. (Bu et al., 2008; Cao et al., 2007; Choi et al., 2008).

Rotavirus infections are the leading cause of severe gastroenteritis and diarrhea in children below 5 years of age. Infection with these non-enveloped double-stranded RNA viruses leads to vomiting, malaise and fever. The mode of transmission is mainly through the faecal-oral route by direct contact to an infected person or consumption of contaminated food or water (Crawford et al., 2017). Rotaviruses use the outer capsid protein viral protein (VP)4 (through its VP8* domain) for adhesion to sialoglycans (such as gangliosides GM1 and GD1a) and to HBGAs (Hu et al., 2012; Huang et al., 2012) on the host cell surface. Interestingly, Ramani and co-authors reported that the infectivity of rotavirus strain G10 P was significantly enhanced by the expression of H type II precursor in CHO cells (Ramani et al., 2013), and proposed that the glycan-binding specificity of certain rotaviruses may explain the tropism for neonates. Importantly, non-secretor individuals were shown to not

be recognized by most human rotavirus A strains (Imbert-Marcille et al., 2014), indicating that secretor status also plays a role in susceptibility to this viral pathogen.

Importantly, ABO blood group antigens were recently shown to influence the risk for infection with the pandemic coronavirus strain SARS-CoV2. Several studies showed that individuals with blood group A bear a greater risk of SARS-CoV2 infection, COVID-19 severity and mortality, in contrast to a protective effect for blood group O (Amoroso et al., 2021; Muñiz-Diaz et al., 2020; Severe Covid-19 GWAS Group et al., 2020; Zhao et al., 2020). However, a recent retrospective case-control study challenges this view and found no significant association between ABO blood groups and susceptibility to SARS-CoV2 infection (Khalil et al., 2020). Future analyses of larger patient cohorts may be needed to define the effect of ABO on SARS-CoV2 susceptibility.

5. Indirect interactions (influencing endogenous microbiota)

The intestinal microbiota is known to have a strong effect on the health and physiology of their hosts. The commensal bacteria contribute to the development and response of the immune system, defense against pathogens and colonization resistance (Ducarmon et al., 2019; Round and Mazmanian, 2009). Moreover, abnormal changes in these communities, termed dysbiosis, are linked to the development and progression of various diseases, such as chronic inflammatory bowel disease (Lane et al., 2017), irritable bowel syndrome (Rajilić-Stojanović et al., 2011) as well as susceptibility to infections (Ubeda et al., 2017).

The gastrointestinal tract of humans and other mammals is covered by a glycosylated mucus layer. The mucus layer acts as a physical barrier between a host and microbial communities, and as a site of host-microbe interactions. Importantly, glycans represent a first interaction point between the host and intestinal microbes, and can thus modulate commensal microbiota compostion (Koropatkin et al., 2012).

5.1. B4GALNT2

Two independent studies demonstrated changes in composition of the gut microbiota in mice lacking intestinal *B4galnt2* expression (Rausch et al., 2015; Staubach et al., 2012). The study by Rausch et al. (2015) further carried out a murine model of *Salmonella*-induced colitis. Under normal circumstances *S*. Typhimurium is unable to successfully colonize the mouse gut and cause inflammation. Thus, Rausch et al. (2015) administered a pretreatment with streptomycin to break the colonization resistance of the resident microbiota (Barthel et al., 2003), revealing a lack of intestinal *B4galnt2* expression to be associated with reduced gut inflammation. Moreover, the severity of inflammation in the experiment positively correlated with the extent of change in microbiota composition before and after infection with *S*. Typhimurium. Accordingly, mice lacking intestinal *B4galnt2* expression displayed less microbiota turnover and less inflammation, suggesting a role of the gut microbiota. Intriguingly, fecal microbiota transfer experiments demonstrated that the greater inflammation in *B4galnt2* expressing mice is largely dependent on the *B4galnt2* genotype-specific microbiota, rather than *B4galnt2* expression itself. The mechanism(s) surrounding this effect remain unclear and are a subject of future study, but likely involve differences in resistance and/or resilience of the gut microbiota.

5.2. FUT2

Similar to *B4galnt2*, metagenomic studies in humans and mice have revealed differences in the intestinal microbiota according to *FUT2* genotype (Folseraas et al., 2012; Rausch et al., 2017, 2011; Tong et al., 2014; Wacklin et al., 2011). These studies were based on material from colonic biopsies, bile fluid, endoscopic lavage samples of the cecum and colon, or fecal material from a controlled laboratory mouse setting. In contrast, other large-scale studies analyzing fecal samples failed to observe an association with *FUT2* genotype (Davenport et al., 2016; Turpin et al., 2018). These discrepancies indicate that the overall genotype effect on inter-individual differences may be subtle, and/or that the material/site of the GIT is important. It should be pointed out, however, that even the *FUT2* genotype/secretor status of the maternal lineage was found to be important in some studies (Rausch et al., 2017; Smith-Brown et al., 2016).

Despite inconsistencies between metagenomic studies, there are many biological reasons to consider the *FUT2* gene's influence on intestinal microbes in the context of infection. As mentioned earlier, the functional *FUT2* gene present in secretors facilitates the addition of α-2-fucose residues at the terminal end of glycan chains abundant in the human gut epithelia. In contrast, the gut epithelia of non-secretors lack these fucosylated carbohydrate moieties (Bry et al., 1996; Moran et al., 2011). As a result, the resources available for utilization by the gut microbes in the two distinct phenotypes tend to vary depending on the diet of the host (Kashyap et al., 2013). However, when fucose is unavailable through dietary sources, the gut bacteria resort to utilizing the host derived fucose in secretors (Becker and Lowe, 2003).

It is known that only certain bacteria are capable of cleaving host-derived fucose, thereby releasing fucose into the gut environment and making it freely available to be utilized by other non-cleaving microbes (Pacheco et al., 2012). For example, *Bacteroides thetaiotaomicron* can cleave and release host fucose in the intestinal environment, making it readily available for utilization by *Lactobacillus rhamnosus* GG, which lacks the cleaving activity (Becerra et al., 2015; Hooper et al., 1999). Thus, gut commensals like *B. thetaiotaomicron, Akkermansia muciniphila,* segmented filamentous bacteria*, etc.* promote the ecological succession of fucose utilizing bacteria like *E. coli* Nissle 1917*, L. rhamnosus* GG, *Ruminococcus gnavus*, among others, most of which are known for their beneficial effects in the human gut (Becerra et al., 2015; Hooper et al., 1999; Shin et al., 2019; Tailford et al., 2015; Wu et al., 2020). Similarly, (e.g. afte the presence of free fucose (e.g. after antibiotic treatment) can lead to an environment conducive to a number of fucose utilizing pathogens (Ikehara et al., 2001; Stahl et al., 2011; Suwandi et al., 2019). For example, *Campylobacter jejuni*, a common pathogen responsible for pediatric diarrhea, can metabolize free fucose and induce intestinal disease (Stahl et al., 2011; van der Hooft et al., 2018). Other similar examples include *H. pylori, Salmonella* spp., enterotoxigenic *E. coli*, and *Brucella abortus* (Budnick et al., 2018; Coddens et al., 2009; Ikehara et al., 2001; Suwandi et al., 2019).

Another important point to consider with regard to susceptibility to infection is that host fucosylation plays a role in the microbiota-mediated immunity of the host. Fucose-cleaving commensals can directly influence host fucosylation by inducing type 3 innate lymphoid cells (ILC3) to produce interleukin-22 (IL-22), which in turn signals the intestinal epithelial cells (IEC) to produce fucose (Goto et al., 2014). Up-regulation of fucosylation was shown to strengthen barrier function and enhance colonization resistance to invading pathogens (Pham et al., 2014). In this study, *Il22* and *Fut2* were up-regulated during *S*. Typhimurium and *Citrobacter rodentium* infection, and *Il22*$^{-/-}$ mice showed an increased bacterial burden compared to wild-type mice. Additionally, proliferation of the opportunistic pathogen *Enterococcus faecalis* was observed. Interestingly, administration of 2′-fucosyllactose (2′FL), an α1,2-fucosylated oligosaccharide, resulted in significant mitigation of the symptoms in *Il22*-deficient mice (Pham et al., 2014). Another study by Pickard et al., further demonstrated how host fucosylation is used as a defense mechanism in response to pathogen-induced stress, and the role gut microbiota plays in enabling this process (Pickard et al., 2014; Pickard and Chervonsky, 2015). Thus, in sum, many commensal bacteria can take advantage of host fucosylation not only as a source of nutrition and site of adhesion, but also to modify host gene expression and strengthen its colonization resistance towards pathogenic bacteria.

5.3. Viruses

Although it is well-established that host secretor status affects

susceptibility to norovirus and rotavirus infections by modulating viral adherence, recent studies indicate that the gut microbiota can also facilitate the infectivity of these viruses. Accordingly, depletion of the intestinal microbiota with antibiotics significantly reduced the replication of norovirus and rotavirus in the murine gut (Jones et al., 2014; Uchiyama et al., 2014). While the exact mechanism of this suppression is not clear, it was proposed that the gut microbiota may assist viral entry by regulating the expression of host receptors and/or bacterial ligands (Uchiyama et al., 2014). Indeed, it was demonstrated *in vitro* that HBGA-expressing enteric bacteria promoted norovirus infection of human B cells (Jones et al., 2014). Moreover, Rodriguez-Diaz and colleagues reported a negative correlation between the relative abundances of the gut commensals *Faecalibacterium* and Ruminococcaceae and IgA titers against norovirus and rotavirus (Rodríguez-Díaz et al., 2017). *Faecalibacterium* benefits from acetate metabolism and Ruminococcaceae can utilize fucose, and both of these metabolites are supplied by *Bacteroides* spp. (Wrzosek et al., 2013). Interestingly, a higher relative abundance of a *Bacteroides* operational taxonomic unit (OTU) was detected in secretors compared to non-secretors (Rodríguez-Díaz et al., 2017). Taken together, these findings suggest that variation in gut microbiota communities determined by *FUT2* genotype can also affect susceptibility to viral pathogens.

6. Therapeutic applications of blood group-related glycans

As discussed in the previous chapters, FUT2- and B4GALNT2-dependent mucosal glycans can act as receptors to promote microbial adhesion or as nutrients for commensal or pathogenic bacteria. Hence, it is appealing to utilize histo-blood group-related glycans in therapeutic interventions, either as decoy targets to selectively bind pathogens or to support glycan-metabolizing commensals *in situ*. In this case, human milk oligosaccharides (HMOs) serve as inspiration, due to their prebiotic and anti-infective properties (see Walsh et al., 2020 for an excellent review). Structurally, they represent a diverse family (>150 HMOs) of linear or branched oligosaccharides comprised of a lactose core, N-acetylglucosamine (GlcNAc), D-glucose and D-galactose (German et al., 2008). Additionally, the majority of HMOs are terminally sialylated and fucosylated: notably, α(1-2) fucosylation of HMOs is governed by the FUT2 enzyme in secretors (Fig. 1).

HMOs are not digested and reach the large intestine of breast-fed infants, where they provide selective substrates for specific gut commensals such as bifidobacteria and *B. thetaiotaomicron* (Salli et al., 2021). Indeed, it was shown that three major fucosylated components of HMOs, 2′-O-fucosyllactose (2′FL), lactodifucotetraose and 3-fucosyllactose, sustained *in vitro* growth of *Bifidobacterium* spp. isolated from infant fecal samples, while *E. coli* K12 or *Clostridium perfringens* were not able to metabolize fucosylated oligosaccharides (Yu et al., 2013). In a double-blind, placebo-controlled study, oral supplementation with HMOs (2′FL and lacto-*N*-neotetraose, LNnT) was well-tolerated by healthy adults and resulted in a significant increase in relative abundances of Actinobacteria and *Bifidobacterium* (Elison et al., 2016). As of Jan 2021, ClinicalTrials.gov lists six trials (four at the recruiting stage) aiming to investigate the potential benefits of a prebiotic 2′FL therapy in various diseases and conditions, such as hematopoietic stem cell transplant, IBD, bowel dysfunction, and anemia. Several studies explored the effect of 2′FL treatment on Fucα(1-2)-binding pathogens. For example, Weichert et al. demonstrated that 2′-fucosyllactose and 3-fucosyllactose inhibited adhesion of EPEC, *Pseudomonas aeruginosa*, and *S. enterica* serovar Fyris to human intestinal and respiratory cell lines (Weichert et al., 2013). It was also shown that 2′-FL blocked 80 % of *C. jejuni* invasion into human colon carcinoma cells and substantially reduced *C. jejuni* colonization and intestinal inflammation in mice (Yu et al., 2016). Accordingly, high concentrations of α1-2 fucosylated HMOs (2′FL, specifically) in maternal milk had been previously associated with lower susceptibility to *C. jejuni*-caused infant diarrhea (Morrow et al., 2004). An inhibitory effect of fucosylated HMOs on norovirus (Morrow et al., 2005; Shang et al., 2013) and rotavirus (Laucirica et al., 2017; Walsh et al., 2020) adhesion to host cells was also demonstrated.

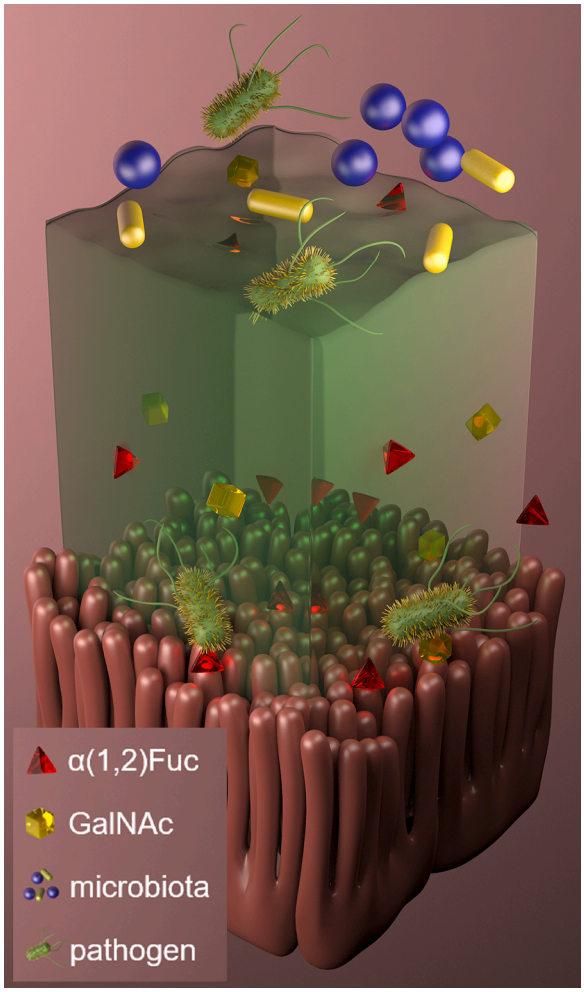

Fig. 2. *Host microbiota and pathogens utilize B4GALNT2- and FUT2-dependent glycans as nutrients and/or adhesion sites.* Commensal microbes can cleave α(1,2)-Fuc of histo-blood group antigens (HBGAs) which are expressed in abundance on mucins. Many pathogens (including *S.* Typhimurium) are able to metabolize free fucose (red pyramids) present in the mucus (green). Furthermore, pathogens can penetrate the mucus inner layer and adhere to the mucosa by employing multiple adhesins. Many of these adhesins can attach to host HBGAs: for example, to bind terminal α(1,2)-Fuc residues, *S.* Typhimurium employs Std fimbriae while *H. pylori* utilizes BabA adhesin (Borén et al., 1993). The *B4GALNT2*-dependent GalNAc-containing glycans (yellow cubes) may act as nutrients and enhance colonization resistance (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

The therapeutic potential of free monosaccharides (fucose (Ke et al., 2020), galactose (Pfeiffer, 2020)), of porcine mucin glycans (Pruss et al., 2020), and of synthetic glycoconjugates, including so-called "glycomimetics" (Imberty et al., 2008; Kalas et al., 2018; Meiers et al., 2019), is also very promising. For instance, an inhalation of fucose and galactose significantly reduced *P. aeruginosa* burdens in the sputum of patients with cystic fibrosis, presumably by binding bacterial lectins LecA and LecB and thus competing with the epitopes expressed on lung epithelia (Hauber et al., 2008). Once a glycan-binding affinity of a given pathogen is characterized (see Chapter 4), it is possible to enhance decoy properties by rational design. Boukerb et al. synthesized calix[4]arene-based glycoclusters functionalized with galactosides/fucosides, which induced *P. aeruginosa* clumping in a LecA-dependent manner and reduced biofilm formation, adhesion to epithelial cells, and alveolar injury (Boukerb

et al., 2014). Another interesting strategy was recently proposed by Meiers et al. (2020): conjugation of glycomimetics targeting *P. aeruginosa* LecA and LecB to ciprofloxacin resulted in accumulation of the antibiotic/carbohydrate in *P. aeruginosa* biofilms, as well as in reduced host cytotoxicity. However, the authors noted that an attachment of glycomimetics also decreased the antibiotic activity of ciprofloxacin (Meiers et al., 2020).

In summary, recent technological advances combined with a deeper understanding of host-microbial glycobiology offer an opportunity to employ fucosylated HMOs naturally occurring in human milk or synthetic glycomimetics as novel therapeutic approaches.

7. Conclusions

The expression pattern of histo-blood group glycans in blood, epithelia, mucus and bodily secretions exposes them to intimate contact with commensal and pathogenic bacteria, viruses and fungi. FUT2 and B4GALNT2 glycans modulate the intestinal microbiota and influence susceptibility to gastrointestinal infections by several mechanisms (Fig. 2). A more detailed understanding of the complex mechanisms of interaction between pathogens and host glycans is needed in order to develop novel therapeutic treatments by targeted modification of these glycans or inhibition of the interaction of pathogens with these glycans. This may ultimately lead to new treatments to prevent or cure infections and possibly other glycan-related diseases.

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Declaration of Competing Interest

The authors report no declarations of interest.

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