REVIEW

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Epithelial glycosylation in gut homeostasis and inflammation

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Intestinal epithelial cells apically express glycans, especially α1,2-fucosyl linkages, which work as a biological interface for the host–microbe interaction. Emerging studies have shown that epithelial α1,2-fucosylation is regulated by microbes and by group 3 innate lymphoid cells (ILC3s). Dysregulation of the gene (*FUT2*) encoding fucosyltransferase 2, an enzyme governing epithelial α1,2-fucosylation, is associated with various human disorders, including infection and chronic inflammatory diseases. This suggests a critical role for an interaction between microbes, epithelial cells and ILC3s mediated via glycan residues. In this Review, using α1,2-fucose and *Fut2* gene expression as an example, we describe how epithelial glycosylation is controlled by immune cells and luminal microbes. We also address the pathophysiological contribution of epithelial α1,2-fucosylation to pathogenic and commensal microbes as well as the potential of α1,2-fucose and its regulatory pathway as previously unexploited targets in the development of new therapeutic approaches for human diseases.

The intestine is a unique organ that is constitutively exposed to luminal environmental antigens, including innumerable pathogenic and nonpathogenic microorganisms. Hosts have developed a multilayered biological system for the creation and maintenance of an intestinal homeostatic environment and the establishment of bidirectional cross-talk between the host and microbial symbionts. The host is equipped with a first line of defense, consisting of the intestinal epithelial and mucus layers at the surface of gastrointestinal tract, to restrict undesired intrusion of luminal microorganisms. The intestinal epithelium consists of a variety of epithelial cells (ECs), including enterocytes, goblet cells, enteroendocrine cells, Paneth cells and M cells, connected by tight junctions; these function as a physical and cellular barrier against external antigens[1,2]. In addition, a mucus layer produced by goblet cells covers the surface of intestinal ECs and is important in the containment of microorganisms in the lumen[3]. ECs, especially Paneth cells, also yield antimicrobial peptides such as α-defensin and RegIIIγ for protection against microbial infection and for spatiotemporal regulation of colonization by commensal bacteria[4–7]. As a second barrier system, the gut innate and acquired immune systems distinguish between beneficial and pathological antigens, exerting immunological functions to tolerate or eliminate these, respectively[8].

These first and second barriers operate cooperatively (not independently) to eradicate harmful antigens, while establishing symbiotic conditions in regard to nonpathogenic microbes. Bidirectional interactions between intestinal ECs and immune cells can shape the gut immune system[9]. For instance, ECs help induce T helper 17 (T_H17) cell differentiation by producing serum amyloid A (SAA)[10–12], while intestinal T_H17 cells produce interleukin 22 (IL-22) and IL-17A, leading to the production of antimicrobial molecules from ECs. This interplay between ECs and T_H17 cells is an example of coordinated cross-communication to create a protective platform against pathogenic bacterial infection[12].

In contrast to the fate of pathogens, which induce transient inflammatory immune responses, commensal microorganisms on the luminal side of epithelial surfaces constitutively educate the host mucosal immune system without producing any pathological symptoms[13,14]. Therefore, how the host achieves a divergent barrier system, allowing a symbiotic relationship with commensals and a protective platform against pathogens, is an important question in regard to our understanding of host–microbe communication. Recent reports have shown that intestinal epithelial glycans play a crucial role in the host–microbe interplay and that their glycosylation is modulated by microbial stimulation and the gut immune system[15–17]. Notably, epithelial glycans contribute to the maintenance of gut microbiota homeostasis and are linked to the virulence of selected pathogenic bacteria and viruses, serving as the entry receptors for bacterial toxins and viral particles[18–20]. These findings shed light on the important roles of epithelial glycans and glycosylation as communication tools and immunological factors for the control of luminal microbes. Here, we review the physiological and immunological contributions of intestinal epithelial glycans, especially α1,2-fucose, as the biological and interactive molecule for the host–microbe cross-communication. Interestingly, emerging findings have revealed a previously unknown mechanism of epithelial α1,2-fucosylation regulated by group 3 innate lymphoid cells (ILC3s) situated under the gut epithelium and by luminal commensal bacteria[15]. This interactive network system of mucosal immune cells, ECs and luminal microorganisms for the induction and regulation of epithelial glycosylation and subsequent

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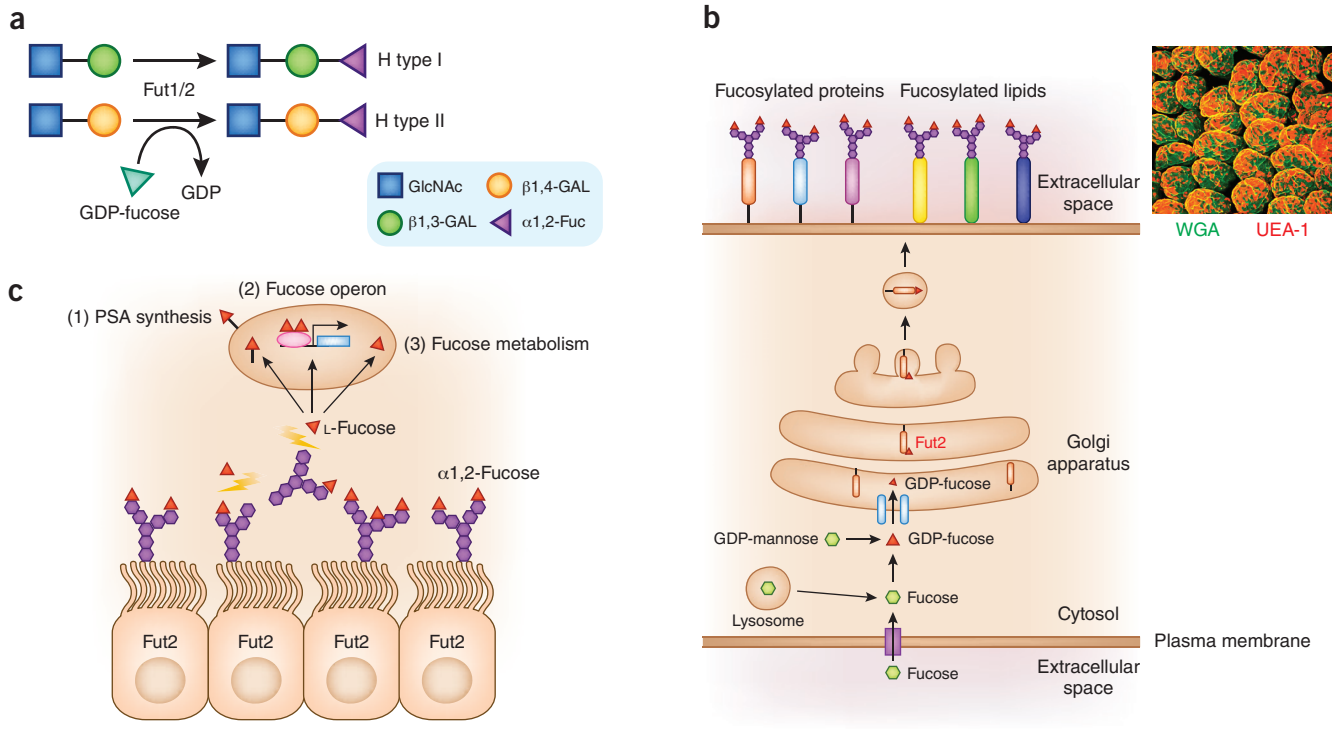

Figure 1 Intestinal epithelial α1,2-fucose synthesized by fucosyltransferases is a symbiotic molecule between host and microbes. (**a**) H type I and II antigens are synthesized by Fut1 and Fut2, respectively (denoted collectively as Fut1/2). (**b**) Fucose incorporated from extracellular spaces is converted into GDP-fucose in the cytosol. GDP-fucose is also produced from GDP-mannose. After GDP-fucose is incorporated into the Golgi apparatus, Fut2 mediates the decoration of peripheral terminal β-D-galactose on proteins and lipids with α1,2-fucose. α1,2-fucosylated proteins and lipids are subsequently transferred to the plasma membrane. Photo at top right shows whole-mount staining of murine ileal villi stained with the lectins UEA-1 and WGA. UEA-1 and WGA bind to α1,2-fucose and *N*-acetyl-D-glucosamine, respectively. (**c**) Membrane-bound and secreted α1,2-fucose are cleaved by bacterial fucosidase, and liberated L-fucose is incorporated by selected symbionts such as *Bacteroides*. *Bacteroides* have a set of genes that recycle host-derived L-fucose. L-Fucose is utilized to (1) synthesize fucosylated polysaccharides (PSA), (2) regulate gene expression through the fucose operon and (3) undergo catabolism for energy.

establishment of intestinal homeostasis represents a potentially attractive target for the development of new treatments for host infectious and inflammatory diseases.

Epithelial sugar chains mediate host–microbe communication

In living cells, cell surface proteins and lipids are decorated by polysaccharides, which are processed by enzymes responsible for the addition of specific sugar residues to the substrates[21,22]. Carbohydrate moieties expressed on cells have diverse and useful biochemical properties, such as molecular trafficking and clearance, cell adhesion, immune surveillance, hematopoiesis, inflammation, inter- and intracellular signaling, receptor activation and endocytosis[21,22]. Unique carbohydrate moieties expressed in various cell subsets confer different functional properties upon each cell type in cell-specific, site-specific and protein-specific manners[23]. Glycans expressed on and secreted from the apical surfaces of mucosal ECs possess unique physiological, immunological and functional characteristics in line with their specific distribution in tissues, where they are in continuous contact with surrounding environmental antigens. One important characteristic of the mucosal epithelial glycan system is that its glycosylation is pliably and adaptively operated in response to environmental stimuli[24]. In fact, carbohydrate moieties expressed on the apical surfaces of ECs are constantly renewed, turning over approximately every 6–12 h in the murine jejunum[25]. Membrane-bound glycoproteins and glycolipids on mucosal ECs function as important communication tools between the host and luminal microbes. For example, enteric bacteria such as pathogenic *Escherichia coli* and *Salmonella typhimurium* bind to glycoprotein 2 (GP2), a 75-kDa glycosylphosphatidylinositol (GPI)-anchored protein[26] that is specifically expressed on the apical membrane of M cells via the bacterial type I pili of these pathogens as a means of invasive entry thorough the host intestinal epithelium[27]. A recent study has shown that *Vibrio parahaemolyticus* infects host cells by using its type III secretion systems I and II to target epithelial-surface-associated biotransformation molecules, including sulfation and fucosylated glycans, respectively[28]. A microbial toxin produced by pathogenic bacteria targets glycolipids on intestinal ECs[18]. For instance, cholera toxin, produced by *Vibrio cholerae*, binds to GM1 ganglioside on intestinal ECs[18]. In addition to bacteria, enteric viruses such as norovirus (Norwalk virus) bind to α1,2-fucose residues via histo-blood-group antigens expressed on intestinal ECs[20]. Therefore, intestinal epithelial glycans are critical in the interplay between host and luminal microorganisms.

Epithelial α1,2-fucose governs host–microbe mutualism

Fucose is a deoxyhexose that is one of major components of N- and O-linked glycans[29]. Fucosylated sugar chains are synthesized by fucosyltransferases (Fut)[30]. So far, 13 fucosyltransferase genes have been identified in the human genome[30]. In human and murine intestine, the *Fut1* and *Fut2* genes, encoded on chromosome 19 and 7, respectively, are expressed in ECs[31,32]. FUT1 and FUT2 mediate the addition of L-fucose via an α1–2 linkage to the terminal β-D-galactose residues of mucosal glycans including type 1 or 2 *N*-acetyllactosamine, subsequently producing H type 1 or type 2 antigens of ABO histo-blood group, respectively[33,34] (**Fig. 1a**). It has been reported that ABO histo-blood-group antigens governed by FUT2 are secreted into the oral cavity and intestinal lumen and determine secretor status in humans[35]; thus, *FUT2* is

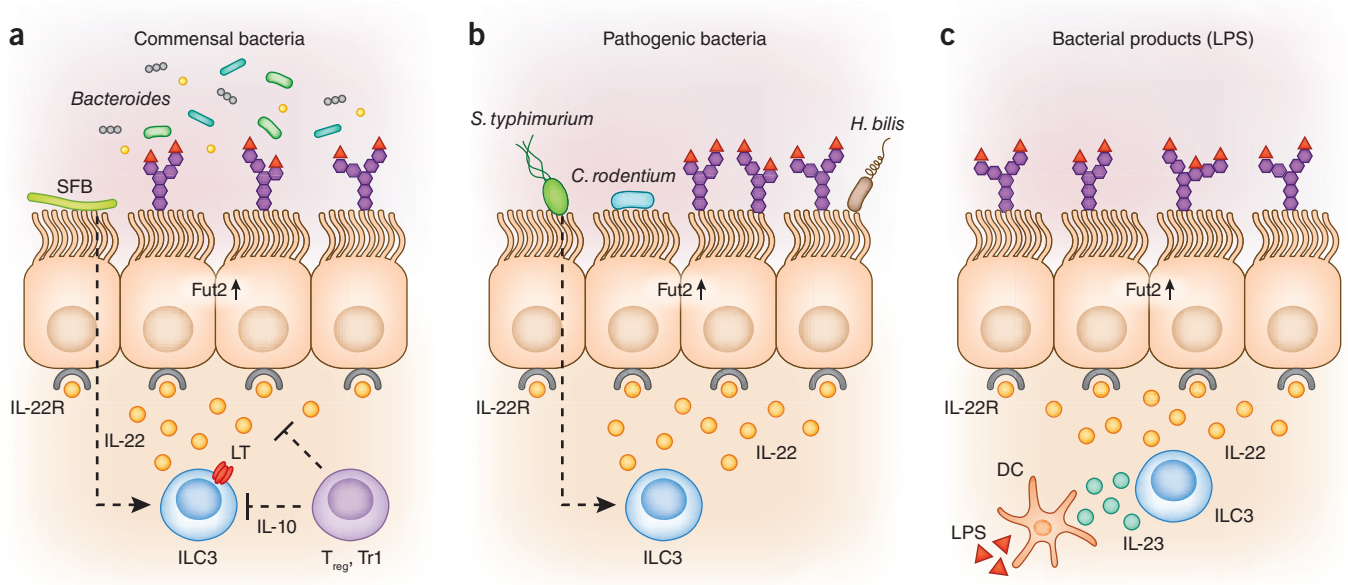

Figure 2 Intestinal epithelial α1,2-fucosylation is regulated by bacterial signals and immune cells. (**a**) Commensal bacteria, especially segmented filamentous bacteria (SFB) and *Bacteroides*, induce epithelial Fut2 and α1,2-fucose expression. IL-22 and lymphotoxin (LT) from group 3 innate lymphoid cells (ILC3s) mediate SFB-induced epithelial α1,2-fucosylation. (**b**) Pathogenic bacteria such as *S. typhimurium*, *C. rodentium* and *H. bilis* have the potential to induce epithelial Fut2 and α1,2-fucose. ILC3s and IL-22 are critical for epithelial α1,2-fucose induced by *S. typhimurium* and *C. rodentium*. (**c**) Bacterial components such as lipopolysaccharide (LPS) stimulate gut dendritic cells (DCs) via the TLR–Myd88 pathway. IL-23 produced by gut dendritic cells induces IL-22 production from ILC3s, subsequently promoting epithelial Fut2 and α1,2-fucosylation.

known as a secretor gene[33,36]. FUT2 transfers fucose from the activated monomeric form, guanosine diphosphate (GDP)-fucose (**Fig. 1b**). GDP-fucose is synthesized from GDP-mannose and fucose incorporated from extracellular milieu or released from fucosylated glycan resides in lysosomes (**Fig. 1b**)[37]. GDP-fucose is catabolized and transferred to acceptor sugar substrates on glycoproteins and glycolipids in the Golgi apparatus (**Fig. 1b**). One study showed that *Fut1* is ubiquitously expressed, whereas *Fut2* is preferentially expressed in ECs of the oral cavity and gastrointestinal and urogenital tracts[32]. Recent reports also have demonstrated specific patterns of *Fut1* and *Fut2* expression in the epithelial subsets of gastrointestinal compartment. α1,2-Fucose on enterocytes and goblet cells is specifically regulated by Fut2, while Fut1 regulates α1,2-fucose on M cells located in the dome epithelium of Peyer's patches[15,24]. α1,2-Fucose on Paneth cells is detected even in Fut2-deficient mice, suggesting that its expression on these cells is restricted by Fut1 (ref. 15).

α1,2-Fucose peripherally decorating glycans is expressed both on the apical surface of ECs (**Fig. 1b**) and in luminal compartments as secretory glycosylated antigens[15]. This unique expression pattern provides the opportunity for α1,2-fucose to contact and interact with luminal microorganisms, especially commensal bacteria. Interestingly, several symbionts in the gut possess fucose-salvage enzymatic pathways that enable them to recycle host-derived fucosylated glycans[38]. The symbionts *Bacteroides thetaiotaomicron* and *Bacteroides fragilis* produce fucosidase, which cleaves α1,2-fucose from ECs; the symbionts then incorporate the liberated L-fucose[38] (**Fig. 1c**). Incorporated L-fucose is catabolized by a set of fucose-degradation enzymes[38]; recycled as fucosylated capsular polysaccharides, which are components of the bacterial cell wall[39]; and used in the regulation of fucose-operon genes[40] (**Fig. 1c**). Epithelial α1,2-fucose allows wild-type *B. fragilis* to colonize with competitive advantages over mutants with defective enzymes for fucosylated polysaccharide synthesis[39], suggesting that epithelial α1,2-fucose has an important role in colonization by symbionts (**Fig. 1c**). Given these findings, it is not surprising that Fut2-deficient mice have abnormal commensal microflora (called dysbiosis) and metabolites derived from commensals[41,42], which may exacerbate intestinal inflammation induced by *Citrobacter rodentium*[16]. An important change in our understanding of commensal microbes in Fut2-deficient mice is the reduction in the size of an unclassified genus within the order *Clostridiales* and the expansion of *Parabacteroides*, *Eubacterium*, *Parasutterella*, *Bacteroides* and family *Lachnospiraceae*[41]. One of the major roles of α1,2-fucose is the maintenance of commensal symbionts and the intestinal microenvironment. In addition, mucus L-fucose liberated from ECs by *B. thetaiotaomicron*–derived fucosidase represses the expression of enterohemorrhagic *E. coli* (EHEC) virulence genes through the activation of the fucose sensor FusKR[43]. Therefore, epithelial α1,2-fucose governed by Fut2 plays pivotal roles in the modulation of luminal pathogenic and nonpathogenic bacteria.

Microbial stimuli induce epithelial α1,2-fucose expression

Several recent studies have explored the inductive mechanism of Fut2 and α1,2-fucose in intestinal ECs. Various environmental stimuli, such as oral administration of chemical mediators including cycloheximide, dextran sodium sulfate and nonsteroidal anti-inflammatory drugs, induce Fut2 and α1,2-fucose expression on ECs[24,44]. These chemicals are inflammatory agents and provoke dysfunction of the epithelial barrier, suggesting that such danger signals may alter epithelial physiology, thereby triggering the expression of epithelial Fut2 and α1,2-fucose. Indeed, Na^+-H^+-exchanger isoform 3 (NHE3) null mice have ectopic epithelial α1,2-fucosylation, leading to overgrowth of *B. thetaiotaomicron*[45]. This finding indicates that dysregulation of epithelial ion transport induces epithelial expression of α1,2-fucose, supporting the notion that disruption of epithelial homeostasis triggers epithelial α1,2-fucosylation.

Colonization of host gut by commensal bacteria initiates the process of epithelial α1,2-fucosylation (**Fig. 2a**). Germ-free mice show impaired α1,2-fucose expression on intestinal ECs, but this is restored

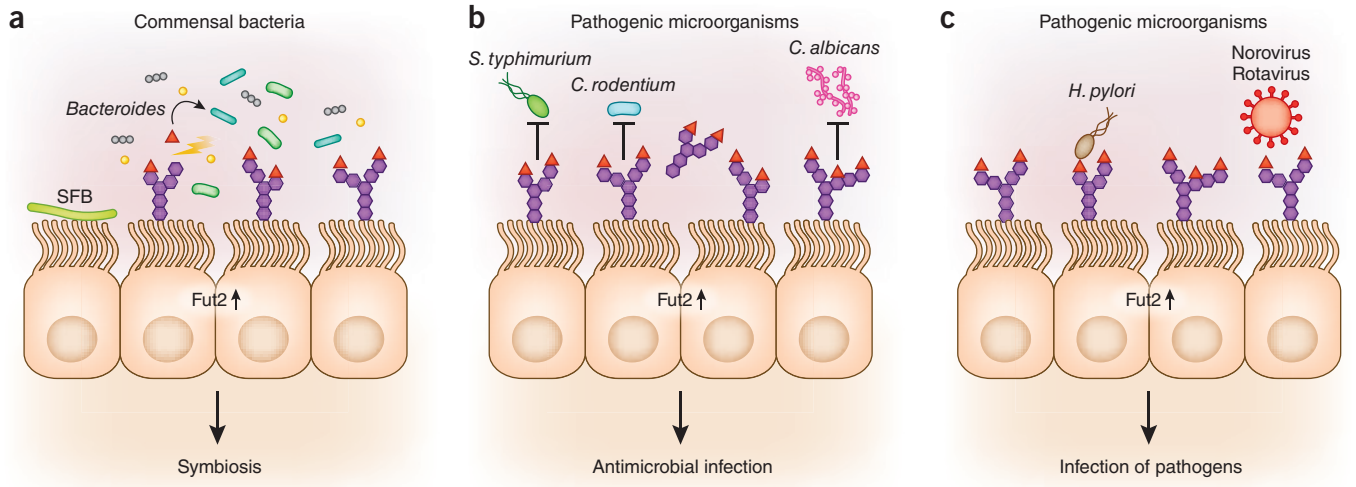

Figure 3 Biological trade-off mediated by epithelial α1,2-fucose. (**a**) Epithelial α1,2-fucose creates a symbiotic environment for the host and commensal bacteria. Commensal bacteria, especially *Bacteroides*, cleave epithelial α1,2-fucose via fucosidases. Liberated L-fucose is incorporated and catabolized by these symbionts. (**b**) Epithelial α1,2-fucose creates a protective platform against pathogenic bacterial infection. Epithelial α1,2-fucose inhibits infection by *S. typhimurium*, *C. rodentium* and *C. albicans*. (**c**) Pathogenic microorganisms hijack epithelial α1,2-fucose to achieve colonization and infection of intestinal tissues. α1,2-Fucose is important for the adhesion of *H. pylori* to host gastric ECs. Norovirus and rotavirus attach to α1,2-fucose on intestinal ECs to infect host tissues.

by colonization with commensal microbes[46,47]. Interestingly, the expression patterns of Fut2 and α1,2-fucose on intestinal ECs is spatiotemporally regulated in a commensal-bacteria-dependent manner. α1,2-Fucose expression is predominantly observed in the ileum, but only a few cells express α1,2-fucose in the duodenum and jejunum[15]. This region-specific epithelial α1,2-fucose is initiated immediately after weaning[46]. These findings suggest a possibility that specific commensals colonizing a restricted region of the gut are responsible for the induction of α1,2-fucose. Indeed, commensal bacteria include epithelial α1,2-fucose-inducing and non-α1,2-fucose-inducing bacteria. *B. thetaiotaomicron*, *B. fragilis* and segmented filamentous bacteria (SFB) but not *Lactobacillus murinus*, *Bifidobacterium* and *Peptostreptococcus* induce epithelial α1,2-fucose expression[15,46,48,49]. *Bacteroides* and SFB preferentially colonize the lower parts of gastrointestinal tracts after weaning[11,15,46]. Furthermore, SFB-deficient mice are defective in ileal epithelial fucosylation, suggesting that SFB are major players in ileal epithelial α1,2-fucosylation in the normal state[15,17]. In addition to these α1,2-fucose-inducing commensal bacteria, pathogenic bacteria such as *Salmonella typhimurium* and *Helicobacter bilis* have been reported to induce epithelial Fut2 expression and α1,2-fucosylation (**Fig. 2b**)[15,50]. In addition to these bacteria, *C. rodentium* induce epithelial Fut2 and α1,2-fucosylation in the cecum but not in the small intestine[16,17]. The details of the mechanism whereby *C. rodentium* can induce epithelial α1,2-fucosylation in the cecum but not small intestine are still unknown. It is interesting to speculate that DC- and ILC3-mediated 'cross-barrier' signals of bacteria specifically occurring in the cecum, but not the small intestine, may contribute to the induction of α1,2-fucosylation. Although it is still unclear what kinds of bacterial molecules are essential for the induction of epithelial α1,2-fucosylation, *Bacteroides* mutants with defects in genes associated with the fucose metabolic pathway fail to induce epithelial *Fut2* expression, suggesting that the bacterial fucose metabolic pathway regulates the expression of genes involved in the induction of epithelial α1,2-fucose production[40,49]. In addition, the Toll-like receptor (TLR) pathway is involved in α1,2-fucose induction, because the administration of TLR agonists (for example, lipopolysaccharides) induces epithelial α1,2-fucose in a MyD88-dependent manner[17] (**Fig. 2c**). However, it is still unknown why and how certain commensals and pathogens induce epithelial α1,2-fucosylation. Because SFB and pathogenic bacteria commonly have unique characteristics, in that they tightly attach to ECs and modulate epithelial physiology and gene expression[11,13], physical stimulation (such as bacterial attachment) combined with bacterial ligand signals may be required for the expression of epithelial Fut2 and α1,2-fucose. Thus, other commensals that cannot attach to ECs fail to the induction of epithelial α1,2-fucosylation.

Mucosal immune cells regulate epithelial α1,2-fucosylation

In addition to the commensal and pathogenic bacteria, recent studies have revealed that mucosal immune cells are critical biological elements for the induction of epithelial α1,2-fucose (**Fig. 2**). Innate-type mucosal immune cells, especially ILC3s, are required for the induction of epithelial α1,2-fucose[15,17] (**Fig. 2**). Intestinal ECs specifically express IL-22 receptor; through this means, IL-22 produced by ILC3s provides activation signals to ECs via the IL-22R–STAT3 pathway, leading to the subsequent induction of Fut2 and other defense genes (such as *RegIIIγ* (also known as *REG3G*) and *SAA*)[16]. In addition to IL-22-mediated α1,2-fucosylation, lymphotoxin (LT) produced by ILC3s is also involved[15] (**Fig. 2a**). Although it is still unknown how LT produced by ILC3s induces epithelial α1,2-fucose production, other studies suggest that LT promotes IL-23 production by dendritic cells (DCs), regulating subsequent IL-22 production from ILC3s (refs. 51,52). This DC–ILC3 interaction mediated by IL-23 and LT may be crucial for epithelial α1,2-fucosylation. It will also be important to identify whether IL-22-producing ILC3 subsets express LT in future studies.

Inasmuch as both luminal microbiota and innate immune cells induce epithelial α1,2-fucose expression, the next obvious question is whether these two ecological elements cooperatively regulate the epithelial glycosylation system. In fact, commensal bacteria have been reported to induce IL-22 production from ILC3s through a process that is mediated by DCs[10,17,53,54]. This mechanism of epithelial α1,2-fucosylation may support the specificity of bacteria responsible for epithelial α1,2-fucosyation discussed above, because epithelial attachment by SFB and pathogenic bacteria is crucial for the induction of the gut immune system, including IL-22 expression by ILC3s[11].

Table 1 Effects of nonsense polymorphisms of the *FUT2* gene on human pathophysiological conditions

Condition	Disease or pathology	Evaluation	Polymorphism(s)	Ref(s).
Inflammation	Crohn's disease	Susceptible	rs281379, rs601338, rs602662	69,70
	Chronic pancreatitis		–	71
	Primary sclerosing cholangitis		rs281379, rs601338, rs602662	72
	Acute uncomplicated pyelonephritis		–	73
	Type I diabetes		rs601338	74
	Psoriasis		rs1047781	75
	Behçet's disease		rs632111, rs601338	76
Infection	*Candida albicans*	Susceptible	–	61
	Neisseria meningitidis		–	59
	Streptococcus pneumoniae		–	59
	Haemophilus influenza		–	60
	Urinary tract infection		–	62
	Pathogenic *Escherichia coli*		–	63
	Bacteremia and infection after hematopoietic stem cell transplantation		rs601338	86
Infection	*Helicobacter pylori*	Resistant	rs601338	84,85
	Norovirus		rs601338	86,88
	Rotavirus		rs601338	87,88,89

In contrast to the role of innate immune cells in the induction of epithelial α1,2-fucosylation, acquired immune cells negatively regulate epithelial α1,2-fucose and Fut2 expression[55]. Indeed, a higher number of α1,2-fucosyated ECs was observed in recombination-activating gene (Rag)-deficient mice lacking T and B cells than in wild-type mice[15]. Among acquired immune cells, IL-10-producing T cells, presumably regulatory T cells and/or Tr-1 cells, but not B cells and other T cell subsets have a critical role in the suppression of epithelial α1,2-fucosylation[55]. In addition, augmented numbers of ILC3s and augmented expression of IL-22 by ILC3s have been observed in Rag-deficient mice, suggesting that T cells negatively regulate the number of ILC3s as well as IL-22 production[56]. Thus, acquired immune cells, especially IL-10-producing T cells, appear to exert regulatory effects by competing for ILC3 niches and by producing inhibitory cytokines for epithelial α1,2-fucosylation. Although the physiological mechanism underlying the regulation of epithelial α1,2-fucosylation by T cells is unknown, enhancement of epithelial α1,2-fucosylation in the absence of acquired immune cells may be a kind of 'compensatory' protective response and homeostatic adaptation against luminal microorganisms. Future studies should identify whether specific commensal bacteria and bacteria-derived molecules are involved in the T-cell-mediated downregulation as well as ILC3-mediated induction of epithelial α1,2-fucosylation. What is evident, however, is that the gut immune system is a critical coordinator of epithelial α1,2-fucosylation that creates homeostatic conditions to establish a cohabitation environment with commensal microorganisms (**Fig. 2a**).

Epithelial α1,2-fucose protects against pathogenic bacteria

Secretory and membrane-bound sugar structures cover the mucosal surfaces as an important component of the innate defense system that guards against undesired infection caused by pathogenic and opportunistic microorganisms[3,15,16,57]. Epithelial α1,2-fucose has inhibitory functions against various pathogen. As described above, epithelial α1,2-fucose protect against *C. rodentium* infection by establishing a conventional commensal microbiota[16] (**Fig. 3a**). Another pathogenic bacterium, *S. typhimurium*, can bind to epithelial α1,2-fucose via its Std fimbriae[58]. Interestingly, *S. typhimurium* more effectively infects Fut2-deficient mice, suggesting that epithelial α1,2-fucose has a protective role against infection by *S. typhimurium*[15] (**Fig. 3b**). Although why *S. typhimurium* efficiently infects Fut2-deficient mice is still under investigation, dysbiosis caused by Fut2 deficiency may create an intestinal environment susceptible to *S. typhimurium* infection[41,42]. Another possibility is that epithelial α1,2-fucose may directly prevent *Salmonella* infection. Because α1,2-fucose-containing carbohydrate moieties are secreted by goblet cells[15], secreted α1,2-fucose-containing glycans may interfere with the attachment of *S. typhimurium* to ECs, much as mucin prevents undesired access of bacteria to intestinal ECs[3]. In addition to bacteria, Fut2-deficient mice are susceptible to vaginal *Candida albicans* infection, suggesting that epithelial α1,2-fucose may protect against pathogenic fungal infection[57] (**Fig. 3b**). Taken together, these results indicate that epithelial α1,2-fucose has an important role in the establishment of a protective platform against pathogen infection.

In contrast, selected pathogens can take advantage of the expression of α1,2-fucose on gastrointestinal tracts, using it as a means to gain EC entry and initiate infection[59]. *Helicobacter pylori* produces the adhesin BabA, which binds to α1,2-fucose expressed on gastric ECs[60] (**Fig. 3c**). Epithelial α1,2-fucose may serve as an anchor for *H. pylori* infection, because the efficiency of *H. pylori* infection in the gastric mucosa is considerably lower in Fut2-deficient mice[59]. Although pathogens that bind epithelial α1,2-fucose often distress the host, α1,2-fucose-containing glycans also have the potential to prevent bacterial infection by interfering with bacteria–EC binding. For example, α1,2-fucose-containing milk effectively protects against infection with *Campylobacter jejuni*[61]. This may extend the role of α1,2-fucosylated glycans as therapeutic targets for protection against pathogenic bacterial infection (**Fig. 3**).

FUT2 polymorphism is associated with human diseases

The expression and physiological roles of intestinal α1,2-fucose on the host–microorganism interplay have also been investigated in humans[62–66]. Various polymorphisms of fucosyltransferase genes, especially *FUT2*, have distinct regional distributions in humans[67]. For example, approximately 20% of Caucasians (defined as Europeans and Iranians) and Africans are homozygous for loss-of-function alleles of *FUT2* genes[36,68,69]. Nonsense polymorphisms of the *FUT2* gene, for example 428G→A (Trp143→stop), cause defects of intestinal α1,2-fucose, which are known as "non-secretor" phenotypes[35]. Thus, non-secretors are defective in H-type antigens consisting of α1,2-fucosylated carbohydrate chains expressed on mucosal ECs and luminal fluids.

Approximately 15% of Asians carry the 385A→T (Ile120→Phe) mutation, a common missense polymorphism of Fut2 (refs. 70,71). Evidence from studies of human non-secretors have shown that epithelial α1,2-fucose has multiple physiological functions, including not only communication with microbes but also maintenance of homeostasis of the intestinal and systemic compartments.

A recent genome-wide association study revealed that *FUT2* nonsense polymorphisms in humans are associated with abnormal local and systemic physiological functions and diseases[72–79]. The most important relationship is between *FUT2* hypomorphs and Crohn's disease[72,73] (**Table 1**). Consistent with the fact that commensal bacteria and the host immune system are tightly associated with development of inflammatory bowel disease (IBD, a category that includes Crohn's disease)[80], and several ILC3-related genes, such as *IL23R*, *STAT3*, *LTA*, *LTB* and *CCR6*, are Crohn's disease susceptibility genes[72], *FUT2* appears to be an important target gene for Crohn's disease. Interestingly, the incidence of Crohn's disease and *FUT2* missense mutations reported in Japanese individuals are not correlated with those observed in Caucasians with *FUT2* nonsense polymorphisms[81]. This discrepancy may be explained by the characteristics of Crohn's disease, which is caused by a combination of genetic background and environmental factors. Indeed, *Fut2*-deficient mice do not spontaneously develop any inflammation in the normal state[15].

In addition to being associated with Crohn's disease, *FUT2* nonsense polymorphisms are risk factors for various pathological conditions, including acute and chronic inflammatory disorders such as type I diabetes[77], primary sclerosing cholangitis[75], psoriasis[78], chronic pancreatitis[74], acute uncomplicated pyelonephritis[76] and Behçet's disease[79] (**Table 1**). Thus, *FUT2* nonsense polymorphisms are associated with diverse local and systemic disorders, although the detailed cellular and molecular mechanisms underlying the pathological process associated with *FUT2* nonsense polymorphisms are still unknown. As in the case of Fut2-deficient mice, dysbiosis and dysfunction of metabolism are observed in human non-secretors[82,83]. Indeed, non-secretors have aberrant gut microbiota, with a reduction of *Bifidobacteria*, which may predispose to the development of IBD[83]. Such abnormal microbiota and metabolites in non-secretors possibly affect the promotion of a variety of local and systemic diseases[42,82]. Notably, it has been reported that the colonization of the host by *Bifidobacteria* is aberrant in breastfed infants of non-secretor mothers[84]. In addition, *Bifidobacteria* consume fucosylated glycans such as 2′-fucosyllactose, which is detected in the milk of secretors but not non-secretors[85]. Therefore, *FUT2* status may affect colonization of *Bifidobacteria* in infants through the breast milk[84]. These results suggest that fucosylated glycans in breast milk, as well those that are membrane-bound and in intestinal fluids, contribute to the creation and maintenance of a homeostatic environment for gut microflora. Interestingly, non-secretors are susceptible to infection by pathogenic microbes such as pathogenic *E. coli*, *Neisseria meningitidis*, *Haemophilus influenzae* and *C. albicans*[62–66] (**Table 1**). In addition, bacteremia has been found to occur in individuals with *FUT2* nonsense polymorphism after allogeneic hematopoietic stem cell transplantation[86]. These results emphasize the important role of epithelial FUT2 and α1,2-fucose to protection against pathogenic infection.

Although defects in epithelial FUT2 predispose individuals to several diseases, a high percentage of *FUT2* nonsense polymorphisms are evolutionarily maintained in the human genome[36,67,69]. This evidence allows us to predict that *FUT2* inactivation confers beneficial effects on individuals. Indeed, infection with *H. pylori*, which binds to epithelial Lewis (b) (Le (b)) blood group antigen via BabA adhesin, is abrogated in non-secretors, in accordance with results from Fut2-deficient mice[87,88]. In addition to bacterial infection, epithelial α1,2-fucose also affects human viral infections. Because norovirus, especially GII.4, and the rotavirus P8 genotype bind to the histo-blood-group antigen α1,2-fucose-containing glycan, humans with nonsense polymorphisms of the *FUT2* gene are resistant to infection by these viruses[89–92] (**Fig. 3c**). Augmented serum antibody titers against rotavirus are detected in secretors, supporting the importance of FUT2 and α1,2-fucose in ECs as a target for rotavirus infection and subsequent immune responses including antibody production[93]. Considering these findings together, expression of epithelial FUT2 and α1,2-fucose appears to be an example of a biological trade-off system between host and microorganisms (**Table 1**). This biological trade-off seems to have evolved because of the interactive ecological network of the host immune system, commensals and pathogenic microorganisms in our intestines (**Fig. 3**).

Concluding remarks

The intestinal epithelial surface is the primary interface for the host–microbe interaction. Cooperative interplay between ECs and the gut immune system creates a homeostatic environment for the host–microbe relationship. Based on their specific expression patterns, glycan structures, especially α1,2-fucose expressed on the apical side of ECs, are key molecules that act as communication tools for luminal microorganisms. Among numerous kinds of glycoproteins and glycolipids associated with epithelial α1,2-fucosylation, asialo-GM_1 gangliosides are reported to be α1,2-fucosylated after SFB colonization[94]. Emerging evidence suggests that mucosal immune cells, especially ILC3s, are also critical modulators of the gut immune system and epithelial physiology in response to commensal and pathogenic bacteria. Epithelial α1,2-fucose induced by ILC3s harbors protective and symbiotic roles with respect to luminal microorganisms, suggesting that IL-22- and/or LT-producing ILC3-mediated epithelial α1,2-fucosylation is an important arm of the innate immune system in the digestive tract. Importantly, IL-10-producing T cells, a family of regulatory T cells, are also involved in the downregulation of epithelial α1,2-fucosylation. Therefore, the intestinal innate and acquired immune system cooperatively orchestrate epithelial α1,2-fucosylation for the creation of a homeostatic microenvironment in the intestine.

Selected symbionts such as *Bacteroides*, *Lactobacillus* and *Bifidobacterium*—but not pathogens—have a set of enzymes, including α1,2-fucosidase, to catabolize epithelial sugar residues[95–97], suggesting that commensal bacteria might have evolutionarily acquired the ability to recycle host-derived glycan and adapt to the ecosystem in our intestine. This new perspective suggests that to distinguish between pathogenic and nonpathogenic microorganisms, it is insufficient to understand just the role of the host immune system, especially the microbial recognition system; we also need to understand how each microorganism adapts to its host intestinal microenvironment. Because epithelial glycosylation is a front-line host defense as well as a platform for cohabitation by luminal microorganisms, advancing our understanding of the mechanisms underlying epithelial glycosylation will open the door to innovative approaches for the control of acute and persistent infections and chronic inflammation.

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