Fucose-Mediated Interactions Between Microbiota and Intestinal Epithelial Cells and Their Mechanisms (Postprint)

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Abstract

Fucose is an important glycan in the glycosylation of intestinal epithelial cell mucins, which can serve as an energy substrate for intestinal microorganisms, participates in microbial adhesion, colonization, and immune regulation, and plays a crucial role in promoting intestinal microbial homeostasis and maintaining intestinal health. This review primarily summarizes the fucosylation process, the positive regulatory roles of fucose in the intestine, and the induction of fucose expression by intestinal microorganisms and immune cells, aiming to provide novel insights for maintaining intestinal microbial homeostasis and intestinal health.

Full Text

Fucose as a Mediator of Microbial-Epithelial Interactions in the Intestine and Its Mechanism

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Abstract: Fucose is an important glycan constituent in the glycosylation of mucins produced by intestinal epithelial cells. It serves as an energy source for gut microbiota and participates in microbial adhesion, colonization, and immune regulation, playing a crucial role in promoting gut microbial homeostasis and maintaining intestinal health. This review summarizes the fucosylation process, the positive regulatory roles of fucose in the intestine, and the induction of fucose expression by gut microbiota and immune cells, aiming to provide new insights for maintaining gut microbial homeostasis and intestinal health.

Keywords: fucose; mucin; gut microbiota; intestinal epithelial cells; mechanism

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The gastrointestinal tract harbors a vast population of pathogenic and non-pathogenic microorganisms, representing the most stable, dense, and diverse microbial community in the body. The gut microbiota participates in various host physiological and metabolic activities, playing critical roles in nutrition, metabolism, immune homeostasis, and overall health. The human gut contains approximately 4$×10^{14}$ microbial cells, nearly equivalent to the number of human cells in an adult. Dysbiosis is associated with numerous diseases, including inflammatory disorders, obesity, diabetes, Parkinson' s disease, and rheumatoid arthritis. The host actively promotes interactions with microbes through mechanisms such as the mucus layer, microbial nutrient sources, and bacterial recognition by immune cells. Intestinal epithelial cells form the first line of defense against the external environment, and goblet cells secrete mucus that maintains epithelial integrity while providing lubrication, protection, and immune modulation. Fucose, a key component of mucin glycosylation, participates in microbial adhesion and colonization, playing a vital role in regulating gut microbial homeostasis. Elucidating the regulatory functions of fucose in microbe-epithelial interactions is therefore essential for promoting dynamic balance between gut microbiota and host health.

1 Fucosylation Patterns and Processes in Intestinal Mucins

Intestinal goblet cells secrete mucins into the lumen via Toll-like receptors (TLRs) and the NOD-like receptor protein 6 pathway, forming a two-layered mucus structure consisting of inner and outer layers. The inner mucus layer is tightly associated with epithelial cells, while the outer layer contains epithelium-derived polysaccharides that provide abundant nutrients and exert selective pressure on gut microbiota. Mucins are heavily glycosylated proteins with serine/threonine-rich backbones conjugated to diverse O-linked oligosaccharide side chains, including fucose. In colonic mucus, O-linked oligosaccharides provide specific binding sites for commensal bacteria, promoting their colonization while inhibiting pathogen growth. Studies have shown that loss or truncation of O-linked side chains increases bacterial invasion and triggers intestinal inflammation. Mucin glycans serve as crucial nutrient sources and adhesion sites

for commensals, but also represent primary targets for pathogens. The level of mucin glycosylation largely determines mucosal barrier function, and both microbial stimuli and the intestinal immune system can modulate epithelial glycosylation to enhance microbial adaptation and survival in the lumen.

Fucosylation represents a critical glycosylation pattern in mucins. Fucose constitutes approximately 4–14% of total glycan content and exists primarily as L-fucose, an important energy source for gut microbes. Unlike typical hexoses, fucose lacks a hydroxyl group at the sixth carbon, conferring weaker hydrophilicity and stronger hydrophobicity that enables it to function as a blood group antigen. Fucosyltransferases (Futs) catalyze the attachment of fucose to hydroxyl groups on serine and threonine residues, enabling terminal glycosylation of mucins. Thirteen Fut genes have been identified in the human genome, with Fut1 and Fut2 predominantly expressed in the small intestine, particularly in intestinal epithelial cells. Fut2 is a secretor gene that transports fucose in the form of GDP-fucose, the sole donor substrate for fucosylation.

In mammals, GDP-fucose is synthesized primarily through the de novo pathway, with a minor contribution from the salvage pathway. Three sources for GDP-fucose synthesis have been identified: extracellular fucose, lysosomal fucose residues, and GDP-mannose. GDP-mannose serves as the main substrate for the de novo pathway, undergoing conversion to GDP-fucose via GDP-mannose-4,6-dehydratase and GDP-4-keto-6-deoxymannose-3,5-epimerase-4-reductase. Following synthesis, GDP-fucose is isomerized and transported to the Golgi apparatus or endoplasmic reticulum for terminal modification by Futs. The modified fucose is then transferred to proteins or lipids on the epithelial cell membrane, completing the fucosylation process. Notably, $ $1,2-fucosylation is specifically regulated by Fut2 and occurs primarily on the surface of goblet cells before secretion into the lumen as glycosylated antigens. This unique expression pattern is crucial for interactions between commensal bacteria and intestinal epithelial cells. For instance, the symbiont *Bacteroides thetaiotaomicron* produces fucosidases that degrade $ $1,2-fucose, recycles the residues, and incorporates them into bacterial cell wall components to promote colonization.

[Figure 1: see original paper]

2 Microbial Regulation of Intestinal Epithelial Fucosylation

Microbial induction of fucosylation occurs through two primary mechanisms: commensal-independent and commensal-dependent modes. In the commensal-independent mode, lymphotoxin (LT) $ 1 $2 secreted by group 3 innate lymphoid cells (ILC3) directly regulates Fut2-mediated fucosylation without requiring commensal bacteria. In the commensal-dependent mode, *Bacteroides thetaiotaomicron* has been demonstrated to induce fucosylation in both human and mouse intestinal epithelial cells. Additionally, segmented filamentous bacteria (SFB) can induce fucose expression through the commensal-dependent mode by activating ILC3, thereby upregulating Fut2 and fucose expression to

resist *Salmonella* infection. $ $1,2-fucosylation occurs predominantly in the ileum, with only minor expression in the duodenum and jejunum. In contrast, pathogens such as *Citrobacter rodentium* induce $ $1,2-fucosylation in the cecum rather than the small intestine. These location-specific induction patterns likely reflect the distinct ecological niches occupied by different microbes along the intestinal tract. In germ-free mice, fucosylation occurs in the cecum, colon, and ileum, but following microbial colonization, fucosylation becomes detectable throughout the entire small intestine.

Microbial metabolites also participate in inducing epithelial Fut2 and fucose expression. In weaned juvenile rats, intestinal concentrations of polyamines and fucose increase concurrently, and dietary polyamine supplementation elevates fucosylation levels. Research has shown that *Peptostreptococcus* species can utilize mucin as an energy source, cleave and transport fucose, and promote their own colonization. The tryptophan metabolite indoleacrylic acid produced by these bacteria enhances intestinal epithelial barrier function and reduces inflammatory responses, illustrating how *Peptostreptococcus*-epithelial interactions create a favorable intestinal environment.

3.1 Nutritional Regulation of Gut Microbiota by Fucose

As a carbohydrate, fucose serves as a carbon source for microbes and regulates microbe-epithelial symbiosis through fucosidase-mediated degradation. Microorganisms expressing fucosidases can directly degrade host-derived or exogenous fucose and provide the resulting residues to other bacteria lacking these enzymes. *Bacteroides thetaiotaomicron* upregulates fucose catabolism and metabolism genes via the fucose operon, utilizing fucose as a carbon source when environmental conditions change while simultaneously promoting epithelial fucosylation. *Bacteroides fragilis* participates in intestinal carbohydrate metabolism and uses fucose to enhance colonization and adapt to the gut environment. Notably, *Campylobacter jejuni* can utilize fucose as its sole carbohydrate source, despite typically relying on amino acid or citrate metabolism for carbon acquisition.

[Figure 2: see original paper]

3.2 Barrier Function Against Pathogenic Microbes

As a component of the innate immune system, polysaccharides on the mucus surface resist pathogenic invasion, with fucose acting as a signaling molecule that effectively inhibits infection by certain pathogens. Fut2 deficiency impairs fucose regulation, causing intestinal dysbiosis and exacerbating *Citrobacter rodentium*-induced colitis and *Salmonella typhimurium* susceptibility in mice. As a mucin side chain, fucose can bind to *Salmonella* fimbriae, trapping the pathogen in the mucus and preventing translocation. Studies have demonstrated that fucose inhibits virulence-associated operons in enterohemorrhagic *E. coli* by stimulating membrane receptor phosphorylation, thereby reducing pathogenicity. Further-

more, fucose decreases inflammatory cytokines, increases tight junction protein expression, and upregulates short-chain fatty acid receptors in the small intestine, alleviating mucosal damage.

Fucose also reduces the abundance of pathogenic *Peptostreptococcus* species and decreases intestinal antigen load while increasing beneficial probiotic populations. In Fut2-deficient mice, certain commensal bacteria within the order Clostridiales are reduced. Research indicates that most pathogens lack fucosidases and cannot utilize fucose, whereas some probiotics such as *Bifidobacterium* possess highly active fucosidases that degrade fucose to synthesize their own polysaccharides—a trait that may contribute to their high abundance. However, other studies have reported increased populations of commensals like *Bacteroides* and Lachnospiraceae in Fut2-deficient mice with impaired fucose expression.

[Figure 3: see original paper]

4 Immune Cell Regulation of Intestinal Epithelial Fucose Expression

Immune cells comprise innate and adaptive subsets, with ILC3s representing key innate lymphocytes that regulate fucose expression. Rapid intestinal fucosylation following infection in germ-free mice is closely associated with ILC3 activation. Upon lipopolysaccharide challenge, dendritic cells secrete interleukin-23 (IL-23) in a myeloid differentiation primary response 88 (MyD88)-dependent manner, which subsequently induces ILC3s to release IL-22. IL-22 upregulates Fut2 expression and, as an IL-10 family member, can be activated by both commensal and pathogenic bacteria. IL-22 receptors activate signal transducer and activator of transcription 3 (STAT3) signaling to mediate defensive and tissue repair functions in intestinal epithelium, and IL-22-deficient mice are highly susceptible to intestinal inflammation. Given IL-22' s ability to enhance fucosylation, oral administration of fucosylated polysaccharides improves survival in susceptible mice. ILC3s also secrete the TNF family member LTα, which regulates Fut2 and fucosylation in a commensal-independent manner unaffected by antibiotics. Both IL-22 and LTα expression depend on the ILC3 transcription factors retinoic acid-related orphan receptor γt (RORγt) and inhibitor of differentiation 2 (Id2), though their specific regulatory mechanisms remain unclear. Some reports suggest LTα promotes dendritic cell IL-23 secretion, which subsequently regulates ILC3-derived IL-22 expression, but whether IL-22 reciprocally influences LTα expression is unknown.

Adaptive immune cells also regulate fucosylation, but exert negative control over fucose and Fut expression. Recombination activating gene (Rag)-deficient mice lacking T and B cells exhibit high intestinal epithelial fucosylation compared to wild-type mice, and only IL-10-producing T cell subsets can suppress epithelial fucose expression. Rag-deficient mice also show increased ILC3 numbers and IL-22 expression, suggesting T cells negatively regulate ILC3 populations and IL-22

production—possibly through niche competition or inhibitory factor secretion. The enhanced fucosylation observed in the absence of adaptive immunity may represent a compensatory protective response to promote luminal homeostasis. The intestinal immune system thus serves as a critical coordinator of epithelial fucosylation, maintaining and improving host-microbe symbiosis.

[Figure 4: see original paper]

5 Conclusions and Perspectives

Fucose functions as both an energy source and regulatory molecule that can be utilized by gut microbiota to promote commensal colonization, resist pathogenic infection, and maintain microbial balance through several mechanisms. Fucose may participate in specific microbial metabolic pathways to induce production of host-beneficial metabolites such as amino acids, vitamins, and short-chain fatty acids. It may also influence bacterial gene expression, as evidenced by its suppression of virulence genes in *Enterococcus faecalis*. Additionally, fucose promotes colonization of probiotic bacteria including Verrucomicrobiaceae and *Bacteroides*, thereby maintaining microbial equilibrium. However, not all fucose-utilizing bacteria are beneficial—fucose also serves as an adhesion site for some pathogens. For example, *Helicobacter pylori* in the gastrointestinal lumen secretes adhesins that bind to epithelial fucose to establish infection.

Conversely, microbial metabolites can influence epithelial cells and enhance host defense, creating a mutually beneficial symbiotic relationship that improves resistance to external infections and offers protective effects against various diseases. Nevertheless, critical questions remain unresolved: How does fucose distinguish between commensals and pathogens? How does it participate in different microbial metabolic pathways? Why does fucosylation vary across intestinal regions? Further investigation into these mechanisms will provide important guidance for maintaining intestinal health.

This review has focused on fucose in mucin side chains and its regulatory mechanisms. Exogenous fucopolysaccharides such as fucoidan and sulfated fucans also contain fucose and exhibit anticoagulant, antithrombotic, antiviral, and antitumor activities. Whether dietary fucose supplementation can promote epithelial fucosylation and maintain gut homeostasis when endogenous expression is insufficient warrants investigation, as this could inform human nutrition, animal husbandry, and feed additive development.

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