The Role of Mucin Side-Chain Fucose in Gut Bacteria-Host Interactions: Postprint

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Abstract

The mucus layer lining the gastrointestinal surface contains abundant mucins whose molecular side chains are frequently glycosylated. These glycans play crucial roles in the adhesion, colonization, and immune regulation of intestinal bacteria. Fucose represents an important glycan moiety in the side chains of intestinal mucin molecules. This article summarizes the functions of fucose as an adhesion target for intestinal bacteria, a signaling regulatory molecule, and its role in regulating intestinal functions.

Full Text

Roles of Side-Chain Fucose of Mucin in Host-Intestinal Bacteria Interactions

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Abstract: The mucus layer lining the digestive tract contains abundant mucins that undergo extensive glycosylation. These mucin side-chain carbohydrates play crucial roles in bacterial adhesion, colonization, and immunomodulation. Fucose represents an important sugar moiety in intestinal mucin side chains. This review summarizes the functions of fucose as an adhesion target for intestinal bacteria, a signaling molecule, and a regulator of intestinal function.

Keywords: fucose; intestinal bacteria; host; interaction

The intestinal tract of humans and animals harbors a vast and complex microbial community. Research indicates that the human gut contains over 1,000 species of symbiotic bacteria, with bacterial densities reaching approximately

10^4 cells per gram in the duodenum and 10^{12} cells per gram in the colon. These commensal microbes engage in sophisticated interactions with the host and participate in regulating physiological functions essential for maintaining health. Through crosstalk with intestinal epithelial cells, gut microbiota stimulate intestinal tissue development, modulate gut immune function, and regulate central nervous system and liver function via the gut-brain and gut-liver axes. Over the past decade, the relationship between intestinal microecology and host health has become a major research focus worldwide. Studies have linked gut microbiota to inflammatory bowel disease, food allergies, Alzheimer' s disease, hepatic encephalopathy, and obesity, among other conditions. Elucidating the mechanisms underlying host-microbiota interactions is therefore crucial for understanding the pathogenesis and treatment of these diseases.

1. Overview of Interaction Mechanisms Between Intestinal Bacteria and Mucosal Epithelium

Extensive research has investigated the interaction mechanisms between intestinal bacteria and the host. Generally, intestinal cells recognize bacterial cell wall components through pattern recognition receptors (PRRs), activating non-specific immune responses that prevent bacterial translocation and tissue invasion. Teichoic acids, peptidoglycan, flagellin, and lipopolysaccharide from bacterial cell walls can be recognized by transmembrane Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and cytoplasmic NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) on mucosal M cells. This recognition stimulates dendritic cell maturation and antigen presentation, thereby activating intestinal immune responses. Commensal bacteria regulate intestinal microecology and maintain microbial homeostasis through myeloid differentiation factor (MyD88)-dependent signaling pathways, though some probiotics can modulate mucosal immune function via MyD88-independent pathways. These findings demonstrate that bacteria can activate intestinal immune responses through receptor recognition on mucosal cells, thereby preventing translocation and infection.

However, under normal conditions, intestinal mucosal cells secrete substantial amounts of mucus that forms a protective layer covering the epithelial surface. Consequently, only a small fraction of bacteria can penetrate this mucus layer to be recognized by mucosal receptors and modulate immune responses. The vast majority of bacteria do not directly contact epithelial cells and thus cannot interact through these receptor-mediated mechanisms. This suggests the existence of alternative mechanisms for bacterial adhesion and colonization in the gut. The colonic mucus layer comprises inner and outer strata: the inner layer adheres tightly to the epithelium, is non-fluid, measures 50–100 m thick, and forms a dense, sterile barrier; the outer layer, located on the luminal side of the inner layer, is loosely structured, fluid, 100–700 m thick, and contains numerous bacteria [Figure 1: see original paper]. Both layers consist primarily of glycosylated mucins whose carbohydrate moieties provide recognition and

adhesion sites that constrain bacteria to the loose outer layer.

2. Mucin Side-Chain Fucose as a Key Adhesion Target for Intestinal Bacteria

Fucose constitutes an important carbohydrate component of mucin glycans, accounting for 4–14% of total sugar residues. Abodinar et al. reported that fucose represents 4% of total glycans in porcine gastric mucin. During bacterial recognition, adhesion, and colonization in the digestive tract, fucose residues on mucin glycans likely play a significant role. The *Helicobacter pylori* adhesin BabA recognizes fucosylated moieties on gastric mucins, mediating bacterial attachment to the gastric epithelium. *Campylobacter jejuni* can adhere to and colonize the intestinal mucosal surface through interactions with mucin fucose residues, which may sequester bacteria within the mucus layer and prevent translocation infection. *Pseudomonas aeruginosa* adheres to tissues via its lectin LecB, which specifically binds fucose. *Bacteroides thetaiotaomicron* can stimulate fucosylation of intestinal mucins, reducing sialic acid levels in young animals and promoting intestinal maturation to protect the epithelium from bacterial invasion. Priori et al. found that higher fucose content in porcine jejunal mucin correlated with increased adhesion of enterotoxigenic *E. coli* (ETEC) and was associated with villus height. Studies have also shown that the genotype and expression level of α-1,2-fucosyltransferase 1 (FUT1) in piglet intestinal mucosa closely correlate with ETEC adhesion rates, suggesting that mucin fucose serves as an adhesion target for ETEC F18. These findings indicate that fucosylated residues can specifically bind pathogens, preventing direct contact with intestinal tissues and averting inflammatory responses. However, the role of fucose in probiotic-mediated inhibition of pathogen colonization and invasion remains unexplored.

3. Fucose as a Signaling Molecule Regulating Intestinal Microecology

Fucose functions as both a signaling molecule and bacterial carbon source, participating in the regulation of intestinal microecology. Pacheco et al. demonstrated that fucose induces phosphorylation of membrane receptors in enterohemorrhagic *E. coli* (EHEC), suppressing activation of the virulence-associated LEE operon and reducing pathogenicity. Conversely, fucose can upregulate the activity of the *flaA* promoter in *C. jejuni*, enhancing bacterial virulence. Both *Salmonella* and *B. thetaiotaomicron* possess efficient fucose operons; upon entering bacterial cells, fucose induces expression of catabolic enzymes, activating degradation pathways for use as a carbon source. Fucose can also stimulate *B. thetaiotaomicron* to produce a secreted factor that induces expression of the host fucosyltransferase FUT2 gene, thereby increasing fucosylation levels on mucin glycans. *C. jejuni* lacks conventional bacterial carbohydrate metabolic pathways and relies primarily on amino acid or citrate metabolism for carbon, yet it can utilize fucose as its sole carbohydrate source. Rodríguez-Díaz et al. found that most pathogens do not produce fucosidases and cannot degrade fucosidic

linkages on mucin glycans, whereas probiotic bacteria such as bifidobacteria produce highly active fucosidases that release free fucose, suggesting that probiotics may exert their beneficial effects through fucose liberation. Collectively, these studies show that fucose can act as an inducer or carbon source to modulate microbial balance, though the underlying mechanisms remain unclear. The effects of fucose on pathogen virulence are inconsistent, and its role in probiotic-mediated virulence inhibition has not been reported.

4. Fucose Is Closely Associated with Intestinal Diseases

The level of fucosylation on mucin glycans correlates with inflammatory bowel disease. Genomic analysis of Nordic populations revealed that FUT2 deficiency is directly associated with IBD development, and FUT2-deficient individuals exhibit altered gut microbiota composition, suggesting that mucin fucosylation may directly influence IBD pathogenesis through microecological regulation. Morrow et al. studied 410 premature infants in the United States and found that FUT2 non-secretor status strongly predicted the incidence and mortality of necrotizing enterocolitis (NEC), highlighting the critical role of fucosylation in neonatal intestinal development. FUT1 is an important fucosyltransferase that primarily fucosylates mucins. Hesselager et al. demonstrated in piglets that FUT1 genotype in intestinal mucosa is closely associated with infection resistance. A missense mutation from G to A at nucleotide 307 of FUT1 significantly enhances resistance to ETEC infection, indicating that mucin fucose side chains play an important role in protecting piglets against pathogenic infection.

These findings underscore the essential role of mucin fucosylation in maintaining intestinal health, and deeper mechanistic understanding will have positive implications for the diagnosis, prevention, and treatment of intestinal diseases such as IBD. Fucose plays important roles in bacterial adhesion, colonization, immunomodulation, and microecological balance. Therefore, investigating fucosylation at molecular, cellular, tissue, and organismal levels will further clarify bacterial adhesion mechanisms and identify bacterial components that recognize mucin fucose. Currently, few studies have examined the relationship between mucin fucose side chains and animal intestinal health or microbiota. Comprehensive analysis of fucose' s importance for maintaining animal intestinal health holds significant theoretical and practical value, providing a clearer basis for using probiotics to prevent and treat animal intestinal diseases.

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