



Review Article

The role of glycosylated mucins in maintaining intestinal homeostasis and gut health

Hao Cheng ^{a, b, c}, Hao Li ^{a, b, c}, Zhong Li ^{a, c}, Yun Wang ^b, Liangguo Liu ^b, Jing Wang ^{a, c}, Xiaokang Ma ^{a, c, *}, Bie Tan ^{a, c, *}

^a College of Animal Science and Technology, Hunan Agricultural University, Changsha 410128, China

^b Hunan University of Arts and Science, Changde 415000, China

^c Yuelushan Laboratory, Changsha 410128, China

ARTICLE INFO

Article history:

Received 21 May 2024

Received in revised form

12 January 2025

Accepted 12 March 2025

Available online 4 April 2025

Keywords:

Mucus barrier

Mucin

Glycosylation

Gut health

Gut microbiome

ABSTRACT

The intestinal mucus barrier is a crucial component of the host's innate defense system, playing a vital role in regulating intestinal microecology and maintaining intestinal homeostasis. Glycosylated mucins, the core components of this barrier, are essential for preserving its integrity by preventing bacterial degradation. Additionally, mucins significantly contribute to establishing a balanced symbiotic relationship between the host and microbes. These mucins have the potential to mitigate intestinal epithelial damage by capturing and transporting cell debris and pathogenic bacteria. Meanwhile, certain bacteria help maintain the equilibrium and stability of the gut microbiome by degrading glycosylated mucins to utilize the carbohydrate chains, thus affecting the cytokine expression to regulate the synthesis and secretion of specific glycans. Investigating the complex connections between the mucus barrier and mucin glycosylation holds great promise for advancing our understanding of gastrointestinal disease mechanisms, paving the way for innovative prevention and treatment strategies.

© 2025 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The intestinal tract, as the primary site for nutrient digestion and absorption, is a pivotal organ in mammals, playing a crucial role in defending against bacterial invasion and endotoxin exposure within the intestinal lumen (Tang et al., 2016). At the heart of the innate host defense in the intestine lies a thick layer of mucus, serving as the frontline protector. This dense mucus layer, primarily structured around the hyperglycosylated mucin, effectively protects the epithelial surface from microorganisms and harmful substances (Paone and Cani, 2020). However, when the mucus layer is compromised, the intestinal epithelial tissue becomes vulnerable

to pathogens, leading to various diseases such as enteritis and irritable bowel syndrome (Song et al., 2023). Some intestinal bacteria can degrade mucus glycans, using them as an energy source in competition with other bacteria. Meanwhile, certain gut bacteria can influence the glycosylation of intestinal mucins by altering factors such as energy levels, pH, and cytokine expression in intestinal mucosal cells, thereby regulating the synthesis and secretion of specific glycans (Chun et al., 2019). The dynamic equilibrium among the mucus layer, intestinal epithelial cells, microorganisms, and host immune defense is crucial for maintaining intestinal homeostasis.

Recent scientific and technological advancements have significantly expanded the understanding of the composition and function of the intestinal mucus barrier. This review systematically outlines the roles of the intestinal mucus barrier, with a particular focus on the structure, types, and functions of mucins. Additionally, the latest insights into the intricate interactions between the mucus barrier and the gut microbiota are integrated, emphasizing their influence on host health and disease development. By examining the relationship between glycosylated mucins and the integrity of the intestinal mucus barrier, this discussion aims to provide a

* Corresponding authors.

E-mail addresses: maxiaokang@hunau.edu.cn (X. Ma), bietan@hunau.edu.cn (B. Tan).



Production and Hosting by Elsevier on behalf of KeAi

comprehensive perspective on their physiological and pathological significance.

2. The basic properties of the intestinal mucus barrier

2.1. Composition of intestinal mucus

Intestinal mucus is primarily composed of water (90%), electrolytes, mucin glycoproteins, lipids, immunoglobulin A, bioactive peptides, and metabolites, and is a complex viscoelastic adherent secretion (Hansson, 2020). It is synthesized and secreted mainly by specialized goblet and mucous cells, with mucin as its central constituent (Elderman et al., 2017).

2.1.1. Mucin

Mucin is a macromolecular protein with extensive glycosylation, playing a pivotal role in ensuring the lubrication properties and barrier function of mucus (Pajic et al., 2022). Intestinal mucins can be broadly categorized into two types: 1) Secreted mucins, which primarily include mucin-2, mucin-5AC, mucin-5B, mucin-6, mucin-7, mucin-19, and mucin-9. These proteins form a vast polymer network throughout the gastrointestinal tract, constituting the core framework of the intestinal mucus layer. Secreted mucins can further be divided into gel-forming mucins (mucin-2, mucin-5AC, mucin-5B, mucin-6, mucin-19) and soluble mucins (mucin-7, mucin-8, mucin-9) (Johansson and Hansson, 2016). 2) Membrane-associated mucins, which cover the surface of intestinal epithelial cells and serve as anchors for the secreted mucin network (Wagner et al., 2018).

2.1.2. Trefoil factors

Trefoil factors (TFFs) are primarily secreted by gastrointestinal cells and contain a unique trefoil domain secondary structure, making them important components in maintaining the stability of the intestinal barrier within the mucus (Thim, 1989). The TFF family in mammals includes mammary cancer-associated peptide, spasmolytic peptide, and intestinal trefoil factor (ITF), with ITF mainly secreted by intestinal epithelial cells and binding to mucin-2 to form the first line of defense for the intestinal barrier (Song et al., 2023; Yang et al., 2022). The ITF is a cysteine-rich secretory peptide composed of 42–43 amino acid residues, including six cysteine residues that form disulfide bonds in 1–5, 2–4, and 3–6 configurations (Thim and May, 2005). The ITF protects the gastrointestinal mucosa and promotes mucosal healing, exhibiting properties such as acid resistance, protease resistance, and thermal stability (Braga et al., 2020; Hoffmann, 2020).

2.1.3. The *fc*-binding protein of immunoglobulin G (FCGBP)

The FCGBP is also a component of colonic mucus, containing 13 von Willebrand factor domains, 12 cysteine-rich domains, and 12 pancreatic trypsin inhibitor-like domains (Liu et al., 2022). It is expressed and secreted by colonic epithelial cells, forming heterodimers with ITF through disulfide bonds. The ITF-FCGBP heterodimer interacts with mucin-2 via both covalent and non-covalent bonds, thereby maintaining the integrity of the intestinal mucus barrier (Herath et al., 2020).

Intestinal mucus contains a variety of antimicrobial peptides with broad-spectrum antimicrobial activity, which are essential components of the intestinal innate immune system. These peptides bind to negatively charged lipids in bacterial membranes via their positively charged surface amino acid residues, forming stable transmembrane and ion channels. This disrupts the bacterial cell membrane, inhibiting the growth and replication of pathogens (Song et al., 2023). Furthermore, immunoglobulins in intestinal mucus (especially immunoglobulin A) and bacterial metabolites are

also key in maintaining the integrity of the intestinal mucus barrier. Immunoglobulin A, through its adhesive properties, helps defend against foreign pathogens, while microbial metabolites can regulate mucin glycosylation, influencing both the structure and function of intestinal mucus (Sanchez et al., 2014).

2.2. The structure of intestinal mucus

It has been found that the composition and structure of the mucus layer vary along the length of the digestive tract, corresponding to the shape and function of different intestinal regions (Xia et al., 2021). The small intestine features a single mucus layer that facilitates the smooth passage of nutrients, whereas the colon is enveloped by a thicker barrier, with the most substantial mucus layer in the gastrointestinal tract. The intricate structure of mucus, which includes the mucin domain, proline-threonine-serine (PTS) domains, and densely O-glycosylated regions, is essential for performing its diverse functions (Fig. 1). Mucus is a highly hydrated gel that forms mucous network structure through disulfide bridging between mucous protein units. These units have a backbone consisting of tandem repeats rich in proline, threonine, and/or serine, commonly known as the PTS domains (Herath et al., 2020). Additionally, mucins feature cysteine-rich regions at both the amino and carboxy termini, as well as interspersed locations throughout the PTS domains. These PTS domains are densely O-glycosylated, resulting in a bottlebrush-like appearance with branched oligosaccharide chains, known as glycans, radiating outward from the protein core (Song et al., 2023). One prominent mucin, mucin-2, forms an extensive net-like polymer structure, where the C-termini of individual mucin-2 molecules create dimeric complexes through disulfide bonds, while the N-termini form trimeric complexes.

2.3. The role of intestinal mucus

Intestinal mucus, an essential component of the intestinal epithelium, forms a complex physicochemical barrier that protects the host from the invasion of pathogens, toxins, and mechanical damage. This barrier not only offers physical protection but also plays a crucial role in immune responses and microbial regulation through its chemical constituents.

2.3.1. Physicochemical barrier

Intestinal mucus is a complex hydrogel that provides robust protection against the corrosive effects of gastric acid and digestive enzymes, safeguarding the gastrointestinal epithelium from damage. The physical barrier properties of intestinal mucus not only defend against external threats but also lubricate the surfaces of food as it moves through the digestive tract, helping to prevent damage associated with friction against the intestinal walls (Mcshane et al., 2021; Yuan and Cui, 2024). Additionally, the combination of mucins with electrolytes, lipids, and other smaller proteins imparts viscoelastic, lubricating, and hydrated properties, enabling mucus to adsorb various molecules and particles, such as drugs and other potentially harmful entities (pathogens, toxins, and contaminants) (Bansil and Turner, 2018; Murgia et al., 2018). Furthermore, mucus serves as a dynamic, semipermeable barrier with complex selective permeability, facilitating the exchange of nutrients, water, gases, and hormones while preventing the penetration of most bacteria and many pathogens (Boegh and Nielsen, 2015). Studies have shown that alterations in mucus permeability are associated with diseases such as cystic fibrosis and ulcerative colitis (Fang et al., 2021; Morrison et al., 2019). Dorofeyev et al. (2013) also reported increased permeability of colonic mucus in

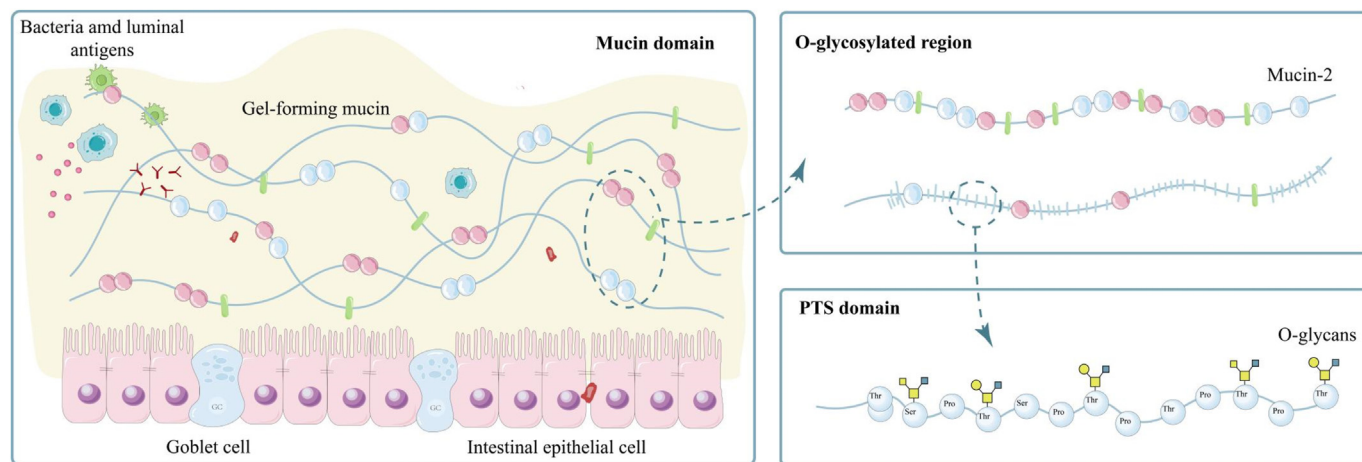


Fig. 1. The structure of intestinal O-glycosylated mucins. The intricate structure of mucus is vital for carrying out its diverse functions and encompasses several key elements, including the mucin domain, proline-threonine-serine (PTS) domains, and densely O-glycosylated regions. Protein core: Intestinal O-glycosylated mucins have a protein core composed of a central tandem repeat domain rich in serine, threonine, and proline residues. This domain provides the attachment sites for O-linked glycan chains. O-glycans are attached to the protein core via O-glycosidic linkages to the hydroxyl groups of serine and threonine residues in the tandem repeat domain. These O-glycans are highly heterogeneous and can vary in composition, length, and branching patterns. They typically contain various monosaccharides such as N-acetylgalactosamine (GalNAc), galactose, N-acetylglucosamine (GlcNAc), fucose, and sialic acid. The O-glycosylated mucin molecule may exhibit secondary and tertiary structures, and mucins can adopt extended, coiled, or globular conformations, which may influence their functional properties.

patients with ulcerative colitis and Crohn's disease, indicating compromised integrity of the mucus barrier.

Components with antimicrobial properties in mucus, such as antimicrobial peptides, immunoglobulins, and other bioactive molecules, help neutralize and eliminate pathogens, reducing the risk of infections. These components are essential for maintaining intestinal health and defending against pathogen invasion, acting as a chemical barrier (Bergstrom and Xia, 2022). Research has found that colonic mucus serves as a reservoir for antimicrobial peptides (AMPs), which can directly cover the mucus layer to kill or inhibit bacterial growth, preventing bacteria from attacking epithelial cells in the intestine (Antoni et al., 2013). Additionally, some antimicrobial peptides exhibit lectin-like behavior, binding to glycosylated proteins, lipopolysaccharides, and bacterial toxins to protect intestinal health (Kudryashova et al., 2014; Moser et al., 2014). Immunoglobulins also play a vital role in maintaining the function of the intestinal mucus barrier by binding to and neutralizing pathogens, preventing microbial penetration through intestinal epithelial cells. As early as four decades ago, Franek et al. (1984) proposed that secretory immunoglobulins are components of mucosal immunity, capable of recognizing harmful bacteria and immobilizing or neutralizing them. Kaetzel (2014) also reported that secretory immunoglobulins in the intestinal mucus layer can adhere to microorganisms, maintaining spatial separation between the gut microbiota and intestinal epithelial cells without affecting microbial metabolic activity.

2.3.2. Immune regulation

Intestinal mucus acts as a bridge between gut microbiota and the immune system. Research by Chen et al. (2021) found that the deletion of forkhead box protein O1 (Foxo1) in intestinal epithelial cells leads to defects in goblet cell autophagy and mucus secretion, resulting in increased susceptibility to intestinal inflammation. Shigemura et al. (2014) discovered that intestinal epithelial cells increase mucin synthesis through the synergistic effects of serum amyloid A3 and tumor necrosis factor- α (TNF- α), effectively protecting epithelial cells from microbial invasion. Similar results were reported by Iwashita et al. (2003). Furthermore, the regulation of gut microbiota by mucus plays a crucial role in immune defense. Certain components in mucus, such as fucose and oligosaccharides

in the sugar chains, serve as nutrients for specific bacteria, supporting the growth of beneficial microbes while inhibiting the proliferation of harmful ones (Alemiao et al., 2021; Pruss et al., 2021).

In summary, mucus is a vital substance in the body, serving multiple vital functions, including lubricating and protecting epithelial surfaces, interacting with the immune system, and capturing and clearing foreign particles. Additionally, mucus supports nutrient absorption and facilitates smooth digestion, while providing a barrier against potential threats to the internal environment. As ongoing research continues to unravel the complexities of mucus and its functions, our understanding of its crucial role in maintaining overall animal health is deepening.

3. Mucin glycosylation

3.1. Mucin-2 is a critical element of the intestinal barrier

The integrity of the mucus layer predominantly relies on mucin-2, a highly glycosylated protein serving as attachment sites for O-linked glycans, and hydroxy-linked carbohydrate chains. Mucin-2 is fundamental to the lubrication, protection, and chemical barrier function of the intestinal mucus layer. It also plays a crucial role in transmitting immunomodulatory signals, thereby reducing the immunogenicity of intestinal antigens and decreasing the likelihood of invasion by bacteria and food antigens present in the intestinal cavity (Arike and Hansson, 2016). The mucus layer formed by mucin-2 dynamically interacts with intestinal epithelial cells, the microbiota, and the host immune defense, contributing to the maintenance of intestinal mucosal homeostasis (Bergstrom et al., 2020). Mucin-2 is a key protective component of the intestine against external stimuli, participating in various stress responses and resisting the invasion of pathogenic microorganisms. Research has shown that weaning-induced stress can disrupt the synthesis and secretion of mucin-2 in the intestine, leading to alterations in intestinal structure and function, which can result in intestinal barrier dysfunction and diarrhea (Sovran et al., 2016). Infections with *Salmonella typhimurium* and *Lawsonia intracellularis* reduce mucin-2 production, damaging the mucus layer and facilitating bacterial invasion (Bengtsson et al., 2015; Kim et al., 2009).

Similarly, infection with *Brachyspira hyodysenteriae* in the colon causes mucoid hemorrhagic diarrhea and changes in the mucus layer, triggering increased mucin-2 secretion. This infection also induces a disorganized mucus structure, with massive mucus production and elevated mucin-2 levels in the colon (Quintana et al., 2017). This response may result from a compromised intestinal barrier, which triggers inflammation and promotes mucin secretion to resist the microbiota, helping to maintain intestinal microbiota balance.

Chronic inflammation or stress may regulate the expression of mucin-2 through related signals such as mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF- κ B), c-Jun N-terminal kinase (JNK), and toll-like receptors 2/4 (TLR2/4). These regulatory mechanisms may lead to abnormal mucin-2 production, disrupting the intestinal mucus barrier. As a result, intestinal microbes can translocate and directly interact with mucosal epithelial cells, exacerbating the inflammatory response. This process may play a significant role in intestinal stress-related diseases, including diarrhea (Paone and Cani, 2020; Vander et al., 2019).

3.2. Different glycan structures produced by O-glycosylated modification are decisive factors for the function of mucin

3.2.1. Core structure of sugar chain

Glycosylation is a post-translational processing modification of mucin, and it is also a decisive factor for the function of mucin (Fig. 2). This multi-step process occurs in the endoplasmic reticulum (ER) and Golgi apparatus (Qu et al., 2021). The mucin monomer, synthesized by ribosomes in the cytoplasm of goblet cells, is first transported to the ER, where it forms dimers through intermolecular disulfide bonds. It is then transported to the Golgi apparatus for O-glycosylation, catalyzed by a series of

glycosyltransferases (Bennett et al., 2012). Mucin undergoes O-glycosylation by two enzymes, core 1 β 1,3-galactosyltransferase (C1GALT1 or T-synthase) and core 3 β 1,3N-acetylglucosamine transferase (C3GNT), leading to the formation of core 1 and core 3 structures, respectively. These structures can further evolve into core 2 and core 4 structures, respectively, through the action of Core 2/4 β 1,6-N-acetylglucosaminyltransferase (C2/4GNT), encoded by the glucosaminyl n-acetyl transferase 3 (GCNT3) gene (Venkatakrishnan et al., 2017). These glycans with core 1–4 structures are commonly found in intestinal mucin, yet their distribution can be influenced by factors such as species, intestinal segment, diet, and microorganisms. For instance, the core 3 structure predominates in human intestinal mucin, while core 2 is more abundant in the duodenum, jejunum, and ileum of mice. In contrast, core 1 and core 3 structures are more prevalent in the colon (Bergstrom et al., 2017).

The major polysaccharides in the colonic mucus layer are mucin O-glycans derived from core 1 and core 3 structures (Sang et al., 2023). Recent studies have shown that the absence of the core 1 structure in mice results in damage to the colonic mucus barrier, leading to impaired intestinal mucosal barrier function (Suzuki et al., 2022). This compromised barrier function makes it easier for pathogens to breach the protective barrier and come into contact with the intestinal epithelium, leading to the onset of spontaneous colitis. Furthermore, mice lacking core 3-derived O-glycans exhibit elevated intestinal permeability compared to their littermates expressing high levels of core 3-derived O-glycans, thereby substantiating the pivotal role played by core 3-derived O-glycans in the preservation of mucosal integrity (Coletto et al., 2023). Core 2-derived O-glycans, synthesized by the enzyme core 2 β 1,6-N-acetylglucosaminyltransferase 2, extend the core 1-derived O-glycans (Pinho et al., 2023; Sang et al., 2023). A study by Ye et al. (2015)

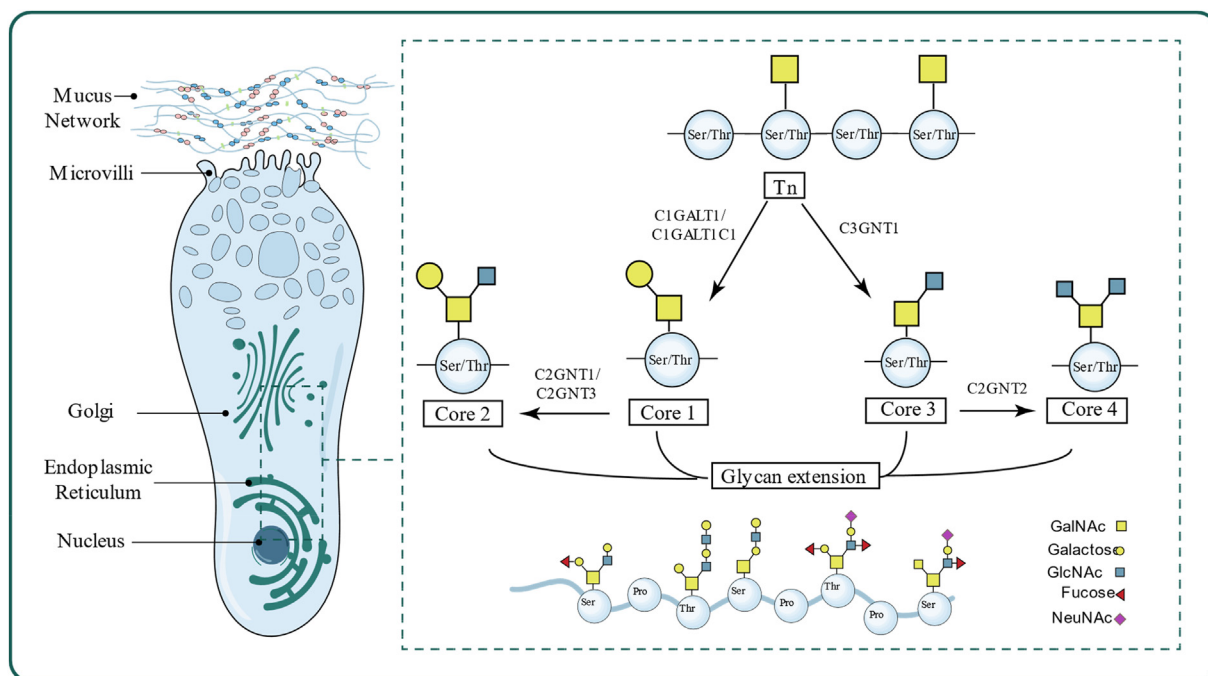


Fig. 2. The process of generation of mucin-type O-glycan. The generation of mucin-type O-glycans occurs in the endoplasmic reticulum (ER) and Golgi apparatus of cells. The process begins in the ER with the addition of a single N-acetylgalactosamine (GalNAc) residue to the hydroxyl group of a serine or threonine residue on a protein substrate. After the initial GalNAc residue is attached, the glycoprotein is transported to the Golgi apparatus, where further elongation of the O-glycan chain occurs. The O-glycan chain can undergo various modifications, including sulfation, sialylation, and fucosylation in the Golgi apparatus. Once glycosylation is complete, the O-glycosylated proteins are transported to their target destinations within the cell or secreted into the extracellular environment. Mucin-type O-glycans are often found on the surface of epithelial cells, where they form the glycocalyx and contribute to cell–cell and cell–matrix interactions. C1GALT1C1 = core 1 β 1,3-galactosyltransferase specific molecular chaperone 1; C3GNT1 = core 3 β 1,3-N-acetylglucosaminyltransferase 1; C2GNT1 = core 2 β 1,3-N-acetylglucosaminyltransferase 1.

demonstrated that core 2 mucin-type O-glycans inhibit the invasion of enteropathogenic *Escherichiacoli* and enterohemorrhagic *E. coli* into intestinal epithelial cells by reducing bacterial adhesion to the epithelium. Similarly, mice deficient in core 2 or core 3 derived O-glycans exhibit baseline impairments in intestinal permeability and increased susceptibility to colitis (Bergstrom et al., 2017).

3.2.2. Modification of sugar chain

Different glycan structures can affect the shape and properties of mucin. Glycosylation is important for keeping mucin in an extended shape, which can influence its overall structure (Witten and Ribbeck, 2017). Furthermore, variations in glycan structure can also have significant implications for the colonization of intestinal microorganisms, as they influence the immunogenicity of mucin and regulate the composition of the gut microbiota (Bergstrom et al., 2020; Gamage et al., 2020; Hansson, 2020).

Fucose is a key sugar residue on mucin sugar chains, making up 4%–14% of total sugar groups and playing a key role in immune activity (Shuoker et al., 2023). It induces the phosphorylation of membrane receptors in enterohemorrhagic *E. coli*, which inhibits the activation of its virulence genes and reduces the strain's pathogenicity (Pacheco et al., 2012). Mutations in fucosylation genes, such as fucosyltransferase 2 (*FUT2*), increase susceptibility to inflammatory diseases like colitis, altering gut microbiota composition and carbohydrate secretion (Cheng et al., 2021). Moreover, fucosylated mucin can serve as substrates for metabolites, energy sources, and adhesion receptors for beneficial bacteria (Lei et al., 2022). Fucose has been shown to promote the abundance of beneficial gut bacteria, such as *Bifidobacteria*, supporting their functions (Kononova et al., 2021). Among the various glycan modifications, sialylation, regulated by sialyltransferase, occurs on mature mucin proteins (Yao et al., 2022). This process involves adding sialic acid to glycans, which is crucial for forming the mucin-2 network structure by providing a negative charge and hydrophilicity (Taniguchi et al., 2023). Sialylated glycan epitopes serve as attachment sites and nutrients for bacteria, protecting the mucus barrier from degradation and maintaining its integrity (Bell et al., 2023).

4. Interaction between intestinal microbiota and mucus barrier

The intestinal microbiota and gut mucin layer engage in interactions that are essential for the development of the mucus layer, microbial colonization, and stability of barrier function in the gut (Fig. 3) (Gamage et al., 2020). The mucus layer, which envelops the epithelial cells of the gut, upholds intestinal homeostasis by blocking certain pathogens, providing nutrients to microorganisms, and averting aberrant immune responses directed toward the microbiota (Luis and Hansson, 2023). The microbiota is an important player in health and physiology with many functions, such as digesting dietary nutrients, producing vitamins, stimulating the immune system, regulating the production and secreting of mucus, etc. (Paone and Cani, 2020).

Host-derived mucus glycans on gut-secreted mucin proteins serve as a continuous endogenous source of microbiota-accessible carbohydrates for resident microbes. The glycosylation chain of mucin could adhere to intestinal symbiotic flora, help probiotics colonize in the intestine, and play a biological barrier role (Qu et al., 2021). Probiotics like *Bifidobacterium* can produce highly active fucosidase and sulfoglycosidase (BbhII), which degrades the sugar chain of mucins, releasing free fucose and N-acetylglucosamine-6-sulfate (Kato et al., 2023; Jess et al., 2011). Porcine mucin glycans have been shown to help restore the microbiota after antibiotic

treatment, inhibit the abundance of *Clostridium difficile* and increase the relative abundance of resident *Akkermansia muciniphila*, thereby delaying the onset of diet-induced obesity, and maintaining the body health (Pruss et al., 2021). The glycan architecture of mucin significantly shapes the behavioral patterns of gut microbiota, influencing aspects such as energy metabolism, signaling pathways, and probiotic functionalities (Shin et al., 2019). Specific glycosylation processes enable mucin to exert immune responses against specific pathogens. For example, mucin sulfation and sialylation, orchestrated by IL-13/IL-4R, contribute to the expulsion of worms and nematodes from the intestine (Earley et al., 2019; Hasnain et al., 2017; Tsubokawa et al., 2017). Specific n-glycosylation supports the proliferation of succinate-consuming bacteria, consequently diminishing the availability of succinate—a crucial metabolite essential for the growth of *Clostridium difficile* (Nagao et al., 2020). Moreover, mucin likely mediates bacterial clearance through the regulation of microbial phenotypes, which attenuates pathogens and thereby facilitates host-mediated clearance (Takagi et al., 2022; Wheeler et al., 2019). To sum up, mucin is the material basis of intestinal mucous layer protection and microbial barrier function and plays a critical role in maintaining intestinal mucosal homeostasis, responding to various stressors, and resisting pathogenic microorganisms.

In a state of normal physiological conditions, the gut microbiota emerges as the foremost influential environmental factor shaping the glycosylation profile of the intestinal mucosa which plays a significant role in the initiation and progression of intestinal inflammation and associated diseases (Padra et al., 2019). The metabolites of symbiotic bacteria and cell surface-active substances, including short-chain fatty acids, tryptophan derivatives, and TLR ligands, may exert an influence on the glycosylation of intestinal mucins which is manifested by impacting cytokine expression of intestinal mucosal cells, the pH, the energy levels, etc. (Chun et al., 2019). Studies conducted previously have documented that the administration of oral probiotics has the capability to effectively restore the glycation profile of intestinal mucins and these probiotics play a protective role in preserving mucin-derived O-glycans from bacterial degradation and help in mitigating the risk of intestinal mucosa infection by opportunistic pathogens (Desantis et al., 2019; Schroeder et al., 2018). The colonization of *Bifidobacterium dentium* has also been shown to be effective in inducing intestinal endothelial cell fucosylation and mucin expression (Qu et al., 2021). Besides, *Bacteroides polymorpha* could stimulate the fucosylation modification of human intestinal mucin, reduce the sialic acid level of intestinal mucin in young animals, and promote the development and maturation of intestinal tissue, thereby protecting the intestinal mucosal epithelium from intestinal bacterial infection (Stahl et al., 2011). However, there are few studies on the interaction between intestinal probiotics and mucin glycosylation modification, and further research is needed to elucidate its mechanisms.

5. Intestinal mucus barrier and gut diseases

Alterations in the permeability, glycosylation profiles, and charge distributions of mucus barriers have been associated with changes in physiology. Abnormal modifications in these aspects may contribute to the onset of gut diseases, including ulcerative colitis, irritable bowel syndrome, metabolic syndrome, Crohn's disease, and others. These conditions are often accompanied by disruptions in the composition and balance of the gut microbiota (Table 1). In addition, intestinal injury is also accompanied by abnormal changes in the intestinal mucus barrier. Inflammatory bowel disease, a chronic non-specific intestinal inflammatory disease comprising ulcerative colitis and Crohn's disease, has been

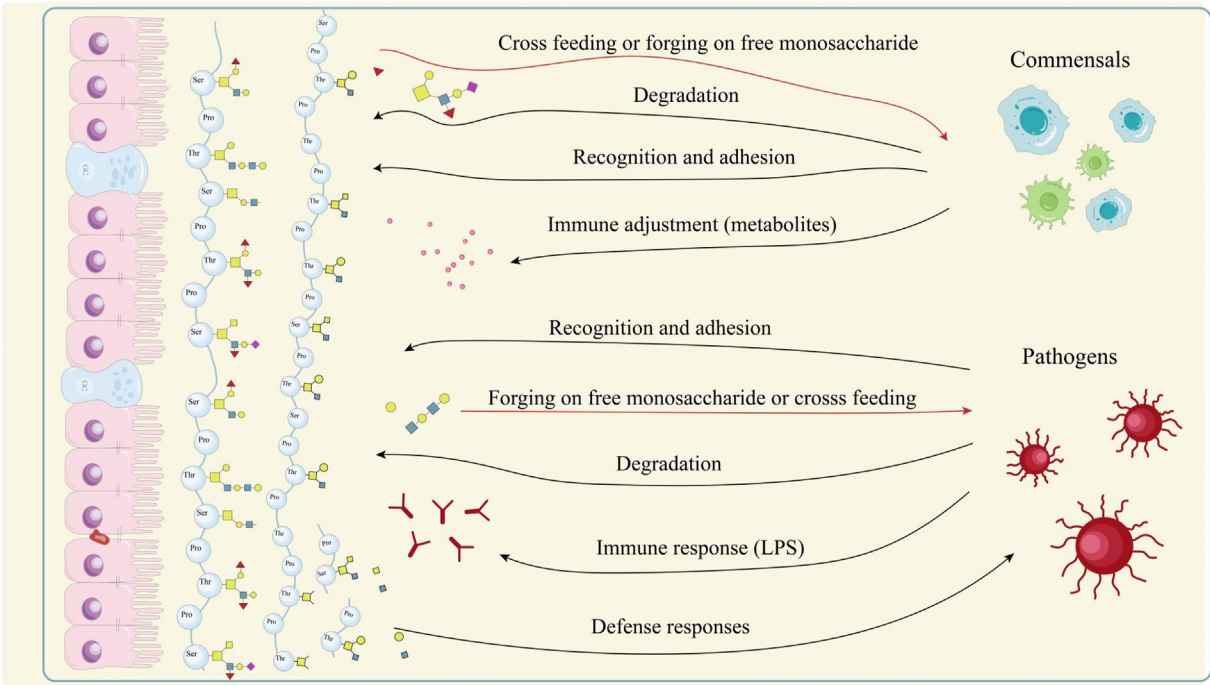


Fig. 3. The interaction of microbe and intestinal mucus barrier. LPS = lipopolysaccharide.

Table 1
Intestinal mucus barrier and gut disease.

Diseases	Changes in the mucus barrier	Symptoms	Cause of gut disease	References
Crohn's disease	Increased mucus thickness, and decreased mucin-2 protein	Pain diarrhea	Not well studied	Doron et al. (2013)
Ulcerative colitis	Decreased mucus thickness, goblet cell, and glycosylation	Bloody diarrhea	Not well studied	Fernandez et al. (2021)
Cystic fibrosis	Abnormal decreased mucus	Pain, obstruction, and pancreatic insufficiency	Inheritance	Morrison et al. (2019)
Pseudomembranous colitis	Thinning of the mucus layer	Flatulence and loss of appetite	<i>Clostridium difficile</i> infections	Rheinallt and Andrew (2021)
Colorectal cancer	Decreased mucus thickness, aberrant mucin expression, and simplified glycosylation	Bloody diarrhea, pain, and flatulence	Variations in the intestinal microbiome and some bacterial metabolites	Song and Chan (2019) , Zhao et al. (2018)
Irritable bowel syndrome	Non-specific inflammatory manifestations	Indigestion, flatulence, and intermittent pain	Brain–gut communication dysfunction, integrity of mucosa, and inflammation	Pappas et al. (2018)
Invasive candidiasis	Perturbations of mucosal microbiota		Intestinal mucosal inflammation	

extensively studied in relation to the mucus barrier. Ulcerative colitis, marked by inflammation restricted to the mucosa and submucosa of the colon, is influenced by a combination of factors including commensal microbiota, genetics, environment, and immune response ([Chen et al., 2014](#)). Research has indicated a substantial reduction in mucin sulfation in patients with ulcerative colitis, underscoring the pivotal role of colonic mucins in maintaining the normal physiological function of the colon ([Kawashima, 2012](#)). Furthermore, in the context of ulcerative colitis, the mucus layer undergoes thinning and partial denudation, potentially creating a condition wherein luminal microbes may invade the mucosa, triggering the onset of the disease ([Dorofeyev et al., 2013](#)). Crohn's disease, another subtype of inflammatory bowel disease characterized by chronic and nonspecific bowel inflammation that can affect any part of the intestinal tract, has also been associated with the mucus barrier. Allelic polymorphisms of mucin-1 and mucin-2 have been linked to Crohn's disease ([Doron et al., 2013](#)). Furthermore, Crohn's disease patients exhibit an altered

microbiome profile characterized by an increased abundance of Enterobacteriaceae, Pasteurellaceae, Veillonellaceae, and *Fusobacteriaceae*, coupled with a decreased abundance of *Erysipelotrichales*, *Bacteroidales*, and *Clostridiales* ([Basoglu and Karakoyun, 2023](#)). In summary, the abnormality of the intestinal mucus barrier may be one of the pathogenesis of various intestinal diseases, involving the changes of flora, gene polymorphism, and other factors.

Research has also proposed that dietary factors can impact the integrity of the intestinal barrier ([Desai et al., 2016](#); [Liu et al., 2023](#)). Dietary fiber, commonly found in the Western diet, has been shown to improve the integrity of the intestinal barrier by increasing mucus secretion, antibacterial proteins, and the production of T-regulatory cells ([Sauvatre et al., 2021](#)). Dietary iron supplementation, through oral administration or injection, could activate mechanistic target of rapamycin complex 1-ribosomal protein S6 kinase β -1 (mTORC1-S6K1) signaling, thereby promoting intestinal mucosal growth and mucus secretion ([Dong et al., 2023](#); [Liu et al.,](#)

2023). Moreover, dietary probiotics such as lactobacillus and bifidobacterium increase host resistance to gastrointestinal diseases, intestinal infections, antibiotic-induced diarrhea, depression, and anxiety (Schroeder et al., 2018). In summary, the integrity of the gut barrier can be improved by adjusting diet, and dietary fiber and probiotics play an important role in this process; however, the exact mechanisms of these dietary effects require further study.

6. Existing problems and future research directions

Despite considerable advancements in comprehending the mucus barrier in recent years, various questions and uncertainties persist. The mechanisms associated with glycosyltransferase levels and activities, as well as the glycan repertoire on mucosal surfaces during inflammation and infection, remain poorly understood. Due to the complex physical and chemical properties of individual O-glycan structures, it is challenging to isolate and purify them from animal sources. Their specific mechanisms of action remain to be further studied. Furthermore, the regulation of the mucus barrier through interactions with the microbiota is an area that requires further exploration. To address these practical questions and advance our understanding of the mucus barrier, additional research is essential.

Credit Author Statement

Hao Cheng: Writing – original draft. **Hao Li:** Data curation. **Zhong Li:** Data curation. **Yun Wang:** Investigation. **Liangguo Liu:** Resources. **Jing Wang:** Supervision. **Xiaokang Ma:** Funding acquisition. **Bie Tan:** Funding acquisition.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (32202692), the Hunan Provincial Natural Science Foundation of China (2022JJ40176), National Key R&D Program of China (2021YFD1300403).

References

- Alemo CA, Budden KF, Gomez HM, Rehman SF, Marshall JE, Shukla SD, Donovan C, Forster SC, Yang IA, Keely S, Mann ER, Omar EME, Belz GT, Hansbro PM. Impact of diet and the bacterial microbiome on the mucous barrier and immune disorders. *Allergy* 2021;76(3):714–34.
- Arike L, Hansson GC. The densely O-glycosylated muc2 mucin protects the intestine and provides food for the commensal bacteria. *J Mol Biol* 2016;428:3221–9.
- Antoni L, Nuding S, Weller D, Gersemann M, Ott G, Wehkamp J, Stange EF. Human colonic mucus is a reservoir for antimicrobial peptides. *J Crohns Colitis* 2013;7(12):652–64.
- Basoglu IA, Karakoyun B. Crohn's disease: etiology, pathogenesis and treatment strategies. *Marmara Med J* 2023;36:249–54.
- Bansil R, Turner BS. The biology of mucus: composition, synthesis and organization. *Adv Drug Deliv Rev* 2018;124:3–15.
- Bell A, Severi E, Owen CD, Latousakis D, Juge N. Biochemical and structural basis of sialic acid utilization by gut microbes. *J Biol Chem* 2023;299:102989.
- Bengtsson RJ, MacIntyre N, Guthrie J, Wilson AD, Finlayson H, Matika O, Wong RP, Smith SH, Archibald AL, Ali TA. Lawsonia intracellularis infection of intestinal crypt cells is associated with specific depletion of secreted Muc2 in goblet cells. *Vet Immunol Immunopathol* 2015;168:61–7.
- Bennett EP, Mandel U, Clausen H, Gerken TA, Fritz TA, Tabak LA. Control of mucin-type O-glycosylation: a classification of the polypeptide GalNAc-transferase gene family. *Glycobiology* 2012;22:736–56.

- Bergstrom K, Fu J, Johansson ME, Liu X, Gao N, Wu Q, Song J, McDaniel JM, McGee S, Chen M, Braun J, Hansson GC, Xia L. Core 1- and 3-derived O-glycans collectively maintain the colonic mucus barrier and protect against spontaneous colitis in mice. *Mucosal Immunol* 2017;10:91–103.
- Bergstrom K, Shan X, Casero D, Batushansky A, Lagishetty V, Jacobs JP, Hoover C, Kondo YJ, Shao BI, Gao L, Zandberg W, Noyovitz B, McDaniel JM, Gibson DL, Pakpour S, Kazemian N, McGee S, Houchen CW, Rao CV, Griffin TM, Sonnenburg JL, McEver RP, Braun J, Xia LJ. Proximal colon-derived O-glycosylated mucus encapsulates and modulates the microbiota. *Science* 2020;370:467–72.
- Bergstrom K, Xia L. The barrier and beyond: roles of intestinal mucus and mucin-type O-glycosylation in resistance and tolerance defense strategies guiding host-microbe symbiosis. *Gut Microbes* 2022;14:2052699.
- Boehm M, Nielsen HM. Mucus as a barrier to drug delivery—understanding and mimicking the barrier properties. *Basic Clin Pharmacol Toxicol* 2015;116(3):179–86.
- Braga EN, Brierley SM, Schroeder CI, Muttenthaler M. Structure, function, and therapeutic potential of the trefoil factor family in the gastrointestinal tract. *ACS Pharmacol Transl Sci* 2020;3(4):583–97.
- Chen Z, Luo J, Li J, Kim G, Xiao S, Snapper SB, Bao B, An DD, Blumberg RS, Lin CH, Wang S, Zhong JX, Liu K, Li QY, Wu C, Kuchroo VK. Foxo1 controls gut homeostasis and commensalism by regulating mucus secretion. *J Exp Med* 2021;218(9):e20210324.
- Chen SJ, Liu XW, Liu JP, Yang XY, Lu FG. Ulcerative colitis as a polymicrobial infection characterized by sustained broken mucus barrier. *World J Gastroenterol* 2014;20:9468–75.
- Cheng S, Hu J, Wu XR, Pan JA, Jiao N, Li YC, Huang YB, Lin XT, Zou YF, Chen Y, Zhu LX, Zhi M, Lan P. Altered gut microbiome in FUT2 loss-of-function mutants in support of personalized medicine for inflammatory bowel diseases. *J Genet Genomics* 2021;48:771–80.
- Chun E, Lavoie S, Fonseca PD, Bae S, Michaud M, Hoveyda HR, Fraser GL, Comeau CAG, Glickman JN, Fuller MH, Layden BT, Garrett WS. Metaboli-sensing receptor ffar2 regulates colonic group 3 innate lymphoid cells and gut immunity. *Immunity* 2019;51:871–84.
- Coletto E, Savva GM, Latousakis D, Pontifex M, Crost EH, Vaux L, Telatin A, Bergstrom K, Vauzour D, Juge N. Role of mucin glycosylation in the gut microbiota-brain axis of core 3 O-glycan deficient mice. *Sci Rep* 2023;13:13982.
- Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, Pulido NA. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* 2016;167:1339–53.
- Dong ZL, Liu S, Deng QQ, Li G, Tang X, Wu X, Wan D, Yin Y. Role of iron in host-microbiota interaction and its effects on intestinal mucosal growth and immune plasticity in a piglet model. *Sci China Life Sci* 2023;66:2086–98.
- Desantis S, Mastrodonato M, Accogli G, Rossi G, Crovace AM. Effects of a probiotic on the morphology and mucin composition of pig intestine. *Histol Histopathol* 2019;34:1037–50.
- Dorofeyev AE, Vasilenko IV, Rassokhina OA, Kondratyuk RB. Mucosal barrier in ulcerative colitis and Crohn's disease. *Gastroenterol Res Pract* 2013;1:431231.
- Doron B, Perets TT, Vilkin A, Niv Y. Mucin function in inflammatory bowel disease. *Clin Rev* 2013;47:106–11.
- Earley H, Lennon G, Balfé A, Coffey JC, Winter DC, Connell PR. The abundance of Akkermansia muciniphila and its relationship with sulphated colonic mucins in health and ulcerative colitis. *Sci Rep* 2019;9:15683.
- Elderman M, Sovran B, Hugenholtz F, Graversen K, Huijskes M, Houtsma E, Belzer C, Boekschoten M, Vos PD, Dekker J, Wells J, Faas M. The effect of age on the intestinal mucus thickness, microbiota composition and immunity in relation to sex in mice. *PLoS One* 2017;12:e0184274.
- Fang J, Wang H, Zhou YP, Zhang H, Zhou HY, Zhang XH. Slimy partners: the mucus barrier and gut microbiome in ulcerative colitis. *Exp Mol Med* 2021;53(5):772–87.
- Fernandez TL, Ortega ML, Chaparro M, Gisbert JP. Gut microbiota and dietary factors as modulators of the mucus layer in inflammatory bowel disease. *Int J Mol Sci* 2021;22(19):10224.
- Franek J, Libich J, Kubin V. Mechanisms of antibacterial immunity of mucous membranes. *Folia Microbiol* 1984;29:375–84.
- Game H, Chong RWW, Bucio ND, Kautto L, Hardikar AA, Ball MS, Molloy MP, Packer NH, Paulsen IT. Changes in dietary fiber intake in mice reveal associations between colonic mucin O-glycosylation and specific gut bacteria. *Gut Microbes* 2020;12:1802209.
- Hansson GC. Mucins and the microbiome. *Annu Rev Biochem* 2020;89:769–93.
- Hasnain SZ, Dawson PA, Lourie R, Hutson P, Tong P, Grecis RK, McGuckin MA, Thornton DJ. Immune-driven alterations in mucin sulphation is an important mediator of Trichuris muris helminth expulsion. *PLoS Pathog* 2017;13:e1006218.
- Herath M, Hosie S, Bornstein JC, Franks AE, Hill YEL. The role of the gastrointestinal mucus system in intestinal homeostasis: implications for neurological disorders. *Front Cell Infect Microbiol* 2020;10:248.
- Hoffmann W. Refoil factor family (TFF) peptides and their diverse molecular functions in mucus barrier protection and more: changing the paradigm. *Int J Mol Sci* 2020;21(12):4535.
- Iwashita J, Sato Y, Sugaya H, Abe T. mRNA of MUC2 is stimulated by IL-4, IL-13 or TNF- α through a mitogen-activated protein kinase pathway in human colon cancer cells. *Immunol Cell Biol* 2003;81(4):275–82.
- Jess RD, Monedero V, Yebra MJ. Utilization of natural fucosylated oligosaccharides by three novel fucosidases from a probiotic *Lactobacillus casei* strain. *Appl Environ Microbiol* 2011;703–5.

- Johansson ME, Hansson GC. Immunological aspects of intestinal mucus and mucins. *Nat Rev Immunol* 2016;16:639–49.
- Kaetzel CS. Cooperativity among secretory IgA, the polymeric immunoglobulin receptor, and the gut microbiota promotes host–microbial mutualism. *Immunol Lett* 2014;162(2):10–21.
- Katoh T, Yamada C, Wallace MD, Yoshida A, Gotoh A, Arai M, Maeshibu T, Kasima T, Hagenbeek A, Ojima MN, Takada H, Sakanaka M, Shimizu H, Nishiyama K, Ashida H, Hirose J, Sureau DM, Nishiyama M. Ki. A bacterial sulfoglycosidase highlights mucin O-glycan breakdown in the gut ecosystem. *Nat Chem Biol* 2023;19(6):778–89.
- Kawashima H. Roles of the gel-forming Muc2 mucin and its o-glycosylation in the protection against colitis and colorectal cancer. *Front Oncol* 2012;35:1637–41.
- Kim CH, Kim D, Ha Y, Cho KD, Lee BH, Seo IW, Kim SH, Chae C. Expression of mucins and trefoil factor family protein-1 in the colon of pigs naturally infected with *Salmonella typhimurium*. *J Comp Pathol* 2009;140:38–42.
- Kononova S, Litvinova E, Vakhtov T, Skalinikaya M, Sitkin S. Acceptive immunity: the role of fucosylated glycans in human host-microbiome interactions. *Int J Mol Sci* 2021;22(8):3854.
- Kudryashova E, Quintyn R, Seveau S, Lu W, Wysocochi VH, Kudryashov DS. Human defensins facilitate local unfolding of thermodynamically unstable regions of bacterial protein toxins. *Immunity* 2014;41(5):709–21.
- Lei C, Sun R, Xu G, Tan Y, Feng W, McClain CJ, Deng Z. Enteric VIP-producing neurons maintain gut microbiota homeostasis through regulating epithelium fucosylation. *Cell Host Microbe* 2022;30(10):1417–34.
- Liu Q, Niu X, Li Y, Zhang JR, Zhu SJ, Yang QY, Zhang W, Gong L. Role of the mucin-like glycoprotein FCGBP in mucosal immunity and cancer. *Front Immunol* 2022;13:863317.
- Liu S, Dong ZL, Tang WJ, Zhou J, Guo L, Gong C, Liu G, Wan D, Yin Y. Dietary iron regulates intestinal goblet cell function and alleviates *Salmonella typhimurium* invasion in mice. *Sci China Life Sci* 2023;66:2006–19.
- Luis AS, Hansson GC. Intestinal mucus and their glycans: a habitat for thriving microbiota. *Cell Host Microbe* 2023;31:1087–100.
- Mcshane A, Bath J, Jaramillo AM, Ridley C, Walsh AA, Evans CM, Thornton DJ, Ribbeck K. Mucus. *Curr Biol* 2021;31:938–45.
- Morrison CB, Markowitz MR, Ehre C. Mucus, mucins, and cystic fibrosis. *Pediatr Pulmonol* 2019;54:84–96.
- Moser S, Chileveru HR, Tomaras J, Nolan EM. A bacterial mutant library as a tool to study the attack of a defensin peptide. *ChemBiochem* 2014;15(18):2684.
- Murgia X, Loretz B, Hartwig O, Hittinger M, Lehr CM. The role of mucus on drug transport and its potential to affect therapeutic outcomes. *Adv Drug Deliv Rev* 2018;124(15):82–97.
- Nagao kH, Leslie JL, Kitamoto S, Jin CS, Thomsson KA, Gilliland MG, Kuffa P, Goto Y, Jenq RR, Ishii C, Hirayama A, Seekatz AM, Martens EC, Eaton KA, Kao JY, Fukuda SJ, Higgins PDR, Kallson NG, Young VB, Kamada N. Interleukin-22-mediated host glycosylation prevents *Clostridioides difficile* infection by modulating the metabolic activity of the gut microbiota. *Nat Med* 2020;26:608–17.
- Pacheco AR, Curtis MM, Ritchie JM, Munera D, Waldor MK, Moreira CG, Sperando V. Fucose sensing regulates bacterial intestinal colonization. *Nature* 2012;492:113–7.
- Padra M, Adamczyk B, Flahou B, Erhaedsson M, Chahal G, Smet A, Jin C, Thorell A, Ducatelle R, Haesebrouck F, Karlsson NG, Linden SK. *Helicobacter suis* infection alters glycosylation and decreases the pathogen growth inhibiting effect and binding avidity of gastric mucins. *Mucosal Immunol* 2019;12:784–94.
- Pajic P, Shen SC, Qu J, May AJ, Knox S, Ruhl S, Gokcumen O. A mechanism of gene evolution generating mucin function. *Sci Adv* 2022;8:1–14.
- Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut* 2020;69:2232–43.
- Pappas GP, Lionakis MS, Arendrup MC, Ostrosky ZL, Kullberg BJ. Invasive candidiasis. *Nature Reviews* 2018;26:18026.
- Pinho SS, Alves I, Gaifem J, Rabinovich GA. Immune regulatory networks coordinated by glycans and glycan-binding proteins in autoimmunity and infection. *Cell Mol Immunol* 2023;20(10):1101–13.
- Pruss KM, Marcobal A, Southwick AM, Dahan D, Smits SA, Ferreyra JA, Higginbottom SK, Sonnenburg ED, Kashyap PC, Choudhury B, Bode L, Sonnenburg JL. Mucin-derived O-glycans supplemented to diet mitigate diverse microbiota perturbations. *ISME J* 2021;15(2):577–91.
- Qu D, Wang G, Yu L, Tian F, Chen W, Zhai Q. The effects of diet and gut microbiota on the regulation of intestinal mucin glycosylation. *Carbohydr Polym* 2021;258:117651.
- Quintana HMP, Navabi N, Mahu M, Venkatakrishnan V, Fernandez HR, Haesebrouck F, Pasmans F, Linden SK. Neutrophil elastase and interleukin 17 expressed in the pig colon during *brachyspira hyodysenteriae* infection synergistically with the pathogen induce increased mucus transport speed and production via mitogen-activated protein kinase 3. *Infect Immun* 2017;85:8.
- Rheinallt MJ, Andrew SN. Gut microbiota in intestinal and liver disease. *Annu Rev Pathol Mech Dis* 2021;16:251–75.
- Sanchez DMF, Romero C, Mascaraque C, Martinez AO. Intestinal inflammation and mucosal barrier function. *Inflamm Bowel Dis* 2014;20(12):2394–404.
- Sang X, Wang Q, Ning Y, Wang H, Zhang R, Fang B, Lv C, Zhang Y, Wang X, Ren F. Age-related mucus barrier dysfunction in mice is related to the changes in Muc2 mucin in the colon. *Nutrients* 2023;15.
- Sauvatre T, Etienne ML, Sivignon A, Mosoni P, Courtin C, Vande WT, Blanquert DS. Tripartite relationship between gut microbiota, intestinal mucus and dietary fibers: towards preventive strategies against enteric infections. *FEMS Microbiol Rev* 2021;45(2):52.
- Schroeder BO, Birchenough GMH, Stahlman M, Arike L, Johansson MEV, Hansson GC, Backhed F. Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. *Cell Host Microbe* 2018;23:27–40.
- Shin J, Noh JR, Chang DH, Kim YH, Kim MH, Lee ES, Cho SY, Ku BJ, Rhee MS, Kim BC, Lee CH, Cho BK. Elucidation of *akkermansia muciniphila* probiotic traits driven by mucin depletion. *Front Microbiol* 2019;10:1137.
- Shigemura H, Ishiguro N, Inoshima Y. Up-regulation of MUC2 mucin expression by serum amyloid A3 protein in mouse colonic epithelial cells. *J Vet Med Sci* 2014;76(7):985–91.
- Shuoker B, Pichler MJ, Jin C, Sakanaka H, Wu H, Gascuena AM, Liu JN, Nielsen TS, Holgersson J, Karlsson EN, Juge N, Meier S, Morth JP, Karlsson NG, Hachem MA. Sialidases and fucosidases of *Akkermansia muciniphila* are crucial for growth on mucin and nutrient sharing with mucus-associated gut bacteria. *Nat Commun* 2023;14:1833.
- Song C, Chai Z, Chen S, Zhang H, Zhang X, Zhou Y. Intestinal mucus components and secretion mechanisms: what we do and do not know. *Exp Mol Med* 2023;55:681–91.
- Song M, Chan AT. Environmental factors, gut microbiota, and colorectal cancer prevention. *Clin Gastroenterol Hepatol* 2019;17(2):275–89.
- Sovran B, Lu P, Linda MPL, Hugenholtz F, Belzer C, Stolte EH, Boekschoten MV, Baarlen PV, Smidt H, Kleerebezem M, Vos PD, Renes IB, Wells JM, Dekker J. Identification of commensal species positively correlated with early stress responses to a compromised mucus barrier. *Inflamm Bowel Dis* 2016:1–15.
- Stahl M, Friis LM, Nothaft H, Liu X, Li J, Szymanski CM, Stintzi A. L-fucose utilization provides *Campylobacter jejuni* with a competitive advantage. *Proc Natl Acad Sci* 2011;108:7194–9.
- Suzuki R, Nakamura Y, Koiwai R, Fuseya S, Murakami Y, Hagiwara K, Sato T, Takahashi S, Kudo T. Global loss of core 1-derived o-glycans in mice leads to high mortality due to acute kidney failure and gastric ulcers. *Int J Mol Sci* 2022;23.
- Takagi J, Aoki K, Turner BS, Lamont S, Lehoux S, Kavanaugh N, Gulati M, Tiemeyer M, Hevey R, Ribbeck K. Mucin O-glycans are natural inhibitors of *Candida albicans* pathogenicity. *Nat Chem Biol* 2012;8:762–73.
- Tang X, Liu H, Yang S, Li Z, Zhong J, Fang R. Epidermal growth factor and intestinal barrier function. *Mediat Inflamm* 2016:1927348.
- Taniguchi M, Okumura R, Matsuzaki T, Nakatani A, Sakaki K, Okamoto S, Ishibashi A, Tani H, Horikiri M, Kobayashi N, Yoshikawa HY, Motooka D, Takeda K. Sialylation shapes mucus architecture inhibiting bacterial invasion in the colon. *Mucosal Immunol* 2023;16:624–41.
- Thim L. A new family of growth factor-like peptides ‘Trefoil’disulphide loop structures as a common feature in breast cancer associated peptide (pS2), pancreatic spasmolytic polypeptide (PSP), and frog skin peptides (spasmolysins). *FEBS Lett* 1989;250(1):85–90.
- Thim L, May FEB. Trefoil factors: structure of mammalian trefoil factors and functional insights. *Cell Mol Life Sci* 2005;62:2956–73.
- Tsubokawa D, Ishiwata K, Goso Y, Nakamura T, Hatta T, Ishihara K, Kanuka H, Tsuji N. Interleukin-13/interleukin-4 receptor pathway is crucial for production of Sd(a)-sialomucin in mouse small intestinal mucosa by *Nippostrongylus brasiliensis* infection. *Parasitol Int* 2017;66:731–4.
- Vander PS, Jabbar KS, Birchenough G, Arike L, Akhtar N, Sjoval H, Johansson MEV, Hansson GC. Structural weakening of the colonic mucus barrier is an early event in ulcerative colitis pathogenesis. *Gut* 2019;68:2142–51.
- Venkatakrishnan V, Quintana-Hayashi MP, Mahu M, Haesebrouck F, Pasmans F, Linden SK. *Brachyspira hyodysenteriae* infection regulates mucin glycosylation synthesis inducing an increased expression of core-2 o-glycans in porcine colon. *J Proteome Res* 2017;16:1728–42.
- Wagner CE, Wheeler KM, Ribbeck K. Mucins and their role in shaping the functions of mucus barriers. *Annu Rev Cell Dev Biol* 2018;34:189–215.
- Wheeler KM, Carcamo GO, Turner BS, Nolan SD, Co JY, Lehoux S, Cummings RD, Wozniak DJ, Ribbeck K. Mucin glycans attenuate the virulence of *Pseudomonas aeruginosa* in infection. *Nat Microbiol* 2019;4(12):2146–54.
- Witten J, Ribbeck K. The particle in the spider's web: transport through biological hydrogels. *Nanoscale* 2017;9:8080–95.
- Xia B, Wu W, Zhang L, Wen X, Xie J, Zhang H. Gut microbiota mediates the effects of inulin on enhancing sulfomucin production and mucosal barrier function in a pig model. *Food Funct* 2021;12:10967–82.
- Yang YQ, Lin ZY, Lin QY, Bei W, Guo J. Pathological and therapeutic roles of bioactive peptide trefoil factor 3 in diverse diseases: recent progress and perspective. *Cell Death Dis* 2022;13(1):62.
- Yao Y, Kim G, Shafer S, Chen ZJ, Kubo S, Ji YL, Luo JL, Yang WM, Perner SP, Kanellopoulou C, Park AY, Jiang P, Li J, Baris S, Aydiner EK, Ertem D, Mulder DJ, Warner N, Griffiths AM, Kori M, Werner L, Ouahed J, Field M, Liu CY, Schwarz B, Boiso CM, Ganesan S, Song J, Ullrich T, Oelerich T, Malaker SA, Zheng LX, Zhang Y, Pan KY, Wu C, Lenardo MJ. Mucus sialylation determines intestinal host-commensal homeostasis. *Cell* 2022;185:1172–88.
- Yuan H, Cui W. The lubricated matter in body. *Prog Mater Sci* 2024:101334.
- Ye J, Pan Q, Shang Y, Wei X, Peng Z, Chen W, Chen L, Wang R. Core 2 mucin-type o-glycan inhibits EPEC or EHEC O157:H7 invasion into HT-29 epithelial cells. *Gut Pathog* 2015;7:31.
- Zhao K, Yu LM, Wang X, He Y, Lu B. *Clostridium butyricum* regulates visceral hypersensitivity of irritable bowel syndrome by inhibiting colonic mucous low grade inflammation through its action on NLRP6. *Acta Biochim Biophys Sin* 2018;50(2):216–23.