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Exploring the mechanism of interaction between Muc2 and intestinal flora on functional constipation

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Abstract: *Intestinal mucus barrier is the first defense barrier, which can separate pathogenic bacteria from epithelial cells in the intestinal lumen and prevent some pathogenic substances from entering the human circulatory system through the intestinal barrier. Studies have shown that patients with functional constipation may have mucus barrier dysfunction and intestinal flora dysregulation, and the mechanism of the interaction between mucin 2 and intestinal flora on functional constipation is still unclear. Therefore, this paper reviewed the interaction mechanism between mucin 2 and intestinal flora, with a view to providing new ideas and directions for exploring the research related to functional constipation.*

Keywords: *Mucin 2, Intestinal flora, Functional constipation*

1. Introduction

Functional constipation (FC) belongs to a kind of functional bowel disease, which mainly manifests as difficulty in defecation, reduced frequency of defecation, or incomplete defecation, and does not meet the diagnostic criteria of constipation-type irritable bowel syndrome (mainly constipated irritable bowel syndrome, IBS-C)[1] . With the progress of the times, people's dietary structure has changed, the increase of crude fiber decreases and the fineness increases, over-eating fat, sweet, thick and greasy products, exercise decreases, and social pressure increases, resulting in the modern population's susceptibility to constipation.

The intestinal mucosal chemical barrier is the first part of the intestinal mucosal barrier composition, in which the intestinal cuprocytes secrete mucin (mucin, MUC) is the main component[2] , there are more than 20 types of mucin identified, the expression site of different types of mucin is not the same, in general, MUC2 is only expressed in the intestinal tract. In general, MUC2 is only expressed in the intestine. However, little is known about the regulation of MUC2 because it is a very complex dynamic system. Some studies have reported that MUC2 interacts with the intestinal flora [3], and in recent years, the study of the intestinal mucosal chemical barrier and intestinal flora has become more popular, so this paper summarizes the research reports on the association between mucin 2 and intestinal flora, aiming to highlight the importance of the mucus layer and mucin 2, and to provide more insights and new directions for the further investigation of the mechanisms of functional constipation and intestinal mucosal chemical barrier dysfunction. The results of this study are summarized as follows.

2. MUC2 structure

Mucins are synthesized and secreted by goblet cells, and MUC2 gene was cloned from the human small intestinal GDNA expression library by Gum et al in 1989. The MUC2 gene was located at 11pl5.3-15.5 on the surface of tracheobronchial mucosa. The expression product of the gene, MUC2, is a secretory mucin[4]. MUC2 is one of the first secreted gel-like mucins to be identified and characterized. It contains multiple structural domains, including three von Willebrand D domains (VWD) at the N-terminus, interspersed with two CysD domains of proline (Pro) and threonine (Thr), Ser) centered tandem repeats, also known as PTS domains. The CysD domain is thought to mediate intermolecular adhesion during the intracellular bioassembly of mucin polymers and possibly after secretion in extracellular mucus hydrogels[5].The structure of PTS is relatively conserved, which makes the analysis of the evolutionary relationships of adhesion sites meaningless[6].As well as the C-terminal

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ones containing 1 VWD and 3.5 von Willebrand C (VWC) structural domains and a cysteine (CK) structural domain[7][8]. disulfide bonds of the CK structural domain of MUC2 form a dimer.The C-terminal domain is a "cystine knot" (CK) that is required for dimer formation in the ER[9].This class of proteins are transported to the Golgi for O-glycosylation, and these dimers are further polymerized into trimers via N-terminal disulfide bonds to form polymers that are loaded into secretory granules or vesicles and finally secreted into the intestinal lumen[10].

3. Muc2 can lubricate the stool to accelerate fecal excretion

Cysteine residues located at the N- and C-termini of MUC2 mucin are highly glycosylated, which increases the hydrophilicity of MUC2 mucin and binds water molecules in large amounts to form hydrated gel-like properties[11], amplifying and forming hierarchical mucus gels[12].The interconnection of the MUC2 molecules enhances the viscoelastic and lubricating properties of the mucus, which provides kinetic level of defense for the intestinal tract and facilitates fecal transport [13]. Constipation is an important manifestation of constipation when fecal retention time in the intestine is prolonged and fecal water content is reduced. It has been demonstrated[14][15] that in the presence of constipation, there is a decrease in the content of goblet cell in the colon and a decrease in the expression of mucins. With the deeper study of MUC2, it has been found that in mice, mucus continuously wraps around passing fecal particles, providing lubrication and promoting unobstructed fecal excretion[16]. Thus it can be demonstrated that MUC2 plays an important lubricating, transporting and protective role in the intestine.

4. Intestinal flora and constipation

4.1. Gut microbiota classification and role

There are a large number of microorganisms hosted in the human gut, which are mainly composed of bacteria, and the total weight of bacteria in the gut of a normal adult can reach 1 ~ 1.5 kg[17] . the body's response to nutrients A series of important life activities, such as digestion and absorption, drug metabolism, immune regulation, and the production of vital factors, all depend on the participation of intestinal bacteria. Its aerobic condition can divide intestinal bacteria into aerobic and anaerobic bacteria. According to the relationship between bacteria and the host, they are divided into three categories: 1.Beneficial bacteria, such as bifidobacterium, peptococcus, etc., which are absolutely dominant in the gut and beneficial to the host; 2.Opportunistic pathogens, such as Escherichia coli, are harmless to the human body at specific locations in the intestine and when the intestinal microecological balance is maintained. Once they are out of the intestinal environment or under specific conditions such as decreased host immunity, they will become invasive pathogens. 3.Pathogenic bacteria, such as Proteus, Pseudomonas, also known as passing bacteria, will not colonize the intestine for a long time, generally not It can cause disease, but if there are more than the body can compensate, it can cause disease[18].

4.2. Study on the relationship between intestinal flora and constipation

In recent years, the results of related studies have shown that there is a significant difference in the type and quantity of intestinal flora in patients with constipation as compared with that of normal people. Xiaoyu Gao [19] et al. used a mouse model of constipation induced by loperamide and found that the intestinal flora of mice in the loperamide group had significant differences in the structure and number of intestinal bacteria compared with that of control mice, and observed that the expression of Muc2 was suppressed in the loperamide group. Hao Lai and his team[20] in also verified that probiotics can alleviate can alleviate hard stools and that intervention-specific changes in intestinal flora are associated with relief of constipation. In addition to that the emerging fecalmicrobiota transplatation (FMT) therapy can be proven to be effective in the treatment of functional constipation. FMT refers to the transplantation of functional fecal flora from healthy people into the patient's gut to rebuild the normal intestinal flora. To treat intestinal and extraintestinal diseases. More and more doctors and researchers are paying attention to this kind of therapy to reconstruct intestinal functional flora. FMT can transplant the intestinal flora of healthy people into the intestine of patients through an appropriate way, improve the disorder of intestinal flora, and thus regulate the intestinal mucosal immunity and intestinal barrier function. Moreover, studies have shown that the total effective rate of FMT in the treatment of patients with functional constipation is 83. 3%. This can prove that gut microbiota is

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closely related to the occurrence of functional constipation[21].Therefore, it can be concluded that the occurrence of functional constipation causes intestinal flora disorders, and the correction of intestinal flora disorders will alleviate the condition of functional constipation, and the two are a kind of mutual influence, but the mechanism of action is still unclear,it need for further investigation.

5. MUC2 interacts with gut bacteria to jointly influence functional constipation

Although the MUC2 mucus barrier is an important barrier preventing intestinal bacteria from contacting colonic epithelial cells, the establishment of a complete MUC2 mucus structure and function requires certain bacteria or their metabolites, so the two interact.

It has been found[22]that the mucus layer in the intestinal mucosal barrier of the human colon is divided into an inner and an outer layer, and the inner mucus layer is impenetrable to bacteria and avoids bacterial effects on the intestinal immune system. The inner mucus is converted by endogenous proteases into an outer mucus layer, which expands four-fold in volume, and which has larger pores and can therefore penetrate bacteria up to a diameter, providing a habitat for symbiotic bacteria. A MUC2 mucin monomer will contain up to 1,600 O-glycans and 30 N-glycans , providing more than 3,300 terminal sugar residues, a massive array of glycans for symbiotic bacteria to utilize to provide nutrition for the gut flora. In turn, the intestinal flora also influences the synthesis and secretion of MUC2, and in mice with ulcerative colitis treated with supplementation of the probiotic Mucoidan Ackermannia, there was an increase in cuprocytes and MUC2 expression, and a thickening of the mucus layer [23]. It was also demonstrated that B. dentatus was able to enhance intestinal mucus layer and goblet cell function by up-regulating gene expression and autophagy signaling pathways, with a net increase in mucin production[24].

In addition to promoting MUC2 expression, intestinal flora are also involved in the metabolism of MUC2, which, due to its high degree of glycosylation, can provide nutrients to the intestinal flora, and certain commensal intestinal flora can use MUC2 glycans as a source of energy to enter and thrive[25].The presence of the genes engBF (endo-α-N-acetylgalactosaminidase) and afcA (1,2-α-l-fucosidase) was detected in several intestinal Bifidobacterium isolates.Two strains of Bifidobacterium bifidum contained both genes, and they were able to degrade high-molecular weight porcine mucin in vitro. The expression of both genes was highly induced in the presence of mucin[26].Some gut microbiota were found to be involved in the metabolism of MUC2.

Under physiological conditions, the inner mucus layer of the colon is intact and dense, and bacteria are unable to penetrate it, maintaining the barrier function of the intestinal mucosa. However, in patients with constipation, inflammatory bowel disease and animal models, it was found that the inner layer of the colonic mucosa was disrupted, the mucus layer was highly permeable, and the decrease in MUC2 expression reduced the denseness of the inner mucus layer, which led to the exposure of the intestinal epithelial cells to the pathogenic bacteria in the outer layer of the mucus, which then induced intestinal injury and triggered an inflammatory response [14][27]. When the mucosal barrier is damaged, studies have demonstrated that analysis of mouse colon tissue shows that a special type of goblet cell, called "sentinel" goblet cells (senGC), is present at the entrance to the colon crypt. This cell responds to nonspecific endocytosis of TLR2/1, TLR4, and TLR5 ligands by activating the Nlrp6 inflammasome downstream of Nox/Duox reactive oxygen species synthesis dependent on TLR and myd88. At the same time, this signal can induce a large amount of Muc2 secretion from adjacent goblet cells in the crypt, thereby expels bacteria and repairs the damaged mucosal barrier.[28].

But, under repeated bacterial stimulation, the intestinal mucosal barrier continues to be damaged, and the goblet cells continue to up-regulate the expression of MUC2 and increase its secretion. However, under this stressful condition, endoplasmic reticulum stress will occur, eventually leading to cell death. In order to alleviate ER stress and protect cells from injury, cells will stimulate the unfolded protein response to degrade the misfolded proteins. However, this unfolded protein response caused by the upregulation of MUC2 ultimately leads to the prolonged secretion and decreased production of MUC2 granules. This reduces mucin secretion, triggering a vicious cycle that further aggravates mucosal barrier damage[29]. In addition, it has been demonstrated that intestinal flora metabolizes MUC2 in addition to decreasing MUC2 synthesis. It has been reported that mice treated with fecal fluid gavage from constipated patients had an abnormal increase of Akkermansia (Akk) bacteria in the fecal flora, accompanied by a severe damage of the intestinal mucosal barrier, and the Akk bacteria degraded intestinal mucins, accelerated fecal drying, and became one of the potential risk factors for the damage of the intestinal mucosal barrier . Akkermansia degrades intestinal mucin and accelerates fecal drying,

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which is one of the potential risk factors for intestinal mucosal barrier damage [30].

6. Reach a verdict

MUC2 mucus barrier dysfunction and its associated bacterial factors play an important role in the development of functional constipation. Mucin 2 interacts with intestinal flora to improve intestinal mucosal barrier function and ultimately relieve functional constipation. And the structure of intestinal flora and the expression of MUC2 can be variable adjusted with dietary fiber or probiotics to achieve the purpose of treating functional constipation.

7. Enlightenment

Of course, it has also been found [31][32]that the number of goblet cells per crypt in the colonic mucosa of patients with constipation is significantly increased, but it can be considered that intestinal epithelial stem cells differentiate into goblet cells to increase the shortage of mucus supply, because patients with functional constipation have an increased demand for mucus in the intestine, so intestinal stem cells differentiate more toward goblet cells and less toward microvillus stromal cells. The number of goblet cells was increased to increase the amount of mucus produced. In this case, the colonic microvilli become thinner and the number of goblet cells per unit area rises as a result of the loss of stromal cells. The oscillation of colonic microvilli is mainly to spread the mucus secreted by goblet cells on the surface of intestinal contents, which is conducive to the discharge of intestinal contents. When the oscillation ability of colonic microvilli decreases to a certain degree, the microvilli cannot evenly spread the mucus secreted by bumped cells, which is more unfavorable to the discharge of intestinal contents. It has also been reported that MUC2-deficient mice have the same number of goblet cells, but these goblet cells do not have typical goblet cell characteristics and cannot secrete mucin particles normally[33].At present, there is no clear answer to the specific reason, which needs to be further explored and studied.

Dietary fiber, also known as the seventh nutrient, is a key nutrient for improving gastrointestinal function along with carbohydrates, protein, fat, vitamins, inorganic salts, trace elements and water. It is a type of plant components that cannot be digested by human gastrointestinal secretions, which can regulate intestinal microbial flora, increase the weight and frequency of stool.It plays an important role in maintaining normal gastrointestinal function[34].A large number of studies have confirmed that increasing dietary fiber intake can significantly improve functional constipation[35][36].Dietary fiber can not be absorbed by gastrointestinal digestive enzymes, and can directly reach the large intestine. It can promote the growth of beneficial intestinal bacteria, inhibit the reproduction of harmful bacteria, and maintain the balance of intestinal flora. Soluble dietary fiber can form a viscous gel in the stomach, delaying gastric emptying, increasing the time for food to pass through the gastrointestinal tract, and slowing the rate of nutrient loss in the small intestine. Insoluble dietary fiber is rich in hydrophilic groups, which has a strong adsorption capacity for water molecules, thus increasing the water content and volume of feces, promoting intestinal peristalsis, and having good moisturizing and defecating functions. Some dietary fiber surfactant groups can bind bile acids and other substances, promote the excretion of cholesterol in feces, shorten the retention time of toxic metabolites in the intestine, and inhibit the intestinal absorption of toxins[37].After supplementing dietary fiber to provide nutrition for intestinal flora, intestinal flora will reduce the degradation of MUC2, so it can protect the intestinal mucosal barrier. However, there is no clear study to prove which specific dietary fiber is decomposed by a certain intestinal flora. It can provide directions for subsequent research.

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