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REVIEW

Ulcerative colitis as a polymicrobial infection characterized by sustained broken mucus barrier

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Abstract

To reduce medication for patients with ulcerative colitis (UC), we need to establish the etiology of UC. The intestinal microbiota of patients with inflammatory bowel disease (IBD) has been shown to differ from that of healthy controls and abundant data indicate that it changes in both composition and localization. Small intestinal bacterial overgrowth is significantly higher in IBD patients compared with controls. Probiotics have been investigated for their capacity to reduce the severity of UC. The luminal surfaces of the gastrointestinal tract are covered by a mucus layer. This normally acts as a barrier that does not allow bacteria to reach the epithelial cells and thus limits the direct contact between the host and the bacteria. The mucus layer in the colon comprises an inner layer that is firmly adherent to the intestinal mucosa, and an outer layer that can be washed off with minimal rinsing. Some bacteria can dissolve the protective inner mucus layer. Defects in renewal and formation of the inner mucus layer allow bacteria to reach the epithelium and have implications for the causes of colitis. In this review, important elements of UC pathology are thought to be the intestinal bacteria, gut mucus, and the mucosa-associated immune system.

Key words: Ulcerative colitis; Mucus; Infection; Bacteria; Etiology

Core tip: Long-term or even life-long medication bothers patients with ulcerative colitis (UC). Existing treatment ignores the cause of UC, so establishing the etiology of UC is the key to resolving this problem. UC can be viewed as a polymicrobial infection that is characterized by a sustained broken mucus barrier with subsequent bacterial migration toward the mucosa and proliferation of complex bacterial biofilms on the epithelial surface. Regulation of mucus secretion and viscosity, suppression of bacterial biofilms, probiotics and immunostimulation should be increasingly considered to treat UC.

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INTRODUCTION

Ulcerative colitis (UC) belongs to a subgroup of inflammatory bowel diseases (IBDs), is characterized as chronic inflammation, and has become a global health threat[1,2]. High disease-recurrence rates, long-term or even life-long medication bothers patients with UC[3-5]. Existing treatment ignores the cause of UC, and is unable to cure UC, which is why patients need long-term medication; therefore, establishing the etiology of UC is the

Table 1 Interaction of mucus and bacteria

Effect of mucus on bacteria	Effect of bacteria on mucus
Limits the direct contact between the host and bacteria	Maintenance of the mucus layer is stimulated by bacterial fermentation products
Serves as a source of nutrients for bacterial growth	Mediate the expression of MUC2
Contributes to the selection of the species-specific colon flora	Dissolve the protective inner mucus layer
Contains several proteins that limit bacterial growth and penetration	

key to resolving this problem. Important elements of IBD pathology are thought to be genetics, the intestinal microbiome, the gut mucosa, and the mucosa-associated immune system[6,7]. Studies using dextran sulfate sodium (DSS) models of colitis also suggest that the key contributors in disease pathogenesis include alteration in the mucosal barrier integrity and function[8,9]. The human gastrointestinal tract is a vast surface inhabited by a complex and diverse community of micro-organisms[10], and the intestinal mucus is an efficient system for protecting the epithelium from bacteria by promoting their clearance and separating them from the mucosal immune cells, thereby inhibiting inflammation and infection[11]. UC is an immune-mediated disorder that results from an abnormal interaction between colonic bacteria and mucosal immune cells in a genetically susceptible host[12]. In this review, UC is thought to be a polymicrobial infection characterized by sustained broken mucus barrier.

ROLE OF MUCUS AND BACTERIA IN UC

The gastrointestinal tract is covered by a layer of mucus that protects the epithelium from luminal antigens and provides lubrication to advance the bolus[13]. A well-developed mucus barrier and not the epithelial cell layer is the first line of defense against a variety of enteric pathogens[14,15]. Leukocytes migrate into and patrol within the mucus layer, executing the surveillance function without any collateral damage. The sticky outer mucus surface offers the opportunity for probiotic strains to grow and build protective interlaced layers, preventing bacterial accumulation and microcolony formation on the colorectal surface[16,17]. Before bacteria can adhere and invade the mucosa, they must first traverse the mucus barrier[17]. The inflammation takes place only after the mucus barrier is broken and the defense is overwhelmed. UC is caused by a weakening in gut barrier, mainly due to increased infiltration of gut bacteria and the resultant recruitment of neutrophils and formation of crypt abscess[18]. Understanding the role of mucus and bacteria and their interaction will help us to establish the etiology of UC more clearly (Table 1).

Role of mucus in UC

Mucus production and secretion is a continuously ongoing process with a renewal of the inner protective mucus in the distal colon within an hour. Rapid renewal of the mucus barrier prevents microbial contact with the epithelial cells. Alteration of the adherent mucus barrier is a predisposing factor for early onset of epithelial cell damage in DSS colitis[19]. Sulfation of the mucins is significantly reduced in UC patients, and suggest that colonic mucins plays an important role in maintaining the normal physiological function of the colon and the possible role of mucus in the pathogenesis of UC[20]. Phosphatidylcholine (PC) accounts for > 70% of total phospholipids within the intestinal mucus layer, and the mucus PC content is reduced by about 70% in UC[21]. MUC2 is the major mucin in the large intestine[22,23], which is secreted by goblet cells, and the expression of it correlated with the activity of disease and the extent of the inflammatory process in the large intestine[24]. Individuals with UC have decreased numbers of goblet cells and reduced mucus thickness at presentation[25], and goblet cell abnormalities play an etiological role in UC. DSS models of colitis were characterized by depletion of goblet cell and adherent mucin[19]. In UC, the cooperation of aberrant expression of Hes1 and the disappearance of caudal type homeobox 2 (CDX2) caused Hath1 suppression, resulting in goblet cell depletion[26], and the present study suggests that Hes1 is essential for Hath1 gene suppression via Notch signaling. Gersemann *et al*[27] also pointed that in UC, the protective mucus layer, acting as a physical and chemical barrier between the gut epithelium and the luminal microbes, is thinner and in part denuded as compared to controls, and this could be caused by a missing induction of the goblet cell differentiation factors Hath1 and KLF4, leading to immature goblet cells. This goblet cell differentiation in UC can lead to defects in renewal and formation of the inner mucus layer and may enable the luminal microbes to invade the mucosa and trigger the inflammation[16,27,28]. So we can easily reach the conclusion that understanding the regulation of goblet cell differentiation and the intestinal mucus turnover and renewal of the inner protective mucus layer is important for novel ways to improve treatment of UC[16,21].

Role of bacteria in UC

UC is a multifactorial disease that is dependent on host genetics, environment, immune response and intestinal microbiota. The dysregulation of the gut microbiota plays an important role in the pathogenesis of UC[29]. The immunoregulatory function of the intestinal microbiota consists of priming the mucosal immune system and maintenance of intestinal epithelial homeostasis. Epithelial barrier dysfunction brings about increased bacterial translocation through the lamina propria[30,31]. Ineffective bacterial clearance leads to excessive Toll-like receptor (TLR) stimulation, secretion of proinflammatory cytokines and activation of innate and T-cell-mediated

immune responses. TLR-2 can bind a wide range of ligands, including lipoteichoic acid from Gram-positive bacteria, bacterial lipopeptides and glycolipids, and fungal β glucan (zymosan). TLR-4 can bind lipopolysaccharide from Gram-negative bacteria. Flagellin has innate qualities through its repetitive structures that are able to bind TLR-5, and also is a polypeptide that is internalized, processed and presented by professional antigen-presenting cells (APCs). Thus, the earliest phases of an immune response are dependent upon the recognition and interpretation of the antigenic composition of the milieu by T cells and APCs as revealed by innate and adaptive immune responses. TLR-9 is able to recognize bacterial DNA[32-34], and the stimulation of TLR-9 causes activation of nuclear factor-κB signaling, and leads to immune response and mucosal inflammation. These features could help to explain the mechanism of UC.

Defects in renewal and formation of the inner mucus layer allow bacteria to reach the epithelium and have implications for the causes of colitis[28]. Neutrophils and mononuclear cells infiltrate the lamina propria and activate nuclear factor-κB translocation, which in turn increases proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α, and inhibits the production of anti-inflammatory cytokines such as IL-10[35]. *Fusobacterium varium* (*F. varium*) was present in the colonic mucosa of a high proportion (84%) of UC patients[36] and contribute to the clinical activity in UC[37]. *L. crispatus* CCTCC M206119 strain is involved in exacerbation of intestinal inflammation in DSS-colitis mice, and may interact directly with colonic epithelial cells or lamina propria mononuclear cells after disruption of the mucosal barrier and balance of gut flora by DSS administration. *Campylobacter* spp.[38], *Escherichia coli*[39-41], *Enterohepatic Helicobacter*[42,43], and *Bacteroides ovatus*[44] are also responsible for the induction of intestinal inflammation.

However, not all the bacteria promote inflammation; *Pediococcus acidilactici*[45], *Lactobacillus* spp.[45], and *Bacteroides* spp.[46] show a variety of beneficial immunomodulatory effects in UC. Their products, rather than live bacteria, may be capable of inducing immunoregulatory effects, and may restore the dysregulated functions of immune cells[47]. Some recent studies have demonstrated that TLR signaling in intestinal sites can also inhibit inflammatory responses and maintain colonic homeostasis[48,49].

Effect of mucus layer on bacteria

The mammalian gastrointestinal tract harbors a vast microbial ecosystem, known as the microbiota. Gut microbiota includes around 1000 different species and > 15000 different strains of bacteria, for a total weight of about 1 kg. The luminal surfaces of the gastrointestinal tract are covered by a mucus layer composed mainly of mucins, which are high-molecular-weight glycoproteins characterized by extended serine, threonine, and proline-rich domains in the protein core[50]. This layer is a biochemically complex medium, rich in carbohydrates, antimicrobial peptides and other proteins, as well as lipids and electrolytes[51]. The inner mucus layer normally acts as a barrier that does not allow bacteria to reach the epithelial cells and thus limits the direct contact between the host and bacteria[52]. The mucus layer covering the gastrointestinal tract also has been reported to serve as a source of nutrients for bacterial growth. Thus, its presence influences intestinal colonization by attracting bacteria that have the ability to survive and multiply within the mucus layer[53,54]. We have also found that the numerous O-glycans on the MUC2 mucin serve as nutrients for the bacteria as well as attachment sites, and as such, probably contribute to the selection of the species-specific colon flora[44]. Overproduction of MUC2 may alter adherence and invasion of *Shigella dysenteriae* into human colonic epithelial cells. At the same time, the mucus also contains several proteins that limit bacterial growth and penetration, such as the antibacterial proteins and IgA[10,20]. These are important for the assembly and stability of the microbiota.

Effect of bacteria on mucus

The mucus barrier, however, can be compromised by environmental or genetic factors as well as specific pathogens such as *Serpulina*, *Fusobacterium*, *Enterobacteriaceae*, or *Gardnerella*. These bacteria can specifically form adherent biofilms on the epithelial surface, compromising the mucus barrier and allowing migration of other indigenous bacteria into the mucosa. The commensal bacteria in the colon live and thrive in the outer loose mucus layer, and can dissolve this layer[55]. Nevertheless, the association of the microbiota with the mucus is not well understood and requires further investigation.

The importance of bacterial exposure to produce a functional mucus barrier is demonstrated by germ-free animals in which the inner mucus layer is thin[56], but can be restored by exposure to bacterial components[56]. Maintenance of the mucus layer is also known to be stimulated by bacterial fermentation products[57]. In conclusion, the bacteria can influence mucus production[56]. Proteins secreted by probiotic bacteria of antimicrobial substances can enhance the mucosal barrier function and compete with enteropathogens for adhesion sites[58,59]. The composition of short-chain fatty acids in the intestine is determined by the composition of the microbiota, and butyrate can mediate MUC2 mRNA *via* activator protein-1 and acetylation/methylation of histones at the MUC2 promoter. The microbiota can also mediate MUC2 mRNA[58], and MUC2 can potentially be modulated in several other ways either during infection, such as at the level of gene expression, or even at the level of secretion into the intestinal lumen. Each regulatory step may influence the biological function of MUC2, which in turn influences how the host responds to enteric pathogens[16]. MUC2 is reportedly overexpressed in response to bacterial components, such as lipopolysaccharide or lipoteichoic acid, in cultured intestinal or airway epithelial cells and also bladder epithelial cells[13,60].

Bacteria can also dissolve the protective inner mucus layer, potentially triggering colitis. MUC2 is the

major colonic secretory mucin. We found that bacteria can produce proteases capable of dissolving the inner protective mucus layer by specific cleavages in the MUC2 mucin and that this cleavage can be modulated by site-specific O-glycosylation. However, because of O-glycosylation, the mucin domains are highly resistant to proteases and are not expected to be cleaved by proteases[52]. However, MUC2 glycosylation can still be metabolized by intestinal commensal or pathogenic bacteria, serving as an energy source, suggesting a role in intestinal microbiota selection[20,61]. The 980-amino-acid-long C-terminal part of MUC2 has two cleavage sites. One is localized to the NR2QA sequence within the VWD4 domain where the cleavage site is surrounded by numerous cysteines that are involved in disulfide bond formation. The second cleavage site is localized prior to the first cysteine in the MUC2 C-terminal VWD4 domain. The enzyme secreted by *Entamoeba histolytica* can dissolve the guanidinium-chloride-insoluble mucus gel that we now know is the major constituent of the inner firm mucus layer[10]. *Porphyromonas gingivalis* also secretes a protease as an active enzyme to cleave MUC2, and this enzyme was isolated and identified as Arg-gingipain B. *Citrobacter rodentium* colonizes the outer mucus layer in high numbers, lacks a functional flagellum and is thus non-motile, and therefore likely utilizes specific mucinases or glycosidases to digest mucin in order to overcome the mucus barrier[16,20].

CHANGES OF BACTERIAS IN UC

The intestinal microbiota of IBD patients has been shown to differ from that of healthy controls; abundant data indicate that the microbiota in IBD patients changes in both composition and localization[62,63], and the changes are not a product of colitis, which has previously been reported[64]. These support an integrative view of microbial ecology relevant to IBD[65], and butyrate-producing bacteria could be important to gut homeostasis[66,67]. The diversity of fecal microbiota is significantly lower in UC patients. *Bacteroides*[68], *Clostridium* subcluster XIVab[66], *Lactobacillus* spp.[67], *Akkermansia muciniphila*[69] and *Clostridium leptum*[70] are decreased in UC patients, and the number of *Enterococcus*[68], *Escherichia coli*[71], *Actinobacteria*[72], *Proteobacteria*[73] and *Campylobacter ureolyticus*[73] are higher in UC patients than in healthy subjects. Sulfate-reducing bacterium levels are also raised in UC[74], and are crucial for induction of DSS colitis in mice. Some research has proposed that *F. varium* might be one of the elusive pathogenic factors in UC[6]. Data also showed that the amount and composition of bacteria clearly differed between the mucus layers in animals not treated with DSS, with significantly higher loads of bacteria in the outer mucus layer[75], and *Lactobacillus crispatus* CCTCC M206119 strain is involved in exacerbation of intestinal inflammation in DSS-colitis mice[76]. Recently, we also found that small intestinal bacterial overgrowth was significantly higher in IBD patients as compared to controls[35]. Despite the requirement of commensal bacteria for normal intestinal function, an abnormal host response to commensal bacteria has been implicated as a crucial factor in the pathogenesis of IBD[77,78]. Recent research has shown that some commensal and pathogenic bacterias are closely related to UC, but it is difficult to draw a definitive conclusion in evaluating the role of microflora in pathogenesis of UC, and to find specific micro-organisms associated with the pathogenesis of UC.

USE OF PROBIOTICS IN UC

Bacteria are closely related to UC, and recently some studies have investigated the use of probiotics in UC[47,79,80]. Probiotics contain viable organisms; sufficient amounts of which reach the intestine in an active state, thus exerting positive health effects[81]. Their mechanisms of action are still unclear, but several have been postulated to contribute to the anti-inflammatory effect of probiotics in the gut, including competitive exclusion of pathogens. Probiotics may potentially alter the intestinal microbiome exogenously or provide an option to deliver microbial metabolic products to alter the chronicity of intestinal mucosal inflammation[82]. Bifidobacteria and lactobacilli produce harmful substances for Gram-positive and Gram-negative bacteria, and they compete with pathogens (*i.e.*, *Clostridium*, *Bacteriodetes*, *Staphylococcus*, and *Enterobacter*) for cell adhesion[83,84]. Production of antimicrobial agents (*e.g.*, IgA) and organic acids, modulation of lymphocyte and dendritic cell function[85,86], enhancement of the epithelial barrier function, modulation of the membrane permeability and mucosal immune system, and keeping pathogens away from the intestinal mucosal surface are also included. Probiotics have been investigated for their capacity to reduce the severity of UC (Table 2). The efficacy of VSL#3 (*Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*) in UC patients has also been demonstrated[94-96]. Also, some natural anti-inflammatory effects have recently been shown for *Lactobacillus salivarius*, *L. plantarum*, *Lactobacillus casei* Shirota, *Lactobacillus reuteri* and *Bifidobacterium* based on experimental colitis models[76,97-99].

CONCLUSION

UC is mainly due to increased infiltration of gut bacteria and the resultant recruitment of neutrophils and formation of crypt abscess[18], and can be viewed as a polymicrobial infection that is characterized by a sustained broken mucus barrier with subsequent bacterial migration toward the mucosa and proliferation of complex bacterial biofilms on the epithelial surface. Regulation of the mucus secretion and viscosity, suppression of bacterial biofilms, probiotics and immunostimulation should be increasingly considered to treat UC and evaluated in the future[17].

Table 2 Probiotics have undergone investigation for their capacity to reduce the severity of ulcerative colitis

Probiotics	Method	Conclusion
B. infantis 35624[87]	Oral administration of *B. infantis* 35624 for 6-8 wk is taken by patients with ulcerative colitis	This microbe can reduce systemic pro-inflammatory biomarkers in UC
L. reuteri ATCC 55730[88]	Mild to moderate UC were received an enema solution containing 10 (10) CFU of *L. reuteri* ATCC 55730 for 8 wk, in addition to oral mesalazine	In children with active distal ulcerative colitis, rectal infusion of *L. reuteri* is effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease
B. breve strain[89]	Mild to moderate UC ingested 1 g of the probiotic powder [10 (9) CFU/g] three times a day, and 5.5 g of GOS once a day for one year	Administration of live *B. breve* strain Yakult and GOS can improve the clinical condition of patients with UC
L. delbruekii and *L. fermentum*[90]	Mild to moderate UC were treated with sulfasalazine 2400 mg/d with a probiotic preparation (which contained powder with 10 (9) CFU of *L. delbruekii* and *L. fermentum*, for eight consecutive weeks	Oral supplementation with probiotics could be helpful in maintaining remission and preventing relapse of UC
L. casei DG[91]	Mild left-sided UC were received oral 5-ASA and rectal *L. casei* DG	Manipulation of mucosal microbiota by *L. casei* DG and its effects on the mucosal immune system seem to be required to mediate the beneficial activities of probiotics in UC patients
EcN[92]	Moderate distal UC were randomly assigned to treatment with either 40, 20, or 10 mL enemas (n = 24, 23, 23) containing 10 (8) *EcN*/mL (n = 20). The study medication was taken once daily for 2, 4, 8 wk	*EcN* is a well tolerated treatment alternative in moderate distal UC
B. longum[93]	The probiotic group ingested one daily capsule consisting of B. longum 2 × 10 (9) CFU	Patients with UC on probiotic therapy experienced greater quality-of-life changes than before

B. Infantis: *Bifidobacterium infantis*; *L. Reuteri*: *Lactobacillus reuteri*; *B. Breve*: *Bifidobacterium breve*; *L. Delbruekii*: *Lactobacillus delbruekii*; *L. Fermentum*: *Lactobacillus fermentum*; *L. Casei*: *Lactobacillus casei*; *EcN*: *E. coli Nissle*; *B. Longum*: *Bifidobacterium longum*; CFU: Colony-forming units; GOS: Galacto-oligosaccharide; 5-ASA: 5-aminosalicylic acid; UC: Ulcerative colitis.

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