Microbiota, Diet and Mucus in Inflammatory Bowel Disease

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Contributor: Samuel Fernández-Tomé

The gastrointestinal tract is optimized to efficiently absorb nutrients and provide a competent barrier against a variety of lumen environmental compounds. Different regulatory mechanisms jointly collaborate to maintain intestinal homeostasis, but alterations in these mechanism lead to a dysfunctional gastrointestinal barrier and are associated to several inflammatory conditions usually found in chronic pathologies such as inflammatory bowel disease (IBD). The gastrointestinal mucus, mostly composed of mucin glycoproteins, covers the epithelium and plays an essential role in digestive and barrier functions. However, its regulation is very dynamic and is still poorly understood. This review presents some aspects concerning the role of mucus in gut health and its alterations in IBD. In addition, the impact of gut microbiota and dietary compounds as environmental factors modulating the mucus layer is addressed. To date, studies have evidenced the impact of the three-way interplay between the microbiome, diet and the mucus layer on the gut barrier, host immune system and IBD. This review emphasizes the need to address current limitations on this topic, especially regarding the design of robust human trials and highlights the potential interest of improving our understanding of the regulation of the intestinal mucus barrier in IBD.

Keywords: dietary compounds ; gastrointestinal barrier ; gut microbiota ; inflammatory bowel disease ; mucus layer

1. Introduction to Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a global disease associated to Western and recently westernized countries [1]. The emergence of this disease was parallel to the industrial revolution in the 1800s [2]. Being a chronic disease diagnosed early in life, the prevalence of this pathology is high and is increasing over time. Prevalence of IBD was 84 per 100,000 population in 2017 [3] and it has been estimated that it will continue increasing in the next generation, affecting tens of millions of people all over the world [4]. Therefore, the cost of this disease for health care systems is considerable and will increase steadily in the future [4][5].

The origin and causes of IBD remain unknown. It is an immune-mediated inflammatory disease and its major causative factors could be genetic, immune and environmental such as the gut microbiome and diet. Genome wide-association studies identified approximately 200 gene loci in IBD, of which more than 50% are also associated with other inflammatory and autoimmune diseases [6]. The exposure to environmental conditions influence the microbiome composition and the consequent dysbiosis (changes in the healthy microbiota) in the gastrointestinal tract can trigger inflammatory responses [7][8].

IBD is a general term encompassing ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to the colon and presents superficial mucosal inflammation that can lead to ulcerations and bleeding. CD can affect any part of the digestive tract and presents transmural inflammation and complications such as fistulas or abscesses [9]; furthermore, IBD is associated to other extra-intestinal pathologies such as arthritis and skin diseases that aggravate the quality of life of these patients. Both IBD subtypes present periods of inflammation and quiescence [10]. Regarding IBD therapeutic approaches, several drugs have been developed over the last years, including biologics that target different molecules involved in IBD pathogenesis [11][12]. However, response to treatment is highly variable [13][14] and, since there is no cure for this disease, the therapeutic goal is to maintain patients' remission. Accordingly, a deeper understanding of the disease is needed to improve treatment of these patients.

In this review, we will focus on the gastrointestinal barrier in IBD with a particular emphasis on the role of the mucus layer in gut health and its alterations in this disease. In addition, the impact of the gut microbiota and dietary compounds as mucus modulatory factors and their complex interaction with the mucosal barrier in IBD is summarized. Data were obtained from articles published in English in journals indexed in PubMed and Web of Science from inception to August 2021 and retrieved using search terms related to (i) gastrointestinal barrier and gut homeostasis; (ii) mucus layer, mucins

and IBD; (iii) modulation of immune system and mucosal inflammation; (iv) gut microbiota, probiotics and IBD; (v) dietary compounds, food bioactives and IBD.

2. Gastrointestinal Barrier

The intestinal mucosal barrier provides adequate containment of microorganisms and molecules, preserving the capacity to absorb nutrients [15]. Intestinal mucosa is covered with a monolayer of intestinal epithelial cells (IECs) that separate the external environment and sub-epithelium [16]. Alterations in this mucosal barrier may result in IBD, stressing its essential role to maintain a healthy gut environment [17]. A key regulator balancing this relationship is the gastrointestinal mucus layer, composed of a secreted mucus gel, which cover the surface of epithelium and the underlying mucosal immune system. Hence, the gut mucosa is protected by two barrier types: chemical and physical. Chemical barriers participate in the segregation of IECs and gut microbiota [18]. IECs are derived from stem cells within intestinal crypts that replicate and migrate towards villi to replenish the active turnover of epithelium [15]. Functionally, secretory IECs, as goblet and Paneth cells, are specialized in maintaining the epithelial barrier function [19]. Paneth cells are involved in the production of chemical barriers such as antimicrobial peptides in the small intestine [20], while goblet cells secrete mucins. Mucins and antimicrobial peptides are important for both physical and biochemical barriers. The different functions of IECs lead to a dynamic barrier, which protects the host from infection and inflammatory stimuli [19]. IECs act as sensors for microbial elements and can integrate signals from commensal bacteria into antimicrobial and immune regulatory responses [21]. These functions are enabled by the expression of pattern-recognition receptors that act as sensors of the microbial environment and are key regulatory elements in mucosal immune responses [19].

Mucosal homeostasis is a vital feature of the gut immune system [22]. One of the critical factors for developing IBD is the failure to maintain an adequate balance between response to pathogens and tolerance to commensal microorganisms and luminal beneficial antigens [23][24]. Under the conditions of gut barrier dysfunction, as it occurs in IBD, the homeostatic equilibrium is lost [25][26]. IBD is related with increased permeability in the gut and the associated disbalance in the immune response that leads to increased recruitment of circulating cells and secretion of pro-inflammatory mediators [15] [27]. Therefore, factors as immune system, genetics and environmental ones influence the gastrointestinal barrier function and are, thus, involved in the “IBD integrome” [28].

2.1. Mucus Layer

The small intestine has a single mucus layer that facilitates the pass of nutrients, while the colon is covered by a thicker barrier. However, in the colon, the mucus layer acts as a physical barrier maintaining bacteria in symbiosis with the host and preventing bacterial infiltration into the epithelium [16][18]. The large intestine epithelium is, thus, covered by two mucus layers: an outer loose layer and an inner firm mucus attached to the epithelia [29][30]. The principal components of the gastrointestinal mucus barrier are O-linked glycoproteins called mucins. They present densely packed oligosaccharides that bind to their terminal region sialic acid and sulfate residues protecting mucins from proteases and glycosidases [31]. Mucins are produced by goblet cells present within the intestinal epithelium [32]. Mucus exocytosis from goblet cells depends on several cellular processes that modulate mucin secretion, including endocytosis and autophagy [32].

There are 18 mucin members in humans classified in two types: transmembrane and secreted mucins. Mucin central domains are composed of proline, threonine and serine (PTS) residues working as attachment sites for O-linked glycans through covalent binding of N-acetylgalactosamine to serine or threonine residues [16]. The secreted mucin MUC2 is the main glycoprotein in the intestinal mucus. MUC2 has an N-terminal domain, two PTS domains and a C-terminal domain. MUC2 N-terminal domain comprises 3 complete von Willebrand factor domains (D1-3) and the C-terminal region of D4 domain. Cysteine residues in N- and C- terminal domains facilitate inter- and intramolecular disulfide bond formation responsible for mucin polymerization [33].

MUC2 polypeptide is synthetized and dimerized in the endoplasmic reticulum of intestinal cells. Then, threonine and serine residues are glycosylated in the cis-Golgi and the trimer formation takes place in the trans-Golgi before MUC2 is packaged into secretory granules. MUC2 is composed of heterogeneous glycan chains [16], which allow MUC2 trimers to form polymers creating mucus networks in the cell surface [31][34]. MUC2 polymers undergo rapid expansion on the intestinal epithelial surface to maintain the mucus barrier during homeostasis; this expansion depends on ionic composition and water availability. Polymers can expand their volume up to 1000 times to form the framework of the mucus gel [35].

On the other hand, intestinal transmembrane mucins (MUC1, MUC3, MUC4 and MUC13) are intercalated in the apical surface of the intestinal epithelium forming the glycocalyx layer [32]. In contrast to the sterile inner layer of mucus, the outer

mucus layer is rich in gut bacteria [29]. These bacteria use diet fiber as energy source; however, under a fiber-free diet they consume MUC2 polysaccharides, leading to a thinner inner mucus layer and dysbiosis [36], as well as bacteria penetration into the lamina propria contributing to IBD development [18].

2.2. Mucus Layer under Inflammatory Conditions

The stability of the mucus layer is crucial for intestinal homeostasis, in which MUC2 is secreted at a basal rate. This secretion can be influenced by mediators as cytokines, microbial products, autophagic proteins, reactive oxygen species and inflammasome components [37][38]. Commensal and pathogenic bacteria can regulate mucin production [28]. In the small intestine, a continuous basal secretion of mucus creates a flow towards the lumen that, together with antibacterial agents, keeps microorganisms away from the epithelial surface. Antibacterial agents are secreted by Paneth cells and enterocytes of the crypt bottom. On the other hand, in the colon, the inner mucus layer is the first line of defense against bacteria [39].

The mucus layer is a natural and selective habitat for the gut microbiota [40], which in turn influences mucus composition and may promote mucus secretion and increase mucus layer thickness [41]. Therefore, the gut microbiota affects mucus layer function, possibly through specific bacteria that shape the glycan profile of the mucus, although molecular details remain incompletely identified [42].

There is high number of enteropathogens that have evolved mechanisms to penetrate the mucus barrier. Most of them produce a kind of serine proteases that cleave glycoproteins such as mucins [43]. Moreover, cytokines are involved in the inflammatory response and regulate many cellular and molecular processes including mucus production. In this regard, TNF-α and IL-1β, which are implicated in inflammatory diseases, stimulate gel-forming mucins [43]. Th2 cytokines are implicated in mucin gene expression up-regulating MUC2 and MUC5AC by binding to IL-4 receptor. Endoplasmic reticulum stress in goblet cells produce immature mucins that trigger inflammation [44][45], whereas IL-10 has been found to inhibit endoplasmic reticulum stress and promote intestinal mucus production [43][46].

MUC2 knockout mice show colonization of gut epithelium by enteric pathogens [47][48]. These results suggest that the principal mucus function is to protect the gut against microbes. Binding to mucin oligosaccharide chains likely contributes to immobilize bacteria and prevents them from damaging the intestinal epithelium. MUC2 has also immune roles; small intestine goblet cells provide the passage of soluble luminal antigens by transcytosis. These low molecular weight antigens are delivered to underlying $CD103^+$ dendritic cells and may favor IgA production and expansion of regulatory T cells, thereby driving gut homeostasis and tolerance [49]. The commensal microbiota, through its relationship with mucus, prevents colonization by pathogens. In this regard, when antibiotics perturb the gut microbiota, niches are opened facilitating disease development. The gut microbiota also breaks down short-chain fatty acids (SCFA) including acetate, propionate and butyrate [50]. Since butyrate regulates MUC2 production, the microbiota is also involved in the homeostasis of the protective mucus layer [51].

Mucin composition is altered in IBD and mucin structural changes play an important role in IBD onset [52][53]. In fact, alterations of mucus barrier and mucins are observed at IBD onset; goblet cell pathology is a hallmark of UC and CD [43]. Recently, it has been observed that the reduced mucus layer in UC is due to a reduction in the number and secretory function of goblet cells because of an inflammatory environment and due to changes in mucin secretion that persist in the absence of inflammatory cells [54].

The mucus layer is thinner in UC than in the healthy colon, while goblet cell depletion and altered MUC2 glycosylation can be also observed; in addition, MUC2 is undersulfated, weakening mucin protective function [55][56][57]. Despite these results, the expression pattern of MUC2 in UC is not clear. Conversely, MUC5AC, is consistently increased during inflammation in UC [58][59] and its reduced expression is associated with endoscopic improvement in these patients [60]. In $Muc5ac^{-/-}$ mice with DSS colitis, there is an increase in bacterial-epithelial contact and neutrophil recruitment to the colon, therefore, the loss of Muc5ac may exacerbate injury and inflammation in experimental murine colitis [61]. This study also showed a significant increase in MUC5AC/Muc5ac expression during colonic inflammation in biopsies from UC patients and DSS-induced mice colitis [61].

In contrast, mucus thickness is normal or greater than normal in CD, maybe due to goblet cell hyperplasia or increased MUC2 expression, although with a 50% reduction in oligosaccharide chain length [62]. Hence, several changes in the mucosal barrier underlie the complex pathology of IBD.

3. Gut Microbiota and the Mucus Layer in IBD

The microbiome plays key roles in the development of mucosal immune responses, pathogen resistance and nutrient metabolism. This fact is in part due to the interaction of the microbiota with components of the mucus layer and the IECs underneath following mucus breakdown. Intestinal barrier, antimicrobial and immunomodulatory functions are influenced by several members of the gut microbiota, as reviewed in the present review.

4. Dietary Compounds and the Mucus Layer in IBD

Dietary factors need to be considered when evaluating the complex relationship between the host, microbiota and the mucus layer. Dietary patterns and specific foods or nutrients may affect the gut barrier directly or indirectly by shaping microbial species known to influence mucosal protection and inflammatory processes. The influence of the different food groups/compounds in the mucus barrier was summarised in the present review.

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