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REVIEW

Mend Your Fences

The Epithelial Barrier and its Relationship With Mucosal Immunity in Inflammatory Bowel Disease

Eva Martini,[1] Susanne M. Krug,[2] Britta Siegmund,[3] Markus F. Neurath,[1] and Christoph Becker[1]

[1]Medical Clinic 1, Friedrich-Alexander-University, Erlangen, Germany; [2]Institute of Clinical Physiology, Charité–Universitätsmedizin Berlin, Berlin, Germany; and [3]Department of Gastroenterology, Rheumatology and Infectious Diseases, Charité–Universitätsmedizin Berlin, Berlin, Germany

SUMMARY

Intestinal epithelial barrier integrity defects are frequently seen during intestinal inflammation. This article highlights the composition of the intestinal epithelium and summarizes mechanisms that lead to the disruption of barrier integrity promoting the development of inflammatory bowel diseases.

The intestinal epithelium can be easily disrupted during gut inflammation as seen in inflammatory bowel disease (IBD), such as ulcerative colitis or Crohn's disease. For a long time, research into the pathophysiology of IBD has been focused on immune cell–mediated mechanisms. Recent evidence, however, suggests that the intestinal epithelium might play a major role in the development and perpetuation of IBD. It is now clear that IBD can be triggered by disturbances in epithelial barrier integrity via dysfunctions in intestinal epithelial cell–intrinsic molecular circuits that control the homeostasis, renewal, and repair of intestinal epithelial cells. The intestinal epithelium in the healthy individual represents a semipermeable physical barrier shielding the interior of the body from invasions of pathogens on the one hand and allowing selective passage of nutrients on the other hand. However, the intestinal epithelium must be considered much more than a simple physical barrier. Instead, the epithelium is a highly dynamic tissue that responds to a plenitude of signals including the intestinal microbiota and signals from the immune system. This epithelial response to these signals regulates barrier function, the composition of the microbiota, and mucosal immune homeostasis within the lamina propria. The epithelium can thus be regarded as a translator between the microbiota and the immune system and aberrant signal transduction between the epithelium and adjacent immune cells might promote immune dysregulation in IBD. This review summarizes the important cellular and molecular barrier components of the intestinal epithelium and emphasizes the mechanisms leading to barrier dysfunction during intestinal inflammation. ***(Cell Mol Gastroenterol Hepatol 2017;4:33–46; http://dx.doi.org/10.1016/j.jcmgh.2017.03.007)***

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The intestine has to meet a lifelong service of proper food digestion and nutrient absorption; however, this responsibility for import from the outside to the inside of the body is not without challenges. The intestinal tract is exposed to a plethora of food-borne antigens and bacterial antigens in the microbiota. At the same time the gut harbors a large part of the immune cells of the body whose task is to identify and fight off foreign antigens and microbial threats. The epithelial cell layer prevents excessive contact of these antigens with the immune cells and thereby also protects the gut from unwanted immune reactions. This is achieved by the sophisticated organization of the intestinal epithelium, which establishes a tightly regulated barrier.[1] The intestinal epithelium is built of monolayered columnar epithelial cells that are tightly connected by tight junctions (TJs).[2] Although TJs can be considered as a part of the physical barrier, specialized intestinal epithelial cells (IECs), such as goblet cells and Paneth cells, take over miscellaneous functions of antimicrobial defense, which make them crucial parts of the innate immune system. Goblet cells secrete a variety of antimicrobial molecules, such as trefoil factors and mucins.[3] Mucin secretion constitutes a thick mucus layer to prevent excessive direct contact of bacteria to the epithelial cell surface and thereby to protect against invasive pathogens. Paneth cells are professional producers of antimicrobial peptides, which are secreted within the crypts of the small intestine.[4] However, controlled antigen delivery

Abbreviations used in this paper: **BMP, bone morphogenic protein; CD, Crohn's disease; Fz, frizzled; HD, humans α-defensin; IBD, inflammatory bowel disease; IECs, intestinal epithelial cells; IL, interleukin; JAMs, junctional adhesion molecules; Lgr5, leucine rich repeat containing G-protein coupled receptor 5; MARVEL, myelin and lymphocyte and related proteins for vesicle trafficking and membrane link; MLCK, myosin light chain kinase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOD-2, nucleotide-binding oligomerization domain-containing protein 2; STAT, signal transducer and activator of transcription; TAMP, tight junction–associated MARVEL protein; TJ, tight junction; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; UC, ulcerative colitis.**

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to immune cells plays an important role in the education of the gut immune system. For instance, specialized epithelial cells, M (microfold)-cells, which are abundant within the follicle-associated epithelium but also appear along the crypt-villous axis, take up intestinal microbes and their antigens and forward them to resident immune cells in the gut-associated lymphoid tissue, supporting the maturation of the immune system.[5] Thus the intestinal epithelium, rather than a strict barrier, constitutes a highly regulated gate controlling the admission of antigens to serve the host's health. Epithelial barrier integrity is challenged by the high rate of cell turnover. The epithelium is completely renewed within only 4–5 days with cells shedding into the gut lumen at the surface and proliferation of stem cells within the intestinal crypt replacing the constant cell loss.[6] A failure of coordinated replenishment can cause severe barrier defects leading to excessive invasion of luminal antigens and intestinal inflammation, such as seen in patients with ulcerative colitis (UC) or Crohn's disease (CD).

Recent experimental evidence indeed implicates a crucial function of barrier dysfunction in the onset of inflammatory bowel disease (IBD). This article focuses on the role of the intestinal epithelium during maintenance of homeostasis and highlights the mechanisms of epithelial barrier dysfunction during intestinal inflammation.

In the steady state epithelial homeostasis is maintained by proliferation and cell shedding. The intestinal epithelium constitutes a physical barrier by its structural organization, by specialized innate immune cell functions, and by a tight regulation of the ratio between proliferation and cell death. The 3-dimensional structure of the small intestinal epithelium is characterized by invaginations denoted crypts of Lieberkühn merging with protrusions termed villi. In the large intestine villi are lacking resulting in a rather flat mucosal surface. Stem cells at the crypt base give rise to fast cycling progenitor cells, which migrate up toward the villus tip while they differentiate into the mature epithelial cell types. Finally, once reaching the villus tip of the small intestine or the epithelial surface of the colon, IECs are shed into the lumen and replaced by neighboring cells.

Because IECs have a limited lifespan of about 4–5 days, the epithelium has to be constantly replenished to prevent disruption of the intestinal epithelial barrier. This is enabled by multipotent intestinal stem cells, which reside at the crypt base. Stem cells divide, giving rise to epithelial transit-amplifying cells, progenitor cells with very high proliferative capacity. Intestinal stem cells were first identified by several groups in the 1970s after using H_3-thymidine to label and track proliferating cell populations.[7,8] During the last decade especially the group of Hans Clever's elegantly refined stem cell fate mapping by creating a mouse-model to lineage trace a candidate marker for actively dividing crypt base columnar cells, which where intermingled with Paneth cells at the crypt base. These studies ultimately led to the identification of a specific marker for crypt base columnar stem cells, the leucine rich repeat containing G-protein coupled receptor-5 (Lgr5).[9] Since then, several other potential stem cell markers have been identified by in vivo linage tracing or by transgenic fluorescent labelling of cells, which are residing either at the crypt base columnar region or at the +4 position (fourth cell position from the crypt base center) of the crypt. Stem cells at the +4 position are located directly above the Paneth cells and have been described as quiescent, reserve stem cell populations, which are reactivated into a stem cell fate under specific physiological conditions, such as injury.[10]

The constant proliferation at the crypt base is thought to provide the steric force that moves cells up the crypt villus axis. While migrating upward cells start to differentiate into the various mature IECs of the secretory or absorptive cell type.[11] Intestinal epithelial homeostasis not only depends on the ratio between proliferation and cell death, but also the balance between proliferating progenitor cells and differentiating IECs. This is warranted by the specialized microenvironment in which stem and progenitor cells reside, which is defined as stem cell niche. Within this niche, IECs, such as Paneth cells, and neighboring mesenchymal cells at the crypt base secrete signaling molecules that determine proliferation and differentiation. This special expression gives rise to a concentration gradient that regulates the preservation of the stem cell niche, proliferation of progenitor cells, and differentiation of IECs.

The 4 most important signaling molecules regulating the composition and proliferation within the niche are Wnt, Notch, bone morphogenic proteins (BMPs), and hedgehog (Figure 1).[12] Wnt ligands are produced by epithelial cells, Paneth cells, or mesenchymal cells and signaling into target cells leads to the activation of either the canonical and noncanonical Wnt pathway.[13] Canonical Wnt signaling drives proliferation and is mainly concentrated at the lower crypt, where stem cells are located.[14] Wnt signaling extends up to the transit amplifying area where the rapidly proliferating progenies of stem cells reside. In sharp contrast, noncanonical Wnt signaling is predominantly observed in the upper crypt area where proliferation ceases and differentiation becomes important. The expression of Wnt ligands and frizzled (Fz)-receptors was precisely studied by Gregorieff et al,[15] who revealed a strong expression of Wnt3 and Wnt9b by Paneth cells and the Wnt receptors Fz5 and Fz7 on stem cells in the small intestinal crypt, activating the canonical Wnt pathway. Wnt activation leads to the accumulation of β-catenin and subsequently to the transcription of several target genes that govern proliferation of intestinal stem cells. Wnt proteins can also be produced by mesenchymal cells neighboring the crypt, such as myofibroblasts.[16] Myofibroblasts can express Wnt2b, Wnt4, and Wnt5, which lead to the activation of the noncanonical pathway, driving cellular polarity and motility and therefore supporting the differentiation of IECs.[17] Although Wnt ligands and Fz receptors activate Wnt signaling, the pathway can be negatively regulated by antagonistic mechanisms, such as the secreted Fz-related proteins.[18,19] Secreted Fz-related proteins are secreted predominantly by mesenchymal cells in close proximity to Wnt-producing intestinal stem cells to regulate Wnt signalling.[15]

Another important protein family regulating epithelial proliferation and differentiation are BMPs, which belong to