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Review article

Autophagy and tight junction proteins in the intestine and intestinal diseases

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ABSTRACT

The intestinal epithelium (IE) forms an indispensible barrier and interface between the intestinal interstitium and the luminal environment. The IE regulates water, ion and nutrient transport while providing a barrier against toxins, pathogens (bacteria, fungi and virus) and antigens. The apical intercellular tight junctions (TJ) are responsible for the paracellular barrier function and regulate transepithelial flux of ions and solutes between adjacent cells. Increased intestinal permeability caused by defects in the IE TJ barrier is considered an important pathogenic factor for the development of intestinal inflammation, diarrhea and malnutrition in humans and animals. In fact, defects in the IE TJ barrier allow increased antigenic penetration, resulting in an amplified inflammatory response in inflammatory bowel disease (IBD), necrotizing enterocolitis and ischemia-reperfusion injury. Conversely, the beneficial enhancement of the intestinal TJ barrier has been shown to resolve intestinal inflammation and apoptosis in both animal models of IBD and human IBD. Autophagy (self-eating mechanism) is an intracellular lysosome-dependent degradation and recycling pathway essential for cell survival and homeostasis. Dysregulated autophagy has been shown to be directly associated with many pathological processes, including IBD. Importantly, the crosstalk between IE TJ and autophagy has been revealed recently. We showed that autophagy enhanced IE TJ barrier function by increasing transepithelial resistance and reducing the paracellular permeability of small solutes and ions, which is, in part, by targeting claudin-2, a cation-selective, pore-forming, transmembrane TJ protein, for lysosome (autophagy)-mediated degradation. Interestingly, previous studies have shown that the inflamed intestinal mucosa in patients with active IBD has increased claudin-2 expression. In addition, inflammatory cytokines (for example, tumor necrosis factor-α, interleukin-6, interleukin-13, and interleukin-17) whose levels are increased in IBD patients cause an increase in claudin-2 expression and a claudin-2-dependent increase in TJ permeability. Thus, the role of claudin-2 in intestinal pathological processes has been attributed, in part, to the increase of intestinal TJ permeability. Claudin-2 represents a new therapeutic target in treating IBD, diarrhea and malnutrition in animals and humans.

1. The gastrointestinal epithelium in digestion, absorption and defense

In humans and animals, the ingested food and fluid are first processed by the enzymes in the saliva, then the acid in the stomach, and then the enzymes in the lumen and in the intestinal epithelium (IE). The IE is an indispensible barrier and interface between the gastrointestinal interstitium and the luminal environment that regulates water, ion and nutrient transport and absorption while providing a barricade against toxins, pathogens (bacteria, fungi and viruses) and antigens. The selective absorption

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of digested nutrients, ions and water is achieved by transcullular transporters, co-transporters and channels of the microvillus and the apical membrane (Nigot et al., 2015; Shen et al., 2011; Suzuki, 2013; Turner, 2009). Nevertheless, the paracellular permeability of two adjacent enterocytes is achieved by the intercellular junctions that are sealed by, at least, four different types of protein complexes, tight junctions (TJ), adherens junctions, desmosomes and gap junctions. The TJ multiple protein complexes are located at the apical ends of the two lateral membranes of the IE. The TJ barrier (TJB) consists of transmembrane and intracellular scaffold proteins—at least four integral transmembrane proteins, occludin, claudins, MarvelD3 or junctional adhesion molecule (JAM), and tricellulin, have been identified (Turner, 2009). The claudin family has 27 members. The extracellular loops of claudins form a selective barrier in the paracellular pathways with adjacent cells, and the intracellular domains interact with scaffold proteins such as zonula occludens (ZO) proteins and cingulin, which in turn anchor the transmembrane proteins to the actin cytoskeleton. Myosin light chain kinase (MLCK) is associated with the perijuctional actomyosin rings and regulates paracellular permeability through myosin contractility (Amasheh et al., 2002; Furuse et al., 1998, 2001; Gunzel and Yu, 2013; Krug et al., 2014; Rosenthal et al., 2010).

2. The apical intercellular tight junctions, claudins and their associated diseases

The apical intercellular TJ are responsible for the paracellular barrier function and regulate trans-epithelial flux of ions and solutes between adjacent cells. Increased intestinal permeability caused by defects in the IE TJB is considered an important pathogenic factor for the development of intestinal inflammation, diarrhea and malnutrition in humans and animals. In fact, defects in the IE, TJB allow for increased antigenic penetration, resulting in an amplified inflammatory response in inflammatory bowel disease (IBD), necrotizing enterocolitis and ischemia-reperfusion injury. The IE and TJ are integrators of mucosal homeostasis. Tight junction barrier defects allow bacterial products/enterotoxins and dietary and luminal antigens to cross the IE and enter the lamina propria. If the foreign substances are taken up by antigen-presenting cells (APC), APC and Th1 cells can release tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), which signal to IE to increase the TJ leak flux pathway. Leaky TJB allows for the translocation of bacterial products and dietary antigens from the lumen into the lamina propria, which amplifies the cycle of inflammation, ultimately leading to intestinal disease. Alternatively, interleukin-13 (IL-13) released by Th2 cells increases flux across small cation-selective pores, potentially contributing to ongoing disease. Conversely, the beneficial enhancement of the IE TJB activity, for example, treatment with anti-TNF-α antibody, has been shown to resolve intestinal inflammation and apoptosis in both animal models of IBD and human IBD (Heller et al., 2005; Oshima et al., 2008; Prasad et al., 2005; Schmitz et al., 1999; Weber et al., 2008).

Claudins are transmembrane proteins with a molecular weight of 20 to 27 kDa. Since 1998, twenty seven human genes coding for claudin proteins have been found (Krug et al., 2014; Turner, 2009), Claudins, together with other protein components (for example, occludins, tricellulin and MarvelD3) form TJ in the epithelium and the endothelium. The general functions of claudins are: (a) formation of barrier or channel/pore, (b) regulation of cellular polarity, signaling, proliferation, differentiation, receptor function, and motility, and (c) boundary establishment for limiting the intermixing of lateral and apical membrane proteins. Claudins in TJB prevent unregulated passage of solutes and water as well as penetration of luminal toxins and antigens. At the same time, claudins in TJB control paracellular permeation, both absorptive or secretory transport, by: (a) water selectivity, (b) cation selectivity, and (c) anion selectivity (Rosenthal et al., 2010). Alterations in abundance or molecular structure of claudins can generally result in three typical effects: (a) decreased absorption, (b) increased secretion of water and small solutes causing leak flux diarrhea, and (c) increased absorption of macromolecules which may induce inflammatory response and result in intestinal inflammation and symptoms like weight loss, abdominal pain or diarrhea.

Claudins show differential expression patterns throughout the intestine. In intestinal diseases, claudins are involved in alterations of expression as well as localization and distribution along the lateral membrane and the intercellular space. These alterations may lead to severe disturbances in the regulation of water, ion and solute transport as well as macromolecule uptake in affected areas, resulting in the specific clinical phenotype, such as IBD and Celia disease. Table 1 lists the changes of claudins in major intestinal diseases (Lu et al., 2013; Milatz et al., 2010; Suzuki et al., 2011; Thuijls et al., 2010; Zeissig et al., 2007).

2.1. Inflammatory bowel disease

Inflammatory bowel disease comprises two major entities, Crohn's disease (CD) and ulcerative colitis (UC). In CD, the whole intestinal tract from the oral cavity to the colon can be infested. In contrast, UC is limited to the colon spreading from distal to proximal and always affects the rectum. In both diseases, extra-intestinal manifestations can occur, affecting joints, liver and skin. Patients mostly suffer from episodic inflammation with frequent, often bloody diarrhea and abdominal pain. Both diseases particularly affect younger persons in their 30's and 40's, but older persons can also be affected, known as late onset IBD (Heller et al. 2005; Weber et al., 2008).

2.2. Crohn's disease

Crohn's disease is characterized by a dysregulated IE TJB function. Epithelial resistance was reduced by about 40% in colonic biopsies of CD patients with mild to moderate inflammation. Crohn's disease is presented with reduced and discontinuous TJ strands and altered claudin expression and localization (Table 1). As reported, claudin-2 expression was significantly increased and localized to crypt bases of the colon and the duodenum of active human CD patients (Goswami et al., 2014; Zeissig et al., 2007). It is thought that CD exhibits a predominant Th1 immune response, in which proinflammatory cytokines TNF-α and IFN-γ are dominant. Nevertheless, studies have shown that TNF-α and IFN-γ induce claudin-2 expression in HT-29/B6 and Caco-2 cells (Zeissig et al., 2007), where transepithelial electrical resistance (TER) decreases and cation permeability increases. In contract, claudin-3 expression and localization were reduced in the inflamed colon of CD

Table 1
Expression of various claudins in human intestinal diseases.

Inflammatory bowel disease	Upregulated	Downregulated	Reference
Crohn's disease	Claudin-2	Claudin-3, -5 and -8	Goswami et al., 2014; Zeissig et al., 2014
Ulcerative colitis	Claudin-2	Claudin-3, -4 and -7	Heller et al. 2005; Prasad et al., 2005; Weber et al., 2008
Irritabe bowel syndrome	Claudin-2	Claudin-1 and -4	Martínez et al., 2013
Celiac disease	Claudin-2	Claudin-3, -5 and -7	Schumann et al., 2012; Szakál et al., 2010