HHS Public Access

Author manuscript

J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2019 May ; 68(5): 611–614. doi:10.1097/MPG.0000000000002301.

Epithelial Claudin Proteins and their Role in Gastrointestinal Diseases

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Abstract

Our bodies are protected from the external environment by mucosal barriers that are lined by epithelial cells. The epithelium plays a critical role as a highly dynamic, selective semipermeable barrier that separates luminal contents and pathogens from the rest of the body as well as controlling the absorption of nutrients, fluid and solutes (1, 2). A series of protein complexes including the adherens junction, desmosomes, and tight junctions (TJ) function as the principal barrier in paracellular diffusion (3) as well as regulators of intracellular solute, protein and lipid transport (4). TJs are composed of a series of proteins called occludins, junctional adhesion molecules (JAM), and claudins (5, 6) that reside primarily as the most apical intercellular junction. Here we will review one of these protein families, claudins, and their relevance to gastrointestinal and liver diseases.

Keywords

celiac disease; eosinophilic oesophagitis; inflammatory bowel disease; liver disease; tight junction

Introduction

The manner in which the intestines, liver, and pancreas remain intact and functional despite the constant exposure to a myriad of luminal contents remains one of the fascinatingly complex topics in our field. For children, early life exposures to antigens and microbes may dictate immune tolerance or the development of a disease. Increasing awareness of this has promoted approaches to modify the barrier with vitamins, probiotics, nutraceuticals as well as novel and investigational pharmacological preparations. Hence, understanding the structure and function of the mucosal barrier, and in particular, the epithelial barrier is

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critical. Imagining a 3-dimensional luminal view of the epithelial surface permits a full appreciation of the dynamic and complicated manner in which the intercellular netting holds the epithelium together. Epithelial cells are the first cellular barrier to the external environment that are tightly bound together by a series of cell-cell adhesion complexes. TJs are composed of a family of proteins including occludins, junctional adhesion molecules, and claudins. The claudin family (from the Latin word for ‘close’) consists of at least 27 proteins that polymerize to constitute the TJ backbone (7). Due to their dynamic and differential expression in cells and organs of the body, the increasing recognition of the role of claudins particularly those related to epithelial cells suggests their importance in gastrointestinal (GI) and liver health and disease.

Claudins: Expression, regulation, and function in the Gastrointestinal tract

Claudins, encoded by the CLDN genes, are highly conserved 20-27kDa proteins that are differentially expressed along the various epithelial compartments of the gastrointestinal tract (Table 1). They are composed of four transmembrane proteins including a short intracellular NH2-terminal sequence (~1-7 residues), a large first extracellular loop (~52 residues), a shorter second extracellular loop (16 –33 residues), and a cytoplasmic COOH-terminal domain that varies considerably in length between different isoforms (21– 63 residues). These proteins end in an anchoring scaffold-binding PDZ domain (except Claudin-12) (8, 9). Given its structure, it is hypothesized that the larger first extracellular loop is involved with selective ion permeability, while the shorter second extracellular loop may be involved in narrowing of the paracellular cleft and adhesion between the opposing cell membranes (10). The topographical distribution and localization of claudins both in specific organs and on the epithelial cell is quite varied and summarized in Table 1. For instance, in the liver, claudin-1 is expressed at the TJs of hepatocytes and along the lateral membrane of bile duct cholangiocytes (11). The diversity of hepatic distribution is exemplified by the fact that claudin-2 increases from periportal to pericentral hepatocytes, claudin-3 is uniformly expressed, and claudin-5 is restricted to endothelial junctions (12). There are also reports of liver expression of claudins -6, -8, -9, and -14 (13). In the pancreas, claudins 1-5 and -7 are expressed diffusely (12, 13). In the gallbladder epithelium, claudins 1-4 (14) and -10 are expressed strongly whereas claudins -7 and 8- are expressed weakly (15).

Functionally, specific claudin protein family members regulate barrier or intercellular transport of molecules. For instance, claudins -1, -3, -5, -11, -14, -19 regulate epithelial barrier whereas claudins -2, -10 and -15, claudins -10 and -17 and claudin -2, selectively participate in transport of cations, anions and water respectively.

Claudins are expressed at a baseline during health and can change during states of inflammation, disease or cancer. This dynamic regulation can occur at the transcriptional and post-translational level (16). Transcription factors including the transcriptional repressor SNAI1 may regulate CLDN gene expression (17). Key soluble signaling molecules regulating claudin expression include tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β). TNF-α is an important pro-inflammatory molecule involved in intestinal inflammation. Exposure of the epithelium to TNF-α can lead to an increase in

intestinal TJ permeability *in vivo* and *in vitro* (18). NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) mediates TNF-α-induced changes in claudin-1 and the claudin-2 (19). Post-translational modifications of expressed Claudin proteins including phosphorylation, SUMOylation, Ubiquitination, and Palmitoylation contribute to altered Claudin localization, with implications for barrier function, cellular migration and invasiveness (16). The TGF-β family controls numerous cellular functions, including proliferation, differentiation and migration in all tissues of the human body (20). In the intestines, TGF-β signaling pathways play a crucial role in maintaining intestinal barrier function (21, 22), although few have evaluated TGF-β's influence on claudin expression. In endothelial cells, TGF-β activates Activin receptor-like kinase 5 (ALK5), which acts through SMAD2/3 to downregulate claudin-5 (23) In colon cancer, loss of SMAD4, which interacts with TGF-β and SMAD 2/3 complex, causes an increase in claudin-1 (24). Also, SMAD7 overexpression in colon adenocarcinoma cells causes increased expression of claudin -1, -4, and -7 (25). Altered TJ claudin expression patterns play key roles in numerous pathologies including cancers, infections, and diarrheal illnesses; improved understanding of mechanisms of regulation could help in designing innovative therapeutic strategies (26).

Claudins in Gastrointestinal Diseases

Inflammatory bowel diseases

Dysregulation of TJ proteins and epithelial permeability leads to increased paracellular transport of solutes, water, and other macromolecules that partake in inflammatory signaling (27). Changes in claudin expression and localization have been highly associated with dysregulated tight junctions in inflammatory bowel diseases (IBD). Functional consequences of dysregulated TJ protein expression have been found in endoscopic biopsies from patients with mild to moderate Crohn's disease. Biopsies demonstrate changes at ultrastructural level in the subjunctional lateral membrane with decreased TJ strand numbers, increased strand discontinuities, and pearl string-like strands, as well as an impaired barrier (28). This implicates that the structure of a TJ involving one TJ strand associating laterally with another TJ strand of the adjacent cell to form a paired TJ strand is impaired (29). Intestinal inflammation in patients with Crohn's and ulcerative colitis has been associated with the upregulation of the paracellular channel claudin-2 in small and large intestine regulated by interleukin-13, -6, TNF-α, and interferon gamma (30). The impaired barrier could suggest an increase in solute secretion and contribute to diarrhea. Patients with IBD generally demonstrate redistribution from the membrane or downregulation of claudin's -1,- 3, -4, -5, -7, and/or -8 in various parts of the intestinal tract (28, 31) providing support for the concept of a diminished barrier and enhanced luminal uptake of antigenic macromolecules (32). In a recent report, hypoxia-inducible factor-1β drove expression of claudin-1 improving barrier function (33). Upregulation of the cation pore- and water-channel forming claudin-2 have also been associated with disease progression of inflammatory bowel diseases (28, 31). Whether these findings relate to the underlying increased permeability and pathogenesis of IBD is yet to be determined.

Celiac Disease

Celiac disease is characterized by uptake of gliadin via paracellular endocytosis and transcytosis (34). Celiac disease patients are known to have an abnormal TJ structure (35) and increased intestinal permeability (36–38). This may lead to dysregulated paracellular pathways that could either be a primary factor or secondary finding related to gliadin uptake. Similar to IBD, celiac disease is associated with upregulation of cation pore-forming claudin-2, downregulation of tightening claudin-4 and -5 channels, and altered localization of claudin-4 (39). Other similar studies suggest a similar decrease in claudin-3, while no change in claudin-1 or 4 was detected (40). In some cases, the severity of the disease has been linked to an even greater increase in claudin -2 and -3 (41). Increased expressions of claudins -2 and -3 along with downregulation of claudin-5 suggest structural changes of TJ in celiac disease which may contribute to increased permeability observed in celiac disease (41).

Gastroesophageal reflux disease

Whether the pathogenesis of GERD and its related symptoms are related to altered barrier continues to undergo examination (42). The importance of the barrier in the esophagus is emphasized by the fact that the esophageal mucosa is composed of a stratified squamous epithelium in contrast to the single layer columnar epithelium of the rest of the GI tract. Dilation of the intercellular spaces is a prominent morphological feature of acid-induced damage to the stratified squamous epithelium (43). This feature highlights the role of claudins in tightening the intercellular spaces since GERD patients have significantly higher expression of claudin-1 and -2 (44) and lower expression of claudin -4 compared to healthy patients (45). Studies have shown that an early event in the pathogenesis of GERD is an acid-induced increase in paracellular permeability in the esophageal epithelium (46). However, it is still unknown whether the correlation between claudin expression and histopathology of GERD are directly related.

Eosinophilic Esophagitis

The contribution of an altered barrier to the pathogenesis of EoE has been suggested by the 2-hit theory. If a genetically predisposed host (altered expression/mutations of genes such as eotaxin-3, filaggrin, TSLP) develops altered barrier from an exogenous insult (GERD), the underlying immunomicromilieu may become activated to promote an eosinophilic response (47). Supportive of this is some early histological findings that reveal a reduction of claudin-1 protein expression in EoE patients compared to healthy individuals (48) that could indicate impairment of the TJ-barrier (49). Spongiosis of esophageal epithelium increases in correspondence with reduced claudin-1, that when treated with topical steroids returns to normal (50). Along with claudin-1 downregulation, active EoE subjects also showed increased epithelial expression of interleukin-9 (IL-9) receptor expression which negatively affects E-cadherin expression that might play a significant role in epithelial barrier disruption in EoE(51). Claudin-7 expression is attenuated in pediatric subjects with active EoE, mediated in part by TGF-β1, resulting in decreased epithelial barrier function (22). Though the differential expression of claudins in EoE has not been extensively studied, the

impact of claudins on the esophageal epithelial barrier and its regulation of inflammatory cytokines contains much potential for therapeutic targets.

Hepatobiliary diseases

Although not directly exposed to ingested luminal proteins, the hepatobiliary tree contains an epithelial surface that interfaces luminal products. In this regard, dysregulation of claudin expression may contribute to disease pathogenesis. For instance, claudin-3 knock out mice tends to develop cholesterol gallstone disease thought to be secondary to increased phosphate ion permeability (52). Diminished expression of claudin-1 in cholangiocytes and hepatocytes has been shown to be critical to the development of neonatal sclerosing cholangitis. The most notable host-pathogen role for a Claudin protein is the crucial role of Claudin-1 as a portal of cellular entry for the Hepatitis C virus. Here preclinical studies are targeting Claudin-1 directed antibodies as a therapeutic option (Reviewed in (53)).

Conclusion

Claudins are an essential component of TJs in the gastrointestinal epithelial barrier and its functional regulation of paracellular transport. As summarized here, altered expression may contribute to the development of GI and liver disease or develop as a function of inflammation. Claudins also may play roles in infectious diseases, tumorigenesis and epithelial-mesenchymal transition in the gut and elsewhere (27, 53). Although no claudin specific treatments are available to date, future studies determining the claudin's expression, mediation, and regulation are critical to developing further understanding of the barrier's role in gastrointestinal and liver diseases.

Acknowledgments

Supported by: NIH 1K24DK100303 (Furuta GT) and K01-DK106315 (Masterson JC).

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Learning points

1. The epithelium and tight junctions are a complex, dynamic organ that protects the body from exogenous particles and alters the luminal contents with the secreted product.
2. No FDA approved drug directly improves or heals the tight junctions to date.
3. Claudins are one of many proteins that are acting in the tight junction to maintain barrier and solute flow.

Table 1:

Claudin expression in the gastrointestinal tract

Tissue	Claudin's expressed	References
Esophagus	1, 4, 7,15	24
Stomach	1, 2, 3, 4, 5, 12, 18, 23	54–59
Small Intestine	1, 2, 3, 4, 5, 7, 8, 12, 15	42, 59–62
Large Intestine	1, 3, 4, 7, 8, 12, 13, 15	59, 60, 63
Liver	1, 2, 3, 5, 6, 8, 9, 14	11–13
Pancreas	1, 5, 7	12, 14
Gallbladder	1, 2, 3, 4 10, 7, 8	15, 16