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Review

Claudin-related intestinal diseases

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ABSTRACT

With up to 200 m^2 the human intestine is the organ with the largest absorptive surface of the body. It is lined by a single layer of epithelial cells that separates the host from the environment. The intestinal epithelium provides both, selective absorption of nutrients, ions, and water but also a highly effective barrier function which includes the first line of defense against environmental antigens. The paracellular part of this barrier function is provided by tight junction (TJ) proteins, especially the large family of claudins. Changes in abundance or molecular structure of claudins can generally result in three typical effects, (i) decreased absorptive passage, (ii) increased secretory passage of small solutes and water causing leak flux diarrhea and (iii) increased absorptive passage of macromolecules which may induce inflammatory processes. Several intestinal diseases are associated with such changes that can result in intestinal inflammation and symptoms like weight loss, abdominal pain or diarrhea. This review summarizes our current knowledge on barrier dysfunction and claudin dysregulation in several intestinal diseases gastroenterologists are often faced with, like inflammatory bowel disease, microscopic colitis, celiac disease, irritable bowel syndrome, gallstones and infectious diseases like HIV enteropathy, *Campylobacter jejuni* and *Clostridium perfringens* infection.

Contents

1. Properties and pathophysiologic principles of claudin alterations 31
2. Reduced paracellular transport of solutes and water 31
   2.1. Gallstones and cholestatic liver disease 31
3. Increased paracellular transport of solutes, water, and macromolecules 32
   3.1. Inflammatory bowel disease 32
      3.1.1. Ulcerative colitis (UC) 32
      3.1.2. Crohn's disease (CD) 33
      3.1.3. Microscopic colitis 33
   3.2. Diseases of the small intestine 33
      3.2.1. Celiac disease 33
      3.2.2. Irritable bowel syndrome 34
   3.3. Infectious diseases 34
      3.3.1. HIV enteropathy 34
      3.3.2. *Campylobacter* enteritis 35
      3.3.3. *Clostridium perfringens* infection 35
4. Concluding remarks 36
   Acknowledgement 36
   References 36

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1. Properties and pathophysiologic principles of claudin alterations

Claudins are small transmembrane proteins with a molecular weight of 20–27 kDa. They form – together with the proteins of the TAMP family occludin, tricellulin and MarvelD3 – the molecular components of tight junctions (TJ) in epithelia and endothelia and can be found in all organs of the body. During the decade following the discovery of the first two claudins in 1998 [1], 27 distinct claudins were described in mammals [2]. The functions of the claudins can be generally described by (i) barrier or channel formation ("gate function") and (ii) non-barrier/channel functions affecting cellular signaling, proliferation, differentiation, receptor function, and motility/migration. A third function, not reviewed here, consists of a "fence function" by which the TJ limits the intermixing of lateral and apical membrane proteins. By its barrier and channel function, claudins prevent on one hand unlimited passage of solutes and water as well as invasion of luminal antigens and on the other hand constitute paracellular permeation sites to allow absorptive or secretory transport through the tight junction. As to current knowledge, claudins forming paracellular channels exhibit three types of selectivity: (i) anion selectivity (e.g. claudin-10a, -17), (ii) cation selectivity (e.g. claudin-2, -10b, -15) and (iii) water selectivity (so far only claudin-2). Other claudins exhibit strict barrier properties in an almost charge- and size-nonselective way (e.g. claudin-1, -3, -5) or they exhibit barrier properties with higher effectivity for one or the other charge (e.g. claudin-4, -8 and -14). The channel and barrier functions of claudins have been reviewed in full detail elsewhere [3,4].

Claudins exhibit differential expression patterns throughout the intestine (Fig. 1). The intestinal diseases claudins are involved in exhibit changes in 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 solute and water transport as well as macromolecule uptake in affected organs and result in the specific clinical phenotype (e.g. inflammatory bowel disease (IBD)). Table 1 lists the changes of claudins in major intestinal diseases.

This review summarizes current knowledge about claudin involvement in diseases of the intestinal tract. Its outline follows three major pathophysiologic mechanisms, (i) reduced paracellular transport of solutes and water, (ii) increased paracellular transport of solutes and water and (iii) increased paracellular transport of macromolecules. Because (ii) and (iii) appear together in several diseases they are reported conjointly.

2. Reduced paracellular transport of solutes and water

2.1. Gallstones and cholestatic liver disease

Gallstones are a common clinical entity that affects 15% of the population in Western societies. Of these, approximately 25% become clinically apparent and usually result in surgical removal of the gallbladder. Gallstones develop because of an imbalance in bile composition [5,6]. Bile composition relies, among other things, on the content of water but the exact molecular mechanisms how water flow is regulated and how it contributes to bile flow in the hepatobiliary system is still unresolved. Regarding the paracellular

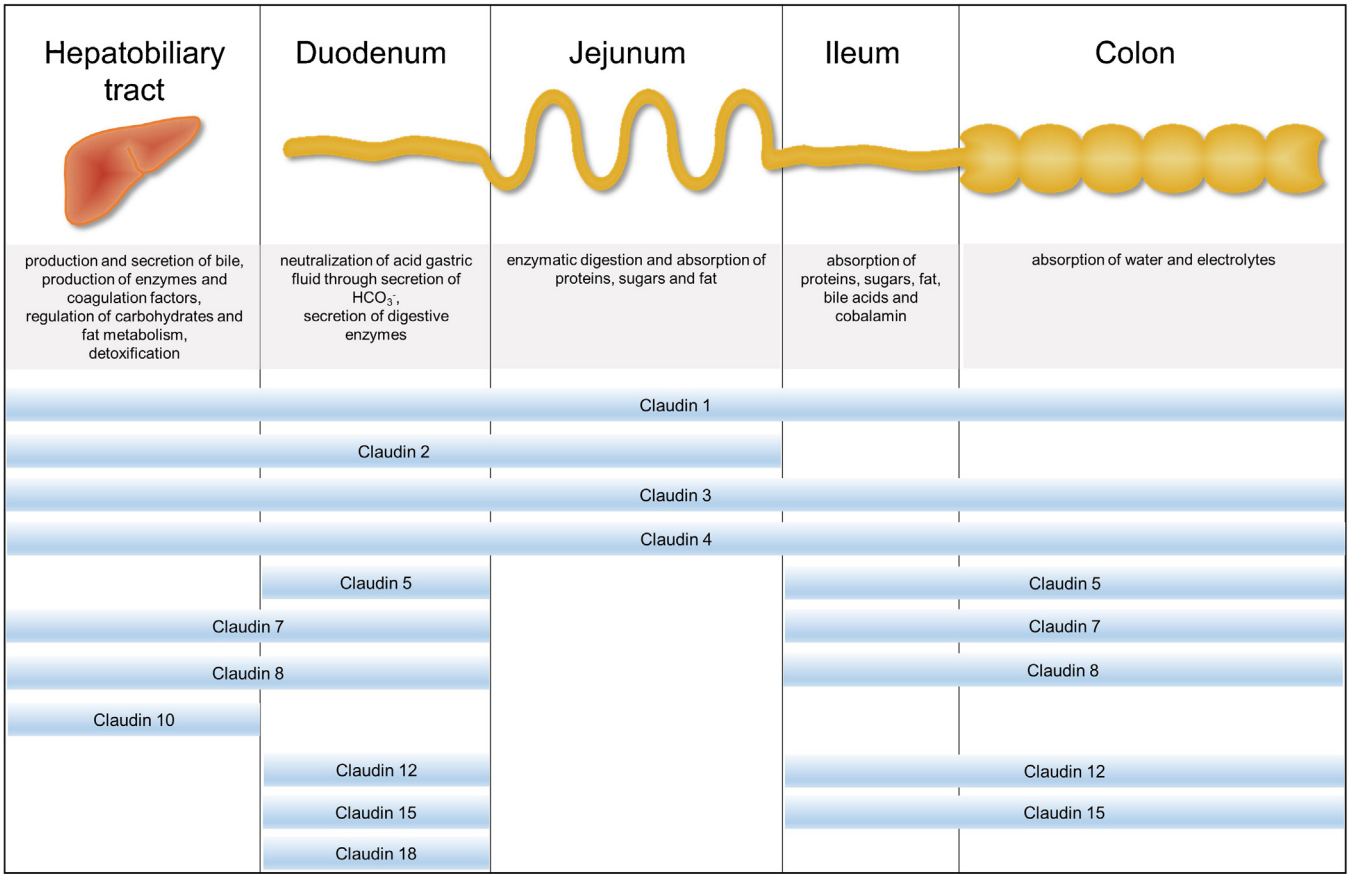

Fig. 1. Expression of different claudins in the human intestine and hepatobiliary tract. References: duodenum [100–102], jejunum [56], ileum [100,103], colon [25,100], hepatobiliary tract [104].