MAR Oncology and Hematology (2026) 6:3

Review Article

Claudins in Gastrointestinal Disorders

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Received: 04 March 2026

Published: 10 March 2026

DOI: https://doi.org/10.5281/zenodo.18932938

Abstract

The gastrointestinal (GI) tract relies on a dynamic epithelial barrier, with claudins serving as pivotal determinants of paracellular permeability and cellular signaling. Dysregulation of claudins has been increasingly implicated in the pathogenesis of diverse GI disorders, including malignancies, inflammatory diseases, infections, and barrier dysfunction syndromes. This narrative review synthesizes current evidence on claudin biology in health and disease, highlighting how isoform-specific expression and localization shape barrier integrity and influence signaling pathways such as Wnt/β-catenin, Src kinase, and ERK. In cancer, aberrant claudin expression exhibits dual roles: tumor-suppressive when maintaining adhesion, yet oncogenic when mislocalized or overexpressed, driving epithelial-to-mesenchymal transition, stemness, and therapeutic resistance. Inflammatory and immune-mediated conditions such as inflammatory bowel disease, celiac disease, and eosinophilic esophagitis demonstrate characteristic shifts toward increased pore-forming claudins (e.g., claudin-2) and decreased sealing claudins (e.g., claudin-7, -8), thereby exacerbating barrier leakiness and immune activation. Infectious and metabolic disorders further exploit claudins, as exemplified by hepatitis C virus utilizing claudin-1 as a coreceptor. Beyond pathogenesis, claudins hold promise as diagnostic biomarkers and therapeutic targets: monoclonal antibodies against claudin-1, claudin-binding toxins, and anti-claudin-18.2 therapies are under investigation, with potential applications in gastroesophageal, gastric, pancreatic, and hepatic cancers. Emerging imaging tools leveraging claudin affinity further underscore their translational potential. By integrating findings from human studies, animal models, and mechanistic experiments, this review delineates the multifaceted roles of claudins in GI disorders and evaluates opportunities and challenges in harnessing these proteins for clinical intervention.

Keywords: claudins, gastrointestinal, cancer, inflammatory bowel disease, celiac disease

Introduction

The gastrointestinal (GI) tract is lined by a continuous epithelial barrier that separates the host's internal milieu from the external environment. At the core of this barrier are tight junctions (TJs) – multi-protein complexes that seal the paracellular space at the apical end of epithelial cells (1). Claudins are a family of tetraspan transmembrane proteins and key structural components of TJs (2). In mammals, at least 27 claudin proteins (claudin-1 through claudin-27) have been identified (2), each with distinct tissue distributions and functions. By forming homotypic and heterotypic strands between adjacent cells, claudins establish charge- and size-selective paracellular channels that control the permeability of ions and solutes across epithelia (3). Beyond their barrier role, claudins are increasingly recognized as dynamic regulators of cellular signaling, polarity, proliferation, and differentiation (1). Aberrant expression or localization of claudins can thus have profound effects on tissue homeostasis, potentially triggering pathological pathways such as inflammation and neoplasia (4).

Over the past two decades, dysregulation of claudins has been implicated in a wide spectrum of GI disorders, ranging from malignancies (esophageal, gastric, colorectal, hepatic, pancreatic cancers) to chronic inflammatory conditions (inflammatory bowel disease, celiac disease, eosinophilic esophagitis), infections and metabolic diseases (e.g. hepatitis C virus infection leading to liver fibrosis), and other barrier-related disorders (such as gastroesophageal reflux disease). Changes in claudin expression are often accompanied by disruption of the tight junction barrier, altered epithelial permeability, and downstream activation of immune responses (5). In parallel, claudins can act as signaling platforms; for example, certain claudins modulate Wnt/β-catenin, Src kinase, or other pathways that influence epithelial-to-mesenchymal transition (EMT), stem cell behavior, or apoptosis resistance (6, 7). These properties place claudins at the intersection of key processes: barrier integrity, immune surveillance, and cell fate determination that collectively drive disease pathogenesis in the GI tract.

This narrative review provides a comprehensive overview of the role of claudins in GI physiology and disease. We begin by summarizing claudin structure, isoform diversity, and normal functions in the gut, highlighting how their junctional and non-junctional roles are regulated. We then explore, by thematic categories, how claudin dysregulation contributes to GI disease pathogenesis, from cancers to inflammatory and infectious conditions, focusing on mechanisms like tight junction disruption, EMT promotion, stemness, and immune modulation. Relevant evidence from human clinical studies, animal models, and in vitro experiments is integrated to illustrate these concepts. Finally, we discuss the clinical implications of claudins: their potential as diagnostic/prognostic biomarkers and as therapeutic targets, including emerging strategies such as monoclonal antibodies against claudins, claudin-binding toxins, and imaging agents. Through this thematic approach, we aim to illuminate the multifaceted contributions of claudins to GI disease and the opportunities

and challenges in targeting these proteins for clinical benefit.

Physiologic Function of Claudins

At tight junctions, claudins are the primary determinants of barrier properties. Different segments of the GI tract express specific combinations of claudins to balance permeability and sealing. For example, claudin-2 and claudin-15 are known pore-forming claudins that create cation-selective channels, contributing to the "leaky" epithelia of the proximal small intestine (8, 9). Claudin-2 is predominantly localized at TJ regions of intestinal epithelia (especially colon surface cells) and increases paracellular conductance to Na+ and water (5, 10). Claudin-15 similarly permits paracellular Na+flux; mice lacking claudin-15 develop Na+-malabsorption and osmotic imbalances leading to gut dilation (11-13). On the other hand, claudins-1, -3, -4, -5, and -7 are classical "sealing" claudins – they have neutral ECL charges and form tight, ion-indiscriminate seals (3). Claudins-3 and -4, for instance, are abundantly expressed on gastric and colonic epithelial TJs and help establish a high-resistance barrier that limits passive ion leak (14, 15). Claudin-8 is another sealing claudin, enriched at colonic epithelium TJs where it prevents back-leak of luminal sodium in the distal colon (16, 17). Dynamic regulation of claudin phosphorylation and localization allows epithelia to adjust permeability in response to physiological stimuli; e.g. activation of myosin light chain kinase (MLCK) by inflammatory cytokines can trigger endocytosis of claudin-3 and -4, acutely weakening the tight junction barrier (18, 19).

Notably, claudins are not confined to tight junctions: they can also localize along lateral membranes or even be released as extracellular vesicles, mediating non-junctional functions. For example, claudin-7 is found not only at TJs but also on basolateral membranes of colonocytes (20). There, it forms complexes with adhesion molecules like integrin α2 and EpCAM, impacting cell-matrix interactions and signaling cascades (21). Loss of claudin-7 disrupts these complexes and has been shown to activate matrix metalloproteinases (MMPs) and NF-κB signaling, leading to inflammation and compromised epithelial integrity (21, 22). Paradoxically, claudin-7 can also cooperate with EpCAM in cancer stem cells to form a co-transcriptional regulator (the "EpIC" complex) that enhances β-catenin signaling, illustrating a context-dependent signaling role for basolateral claudin-7 in promoting tumorigenesis (23). Claudin-1 offers another example of non-junctional activity: besides sealing TJs in the colon, claudin-1 is often mislocalized to the cytoplasm or nucleus in colon cancer cells, where it has been linked to Wnt/β-catenin pathway activation and increased EMT and invasive behavior (4). Indeed, claudin-1 overexpression in experimental colitis models led to heightened inflammation and impaired mucosal healing via upregulation of ERK and Notch signaling (24). Thus, claudins can influence cellular behavior both through their biophysical barrier function and by serving as platforms or modulators of signaling pathways.

Claudin Isoforms in the GI Tract

Over two dozen claudin genes are expressed in mammals, but their distribution in the GI tract varies widely (3). Claudin-1 is expressed broadly along the GI epithelium, from esophagus to colon, contributing to baseline barrier function. Claudin-3 and claudin-4 are also ubiquitous in GI epithelia and are typically co-expressed; they are highly abundant in the gastric mucosa and colon and moderately in the esophagus and small intestine (1). Claudin-5 is best known in endothelial barriers (e.g. blood–brain barrier), but in the gut it is present in the epithelial tight junctions of the colon as well [49][50]. Claudin-2 is relatively sparse in the healthy colon (mainly in superficial epithelial cells) but is constitutively expressed in the small intestine (intestinal crypts) where it facilitates paracellular nutrient and water transport[24][26]. Claudin-7 and claudin-8 are enriched in the colon – claudin-7 localizes to both TJ and lateral surfaces of colonic cells[33], whereas claudin-8 is found in colonic and distal small intestinal TJs, helping tighten the distal gut barrier[31]. Claudin-12 is an enigmatic family member that lacks a PDZ-binding motif and has a more cell-type specific pattern: it is detected in the intestine (especially ileum) and has been implicated in vitamin D–dependent calcium absorption across enterocytes[51]. Claudin-15 is largely restricted to the small intestine, where it forms Na^+ channels important for paracellular nutrient uptake; claudin-15 knockout mice develop a “megintestine” phenotype with dilated small bowel due to malabsorption[26][27]. In the stomach, a unique claudin is predominant: claudin-18. The CLDN18 gene encodes two tissue-specific splice isoforms – claudin-18.1 in lung and claudin-18.2 in gastric epithelium[52]. Gastric claudin-18.2 is essential for establishing the stomach’s acid-resistant barrier, as it limits proton permeability across gastric mucosa[52][53]. Claudin-18.2 is normally absent from the intestine, so its expression in other locations (e.g. esophagus, pancreas) is often indicative of disease or neoplastic transformation, as discussed later[54][55].

Several claudins have minimal or no known function in the adult GI tract. Claudin-6 and claudin-9 are expressed primarily in embryonic tissues and certain organs (e.g. skin, testis), with little baseline GI expression – though they can be ectopically expressed in some GI cancers and, notably, serve as alternate HCV receptors in the liver[56][57]. Claudin-11 is specific to myelin sheaths and testicular Sertoli cells, and claudin-14, -16, and -19 are critical in the kidney (especially for renal ion reabsorption in the thick ascending limb) and inner ear, but are not significantly present in gut epithelia[58][59]. Claudin-13 is expressed in rodents but the CLDN13 gene is absent in humans[60]. Meanwhile, claudin-20, -21, -22, and -23 are lesser-studied isoforms with some expression in GI tissues: claudin-23, for instance, is enriched in differentiated colonocytes at the luminal surface where it appears to strengthen the mucosal barrier[61][62]. Indeed, claudin-23 knockout in mice leads to a more permeable colonic epithelium and greater susceptibility to inflammation, indicating a homeostatic barrier role that is disrupted during colitis (when claudin-23 expression is downregulated)[63][64]. The CLDN24, CLDN25, CLDN26, and CLDN27 genes are considered putative

claudins – their protein products have been predicted but remain poorly characterized in terms of expression and function[59]. Initial reports suggest claudin-25 (also termed "claudin domain-containing protein 1") is expressed in humans in some tissues (mutations in CLDN25 were linked to a rare neurologic disorder)[65][59], but its presence in the GI tract is not well established. In summary, a subset of claudins (mostly claudin-1 to -8, -12, -15, -18, -23) plays dominant roles in GI epithelial physiology, whereas others are either extrinsic to the GI system or involved in specialized contexts.

Regulation of Claudins

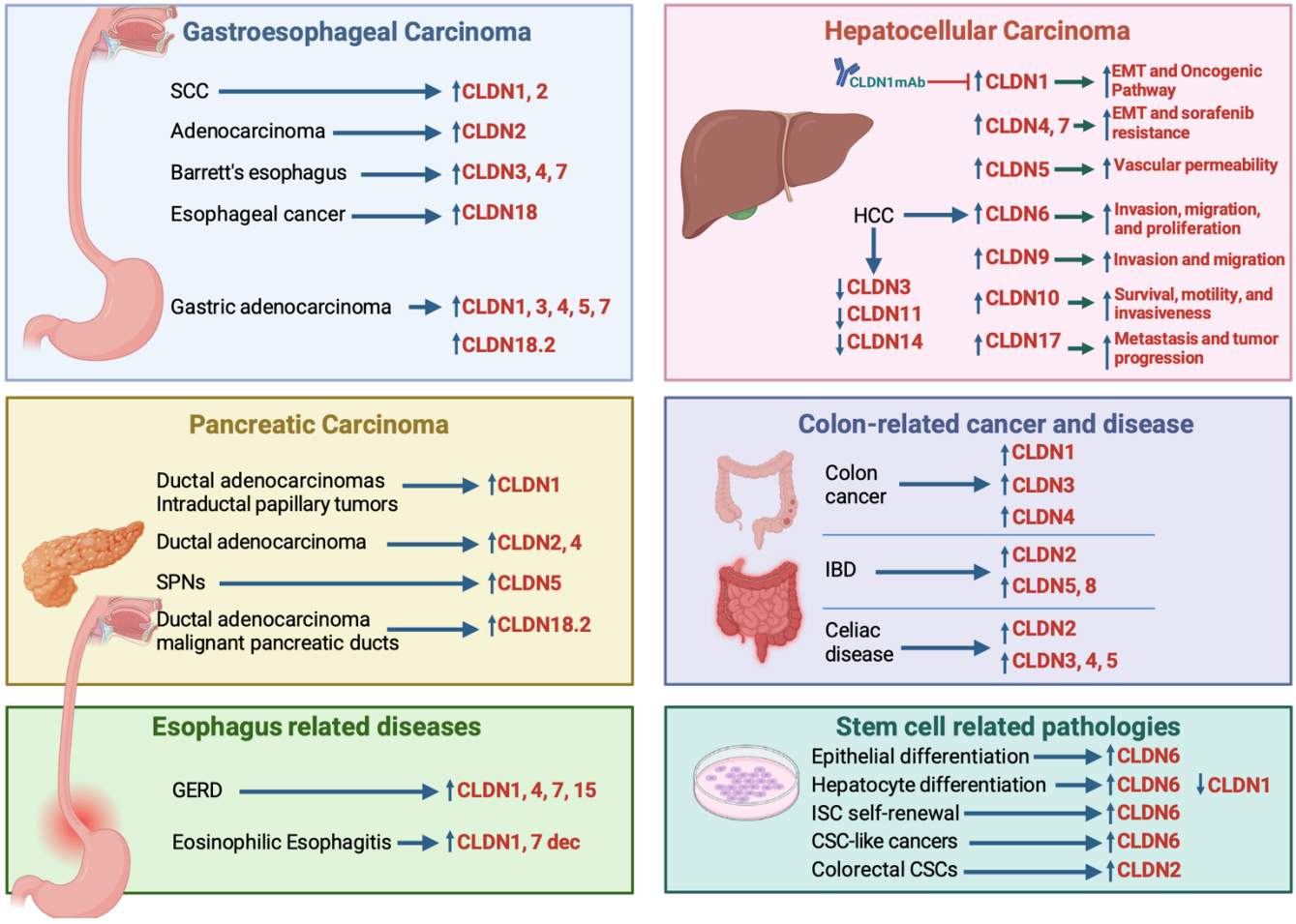
The expression and junctional localization of claudins are tightly regulated by a variety of mechanisms. Pro-inflammatory cytokines prevalent in GI disease can modulate claudin transcription and trafficking. Tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), for example, synergistically activate MLCK and casein kinase in intestinal epithelial cells, leading to phosphorylation and endocytosis of claudin-4 and other TJ proteins, thereby compromising the barrier[32][29]. Interleukin-13 (a Th2 cytokine overexpressed in allergic disorders like eosinophilic esophagitis) has been shown to downregulate claudin-7 and claudin-1 in the esophageal epithelium, partly via induction of microRNA-155 that targets CLDN7 mRNA[66][67]. IL-9 and IL-23, cytokines elevated in active IBD, drive the loss of claudin-8 in the colon through upregulation of microRNAs (miR-21 and miR-223) that suppress CLDN8 expression[68][69]. Conversely, certain growth factors can increase claudin levels: transforming growth factor-alpha (TGF-α) and epidermal growth factor (EGF) signaling were reported to upregulate claudin-2 in intestinal epithelium via a MEK-ERK-dependent pathway, contributing to the proliferative, less-differentiated state of the crypt epithelium[70][71]. Microbial factors also play a role – the presence of a healthy microbiota and probiotic organisms can enhance barrier claudins. In an elegant murine study, colonization with probiotics in early life was shown to induce claudin-3 expression during gut maturation, an effect dependent on toll-like receptor (TLR) signaling (MyD88 pathway)[28][72]. This finding suggests that microbial-epithelial cross-talk helps fortify TJs (via claudin upregulation) as the gut adapts to the external environment. Diet and luminal metabolites likewise influence claudins: for instance, the short-chain fatty acid butyrate (produced by fiber-fermenting colonic bacteria) has been found to increase claudin-23 expression in intestinal cells through SP1 and AMPK signaling, thereby potentially strengthening the barrier[73]. On the other hand, physical insults like acid exposure in the esophagus can redistribute claudins – in reflux conditions, claudin-4 is often delocalized or reduced in superficial squamous cells, weakening the esophageal barrier and rendering it more susceptible to acid injury[74][75]. Overall, claudin biology in the GI tract is governed by a complex network of signals that reflect the physiological state of the tissue. When this regulation is perturbed – whether by genetic, environmental, or inflammatory stimuli – the resulting claudin abnormalities can set the stage for disease, as discussed in the

following sections.

Claudins in Gastrointestinal Cancers

Dysregulated claudin expression is a hallmark of many GI malignancies, often emerging early in preneoplastic lesions and evolving through tumor progression (Figure 1). Claudins can act as double-edged swords in cancer: some function like tumor suppressors by maintaining adhesion and polarity (their loss facilitates invasion), whereas others may actively promote tumorigenic signaling when overexpressed. The net effect is context-dependent, varying by claudin subtype, tissue of origin, and stage of disease[76][77]. Here we review claudin alterations in major GI cancers (esophageal, gastric, colorectal, hepatic, and pancreatic), emphasizing how these changes affect tumor biology such as barrier integrity, EMT, stemness, and therapy resistance.

Esophagus (Esophageal Cancer and Barrett's Dysplasia)



The esophagus provides a clear example of claudin changes during the metaplasia–dysplasia–carcinoma sequence. In the normal esophageal squamous epithelium, claudin expression is relatively low, except for barrier-formers like claudin-1 at the basal layer[78]. In Barrett's esophagus (a metaplastic condition in which

the normal squamous lining is replaced by intestinal-type columnar epithelium), claudin levels shift to a profile resembling intestinal/gastric mucosa. Several studies have reported significant upregulation of claudin-3 and claudin-4 in Barrett's esophagus, compared to normal squamous mucosa[47][48]. Strong claudin-4 immunoreactivity is seen in most Barrett's biopsies, including both non-dysplastic and dysplastic segments[79][80]. Claudin-3 and -4 remain elevated during progression to esophageal adenocarcinoma (EAC); in fact, EAC often shows equal or higher claudin-3/4 expression than the precursor Barrett's lesion[47][79]. This persistent overexpression of claudin-3 and -4 may confer a selective advantage to the metaplastic and neoplastic cells – possibly by tightening the epithelial sheet to resist acid bile injury or by engaging signaling pathways that aid survival. Notably, claudin-4 is a receptor for CPE toxin, but in Barrett's context its role might relate to regulating paracellular permeability to H^+; claudin-4 overexpression could help these columnar cells better withstand acidic reflux. In contrast, claudin-2 is normally absent in squamous esophagus but becomes induced in Barrett's dysplasia/EAC. Abu-Farsakh et al. found claudin-2 to be highly expressed in EAC and its high-grade dysplasia precursors, more so than in Barrett's intestinal metaplasia[81]. Thus, claudin-2 appears upregulated relatively late (during dysplasia and carcinoma) in the esophageal adenoma-carcinoma sequence[81]. Since claudin-2 forms cation-leaky channels, its ectopic expression might paradoxically reduce barrier function in tumors; however, in cancer cells claudin-2 can also activate pro-tumorigenic signals (e.g. EGFR/ERK) that enhance proliferation[82][71]. Indeed, claudin-2 is reported to promote EAC cell growth in vitro by activating EGFR, analogous to its role in colon cancer (discussed below). Claudin-7 shows a unique pattern in esophageal neoplasia. In Barrett's metaplasia and low-grade dysplasia, claudin-7 expression is uniformly present and often strong[83][84]. This suggests claudin-7 may be induced as part of the intestinal differentiation program in Barrett's epithelium. However, as dysplasia progresses to intramucosal carcinoma and invasive EAC, claudin-7 levels tend to drop: only ~50% of EAC cases retain strong claudin-7 immunostaining[84]. The remainder show loss or no change relative to normal[84]. In practical terms, claudin-7 could be a marker distinguishing early Barrett's lesions (where it's high) from invasive EAC (where it's often reduced to baseline)[84]. Functionally, loss of claudin-7 in advancing EAC might contribute to EMT and invasion, since claudin-7 normally helps stabilize cell-cell and cell-matrix contacts. Esophageal squamous cell carcinoma (ESCC), which arises from the squamous mucosa (often linked to smoking or alcohol exposure), exhibits its own claudin aberrations. One study noted claudin-1 is significantly increased in ESCC compared to adjacent normal epithelium[78]. Claudin-1 overexpression in ESCC correlates with more invasive behavior; mechanistically, it may facilitate tumor cell migration by modulating MMPs and interacting with components of the motility machinery[85]. Taken together, esophageal cancers exemplify how claudin dysregulation accompanies neoplastic transformation: a general trend is that tightening claudins (3,4,7) are gained in metaplasia, potentially as an adaptive response to chronic

injury (acid reflux), but as carcinoma develops, some claudins (7, and possibly 4 in squamous cases) are lost to enable invasion, while pore-forming claudins (2) are aberrantly upregulated, aiding proliferative signaling and perhaps creating a more permeable barrier that fosters interaction with stromal factors.

Beyond their roles in pathogenesis, claudins in Barrett's and EAC have clinical significance. Claudin-18 (particularly the -18.2 isoform, normally stomach-specific) has been detected in a subset of Barrett's and EAC tissues[86][87]. In one study, CLDN18 was the most highly expressed TJ protein in Barrett's metaplasia, and experimentally introducing claudin-18 into esophageal cell lines increased their resistance to acid and lowered paracellular permeability to H^+[87]. This indicates claudin-18 might protect Barrett's epithelium against acid injury – but its presence in EAC could provide a therapeutic opportunity, as discussed later (anti-claudin-18.2 therapies). In ESCC, high claudin-1 expression has been associated with poor differentiation and metastasis[85], suggesting it could serve as a prognostic marker or a target for therapy (e.g., blocking claudin-1 to inhibit invasion). Overall, the esophagus showcases the dynamic changes of claudins during carcinogenesis, reflecting shifts in barrier requirements and signaling states from normal epithelium to metaplasia to cancer.

Stomach (Gastric Cancer and Precursors)

The gastric epithelium normally expresses a distinct claudin profile, dominated by claudin-18.2 (a lineage marker of gastric mucosa) and supplemented by claudin-4, -5, and -7 in the glandular tight junctions[88][49]. Preneoplastic changes in the stomach, such as chronic atrophic gastritis and intestinal metaplasia (often caused by Helicobacter pylori infection), are accompanied by significant claudin alterations. Intestinal metaplasia (IM) of the stomach entails the replacement of gastric glands with intestine-like epithelium; fittingly, studies report increased expression of claudin-1, -3, -4, -5, and -7 in IM, reflecting a shift toward an intestinal TJ phenotype[88][49]. In parallel, claudin-18 is markedly downregulated in areas of IM[88][49] – since claudin-18 is a gastric lineage protein, its loss is expected when gastric cells transdifferentiate into intestinal type. These changes have functional implications: loss of claudin-18 may weaken the gastric barrier, potentially allowing more exposure of underlying mucosa to irritants or carcinogens, whereas upregulation of claudin-3/4/5/7 might initially compensate by sealing the altered epithelium. Progressing along the neoplastic cascade, dysplasia and early gastric carcinoma show further claudin dysregulation. In gastric dysplasia (especially arising on a background of IM), claudin-3 and -5 remain elevated, and claudin-4 and -7 become even more strongly upregulated (often showing diffuse intense staining in high-grade dysplasia)[49][89]. Intriguingly, claudin-18 expression appears to rebound in gastric dysplasia/carcinoma – in fact, claudin-18 (particularly the 18.2 isoform) can be highly expressed in certain gastric cancers, notably the diffuse-type gastric adenocarcinoma[89]. One study noted that claudin-18.2 was especially elevated in diffuse gastric carcinoma

lesions, whereas it was lower in IM and only modest in intestinal-type cancers[89]. This seemingly paradoxical re-expression of claudin-18 in diffuse cancers correlates with recent molecular insights: a significant subset of diffuse gastric cancers harbor CLDN18–ARHGAP fusions or mutations that dysregulate claudin-18[90]. In a mouse model, claudin-18.2 knockout led to chronic gastritis and spontaneous gastric tumors accompanied by activation of oncogenic pathways like YAP/Hippo and CD44[53][90]. Thus, claudin-18 may act as a tumor suppressor in the stomach (its loss can promote tumorigenesis through unleashing proliferation signals), yet paradoxically, the residual cancer cells in diffuse gastric carcinoma often overexpress claudin-18.2 on their surface – making it a convenient therapeutic target, as they still "wear" this gastric antigen[54][55].

Besides claudin-18, claudin-4 is frequently aberrant in gastric cancer. Some gastric tumors, particularly of the intestinal type, show increased claudin-4 expression which has been associated with more aggressive features[91][92]. For example, overexpression of claudin-4 in gastric cancer cell lines can enhance invasion and metastatic behavior via activating β-catenin and EMT programs[91]. On the other hand, other studies have found loss of claudin-4 in advanced gastric cancers correlating with poor differentiation and worse prognosis[91][92]. These conflicting reports suggest claudin-4's role may depend on tumor context (molecular subtype, etc.). It is notable that claudin-4's binding partner, claudin-3, is generally maintained or increased in gastric neoplasia, possibly to uphold some barrier function in hyperpermeable tumor tissue. Claudin-1 is another inducible claudin in gastric intestinal metaplasia/dysplasia – its expression is low in normal stomach, but rises in IM and remains elevated in many gastric cancers[88][49]. Given claudin-1's known links to EMT, its upregulation may facilitate the progression of gastric lesions to invasive cancer. Consistently, claudin-1 upregulation (alongside claudin-3 and -5) has been observed at the IM → dysplasia transition[49]. Meanwhile, claudin-5, an endothelial-type claudin, is abnormally present in IM and dysplasia[88][49]; in gastric adenocarcinoma, claudin-5 levels vary, but one study showed it tends to decrease again in invasive carcinoma despite the earlier rise[88]. If claudin-5 is lost in cancer, it might contribute to increased metastatic potential by allowing tumor cells to traverse endothelial barriers more easily (claudin-5 loss in blood vessels is known to increase permeability[93][94], and tumor-derived signals can downregulate claudin-5 to promote angiogenic leakage and intravasation).

Clinically, claudin expression patterns are being explored as biomarkers in gastric cancer. Perhaps the most significant is claudin-18.2, which is present in up to ~30–40% of gastroesophageal adenocarcinomas. Claudin-18.2 has emerged as a target for antibody therapy (as discussed in Clinical Implications), and its detection by immunohistochemistry is used to screen patients for eligibility in trials[95]. The fact that claudin-18.2 is normally confined to gastric mucosa means that its expression in other contexts (like metastatic disease or other organs) strongly suggests a gastric origin; this can help in diagnostic dilemmas (e.g., distinguishing a gastric primary tumor vs. metastasis). Furthermore, the presence of claudin-18.2 in diffuse gastric cancer cells,

despite their scattered, discohesive nature, raises interesting questions about its function: it might support small cell clusters or survival in ascitic environments (since diffuse cells lack E-cadherin, claudin-18 could be one of the remaining adhesion molecules). In summary, gastric cancers undergo a swing in claudin composition: gastric-to-intestinal transdifferentiation (IM) leads to loss of native claudin-18 and gain of intestinal claudins, but as malignancy ensues, some gastric cancers re-express claudin-18.2 and alter claudin-1/3/4/5/7 levels in ways that likely influence their invasiveness and interactions with the tumor microenvironment.

Colorectal Cancer (CRC)

The normal colonic epithelium is characterized by a tight junction network containing claudin-1, -3, -4, -7, -8, and others, which together maintain a robust barrier against the highly bacterial-rich colonic lumen. In colorectal cancer, this orderly architecture is disrupted. A striking feature of many colonic tumors is the "claudin paradox": while some claudins (e.g. claudin-1, -2, -3, -4) are overexpressed and linked to oncogenic properties, others (claudin-7, -8, -23) are downregulated, reflecting loss of differentiation and barrier function. Early evidence of claudin involvement in colon tumorigenesis came from colitis-associated cancer models. In patients with long-standing ulcerative colitis, colon biopsies often exhibit increased claudin-1, -2, -3, -4 expression in areas of active inflammation[96]. This upregulation correlates with inflammatory activity and with activation of the Wnt/β-catenin pathway in these cells[96]. Experimentally, chronic colitis models demonstrate that claudin-1 overexpression promotes dysplasia: claudin-1 transgenic mice show exacerbated colonic inflammation, impaired mucosal healing, and a higher incidence of tumors[39][40]. Mechanistically, claudin-1 appears to drive EMT and stemness in colon cells by activating ERK, SRC and Notch signaling, and by coordinating with β-catenin to alter gene expression[11][97]. A study of human CRC found nuclear and cytosolic accumulation of claudin-1 in invasive fronts of tumors, often alongside nuclear β-catenin, suggesting claudin-1 might physically or functionally interact with the Wnt pathway[11][98]. Clinically, high claudin-1 in colorectal tumors has been associated with increased invasion and metastasis[99], yet intriguingly, among patients with resected stage II colon cancer, those whose tumors had lost claudin-1 had significantly worse prognosis (higher recurrence and mortality)[100][101]. This implies that claudin-1's role is context-specific: while its overexpression can initiate malignant traits, once a cancer is established, a complete loss of claudin-1 may confer additional aggressiveness (possibly by enabling full EMT and detachment of cells).

Claudin-2 is another key player in colon cancer, especially in colitis-associated cancer (CAC). It is uniformly upregulated in IBD tissues and early dysplastic lesions[24][25]. In a mouse model, targeted colonic overexpression of claudin-2 did not increase tumor incidence per se; in fact it made mice more resistant to DSS colitis, by promoting mucosal healing (through enhanced epithelial proliferation and regulatory immune responses)[102][103]. However, in the setting of existing neoplasia, claudin-2 fuels tumor growth: colonic organoid studies showed claudin-2 drives cancer cell proliferation via EGFR/MEK/ERK signaling[82][71].

Moreover, claudin-2 expression is linked to a cancer stem-like phenotype. One group reported that claudin-2 promotes the self-renewal of colon cancer stem cells, supporting tumor initiation and chemoresistance[104]. Thus, claudin-2 may protect colonic epithelium in inflammatory conditions (by keeping the barrier leaky enough to not overburden the epithelium with cytokine stress, and by activating pro-healing pathways), but in cancer, the same molecule can increase the tumor's robustness and survival.

A consistent finding across many CRC studies is the loss of claudin-7 as tumors progress. Claudin-7 is highly expressed in normal colon (particularly on the lateral membrane and TJs of absorptive enterocytes) and in early adenomas, but is frequently reduced or absent in colorectal carcinomas[105][106]. Hypermethylation of the CLDN7 gene promoter has been documented in colon adenomas and cancers, explaining its transcriptional silencing[107][108]. Loss of claudin-7 is functionally important: claudin-7 knockout mice spontaneously develop colonic inflammation and tumors, due to barrier defects that allow bacterial products to provoke chronic inflammation, and due to destabilization of the claudin-7/claudin-1/integrin complex which impairs epithelial adhesion[109][110]. In cell culture, claudin-7 re-introduction can suppress colon cancer cell motility and EMT by inhibiting SRC and ERK signaling[34][111]. However, akin to its dual nature in esophageal cancer, claudin-7 in colon cancer might have a pro-tumor angle too: as noted, claudin-7 can partner with EpCAM in EpCAM-high cancer stem cells to form a transcriptional co-activator driving EMT and metastasis[112]. It is possible that claudin-7's location and binding partners dictate the outcome – when at the membrane with integrins, it is tumor-suppressive, but when engaged in a complex with EpCAM and β-catenin in the nucleus of a stem-like cell, it might promote tumor progression. This nuance is an active area of investigation.

Other claudins in CRC show varied changes. Claudin-3 and claudin-4 are frequently elevated in primary colorectal adenocarcinomas compared to normal mucosa[113]. They contribute to the well-known "claudin-high" phenotype seen in certain molecular subtypes of CRC (often MSI-low, β-catenin active tumors). High claudin-3/4 might confer some cohesive advantage to tumor cells (holding cells together in glands) and also interact with growth signals; for instance, claudin-3 deficiency in mice led to activation of IL6/Stat3 and Wnt signaling and more rapid tumor formation[114][76], whereas overexpression of claudin-3 in a colon cancer cell line enhanced malignancy via EGFR and PI3K/Akt activation[76][115]. Claudin-5 is not normally prominent in colon epithelial cells, but it can be induced in CRC by factors from tumor-infiltrating lymphocytes (through Notch signaling)[116][117]. There is evidence that claudin-5 upregulation in tumor epithelia might initially serve a homeostatic function to maintain some differentiation; however, if claudin-5 is subsequently downregulated (either in tumor cells or local endothelium via VEGF), it could facilitate metastasis by increasing vascular permeability[118][119]. Claudin-8 is downregulated in IBD and remains low in many CRCs[120][121]. Since claudin-8 normally helps seal the colonic TJ, its loss could increase

leakiness and allow growth factors or antigens to permeate the tumor microenvironment. Low claudin-8 has been linked with a more mesenchymal, invasive tumor phenotype (though data in CRC specifically are sparse)[121]. Claudin-12 is reportedly upregulated in sporadic colorectal adenocarcinomas[122], but its role is not understood. Given claudin-12's involvement in calcium flux, one wonders if altering calcium homeostasis in tumor cells (via claudin-12 upregulation) affects proliferation or differentiation. Finally, claudin-23 is often downregulated in colon cancer, especially those arising from inflammatory backgrounds[123][73]. This is consistent with the observation that CLDN23 is a gene target of gut barrier-promoting pathways and is lost when inflammation triggers DNA methylation or transcriptional repression. Low claudin-23 in colon tumors might contribute to the disorganized junctions observed in poorly differentiated or inflamed cancers, potentially allowing more immune cell infiltration (which can either attack the tumor or, paradoxically, provide growth factors for it).

From a clinical perspective, claudin expression patterns might help in stratifying CRC or guiding therapy. For example, claudin-1 has been explored as a therapeutic target: a recent study demonstrated that an anti-claudin-1 antibody could suppress growth of claudin-1^high colon tumors in mice, especially those with active Wnt signaling[124][100]. Conversely, as mentioned, patients with claudin-1^low tumors have poorer outcomes, so assessing CLDN1 by immunohistochemistry could have prognostic value[101]. Claudin-2 might serve as a marker for colitis-driven neoplasia; it tends to be elevated in early colitis-associated dysplasia[125] and could identify patients at risk. Claudin-18.2, while not normally in colon, can appear in some colon cancers (particularly those with gastric differentiation or pancreatic metastases); its presence would open up the possibility of anti-CLDN18.2 therapy, though primary CRC expression of CLDN18.2 is uncommon. On the diagnostic front, pathologists sometimes use claudin immunostains to determine tumor origin: for instance, claudin-4 is positive in virtually all adenocarcinomas (including CRC) but negative in mesotheliomas, so a metastatic colon cancer in peritoneum can be confirmed with claudin-4 staining[126][127]. In summary, colorectal cancers illustrate both the loss-of-function (barrier weakening) and gain-of-function (oncogenic signaling) aspects of claudin dysregulation, and ongoing research is aiming to translate these insights into biomarkers and targeted treatments.

Liver (Hepatocellular Carcinoma and Cirrhosis)

Hepatocytes in the liver are connected by tight junctions as part of the bile canalicular apparatus, though the composition of liver TJs differs from intestinal epithelia. Key claudins in hepatocyte TJs include claudin-1 and claudin-2, with smaller contributions from claudin-3, -5, and -7 in bile duct epithelium and vasculature. In chronic liver diseases that lead to cirrhosis (fibrosis of the liver), claudin expression is altered both in hepatocytes and cholangiocytes. Immunohistochemical studies on cirrhotic liver tissues have shown that

claudin-1 and claudin-7 are upregulated in cirrhotic hepatocytes compared to normal liver[128]. Moreover, if hepatocellular carcinoma (HCC) arises within a cirrhotic liver, those tumor cells exhibit even higher claudin-1/7 levels[128]. This suggests that claudin-1 and -7 may be induced during the regenerative and fibrogenic processes of cirrhosis, possibly as hepatocytes attempt to re-establish cell adhesion in a changing matrix. Claudin-4 is also elevated in cirrhosis, especially in areas of active fibrosis – a study found that claudin-4 (and claudin-7) levels correlated with the grade of fibrosis in chronic hepatitis/cirrhosis, independent of inflammation[129]. One hypothesis is that hepatic stellate cells (the fibrogenic cells of the liver) or inflammatory cytokines (like TGF-β) induce claudin-4/7 in hepatocytes during fibrosis, and these claudins might influence the epithelial-to-mesenchymal transitions that hepatocytes undergo in cirrhosis. Interestingly, claudin-5, which normally is an endothelial TJ protein, can be aberrantly expressed in cholangiocytes in primary biliary cirrhosis, potentially affecting the permeability of biliary epithelium. However, more data exist for claudin-1: it has a recognized role in liver fibrosis beyond the tight junction. A recent study demonstrated that non-junctional claudin-1 in hepatic stellate cells can activate TGF-β and Wnt pathways, contributing to fibrotic progression[130][131]. Blocking claudin-1 with a monoclonal antibody in fibrotic mouse models not only reduced fibrosis but unexpectedly also suppressed HCC development, highlighting claudin-1's fibrogenic and carcinogenic signaling roles[132][133].

In hepatocellular carcinoma, claudin expression patterns are heterogeneous and can correlate with tumor behavior. Some HCCs (particularly well-differentiated tumors) maintain high levels of claudin-1 at their cell–cell borders, essentially retaining some hepatocyte phenotype. In contrast, more poorly differentiated HCCs often show loss of claudin-1 expression[134]. This loss is associated with vascular invasion and metastasis; essentially, when HCC cells downregulate claudin-1 and other junction proteins, they can more easily dissociate and spread. Clinical studies have found that reduced claudin-1 in HCC tissue is linked to worse overall survival[134]. One analysis reported that HCC patients whose tumors had low claudin-1 had significantly shorter survival, whereas those with high claudin-1 had a more favorable prognosis[134]. This might appear contradictory to the idea of claudin-1 as an oncogene in colon cancer, but it underscores tissue context: in liver, claudin-1 is part of the epithelial architecture keeping cells in a differentiated, less invasive state, so its loss denotes a switch to a malignant phenotype. Conversely, some studies suggest very high claudin-1 in HCC can also be problematic – for example, claudin-1 overexpression was found to enhance invasive activity in an in vitro model by promoting MMP2-mediated matrix degradation[85] (that particular study was in oral SCC cells, but similar principles may apply in HCC). It's possible that an optimal range of claudin-1 is needed: too much might activate certain pathways, but too little definitely removes restraints on invasion. Other claudins in HCC are less studied; claudin-9 and -6 are expressed in some hepatocytes (and recall, claudin-6/9 are HCV receptors). HCC arising in an HCV-infected liver might therefore have had unique

claudin perturbations from the viral entry process. Occludin and claudin-12 have been reported to decrease in HCC, consistent with a general trend of TJ downregulation during hepatocyte transformation.

Another type of liver tumor, cholangiocarcinoma (bile duct cancer), also involves claudin changes. Cholangiocytes normally express claudin-3, -4, -7, among others; cholangiocarcinomas often show strong claudin-4 (similar to many adenocarcinomas) and sometimes claudin-18 if they arise near the hepato-pancreatic region (since pancreatic ducts and bile ducts share some claudin profile). However, detailed data on claudins in cholangiocarcinoma are limited. Clinically, claudin expression might help differentiate HCC from metastatic adenocarcinoma to the liver. For instance, claudin-4 is usually negative in HCC (since hepatocytes don't express claudin-4), whereas it's positive in most adenocarcinomas (like colorectal or pancreatic metastases). Pathologists can use a claudin-4 stain to support a diagnosis: a liver tumor negative for claudin-4 and positive for HepPar1 is likely an HCC, while a claudin-4 positive tumor in liver suggests a metastasis[135].

Finally, we must note the interplay with Hepatitis C virus (HCV) – an infectious cause of liver disease that can lead to cirrhosis and HCC. HCV uses claudin-1 (and claudin-6/9) as essential co-receptors to enter hepatocytes[42][43]. This means claudin-1 is not only a structural protein but also part of the viral life cycle in HCV infection. Chronic HCV has been reported to increase claudin-1 expression on hepatocytes, potentially making the cells more permissive to infection spread[57]. Blocking claudin-1 with antibodies can inhibit HCV entry in vitro[136], and such strategies are being considered as antiviral adjuncts. Moreover, HCV core and NS proteins can alter TJ assembly – some studies found HCV infection leads to mislocalization of occludin and claudin-1, which might contribute to the barrier dysfunction seen in HCV-infected livers (this could allow immune cells greater access or foster a pro-fibrotic microenvironment). The HCV-claudin connection has also fueled interest in anti-claudin-1 therapeutics; as mentioned, an antibody developed for its antifibrotic and antitumor effect in liver (by Alentis Therapeutics) was partly motivated by earlier work showing that anti-claudin-1 could block HCV entry[130]. In summary, liver pathologies highlight claudin-1 as a central figure – involved in viral infection, fibrogenesis, and carcinogenesis – with claudin-4, -7 contributing to fibrotic change, and claudin loss being a marker of aggressive HCC.

Pancreas (Pancreatic Cancer and Cystic Neoplasms)

The pancreas, specifically the pancreatic ductal epithelium, shares some claudin features with the biliary tract and intestine. Normal pancreatic ducts express claudin-3, -4, -7, -18 (the latter because pancreatic ducts and acini have some gastric differentiation traits, explaining claudin-18.2 expression). In the context of pancreatic ductal adenocarcinoma (PDAC), claudin dysregulation is pronounced and may contribute to the notorious treatment resistance and invasive nature of this cancer. One of the most consistently overexpressed claudins

in PDAC is claudin-4. Nearly all PDAC tumors show strong claudin-4 membrane positivity[137][138] – so much so that claudin-4 has been considered a potential universal marker and therapeutic target for pancreatic cancer. Functional studies indicated that claudin-4 might promote PDAC cell survival and chemo-resistance by activating downstream signals (e.g. via PI3K/Akt). However, claudin-4's primary impact might be on the barrier between tumor cells: PDAC cells form glandular structures that are often sealed off, creating high intratumoral pressure and poor drug penetration. High claudin-4 could worsen this by tightening cell junctions, contributing to the fibrotic tumor's ability to exclude chemotherapeutics. Indeed, preclinical work has exploited claudin-4's presence by using CPE peptide to selectively lyse pancreatic cancer cells or as a carrier to deliver nanoparticles[139][138]. Encouragingly, toxin molecules based on Clostridium perfringens enterotoxin (which binds claudin-4) have shown potent killing of claudin-4^+ PDAC cells in mice[137][44], underscoring how overexpression of a normally innocuous TJ protein can become a cancer vulnerability.

Claudin-18.2 is another notable claudin in pancreatic cancer. While normal pancreas has low claudin-18, it is found in a significant subset of PDACs – particularly those with gastric-type differentiation or certain molecular subtypes[54][55]. A recent analysis detected claudin-18.2 in roughly 20–30% of PDAC patient samples, and it tended to be focal but intense in those tumors[54]. This ectopic expression is clinically meaningful because it opens the door for claudin-18.2 targeted therapy (e.g. the monoclonal antibody zolbetuximab, discussed later, is being tested in pancreatic cancer after successes in gastric cancer). Biologically, the presence of claudin-18.2 on pancreatic cancer cells suggests some transdifferentiation or lineage ambiguity, as if those cancer cells hijack gastric mucosa traits. It might also confer a growth advantage: claudin-18 knockdown in PDAC cell lines reportedly reduced their invasive capability, hinting that claudin-18 could facilitate cell motility or interactions with the stroma (perhaps via YAP signaling which was seen in claudin-18 KO mice stomach tumors[53]).

In contrast to claudin-4 and -18, claudin-1 is typically downregulated in PDAC. During the progression from pancreatic intraepithelial neoplasia (PanIN, the precursor lesions) to invasive carcinoma, there is a noted decrease in claudin-1 expression[140]. Hyperplastic and early neoplastic pancreatic ducts might express claudin-1, but as they become fully malignant, claudin-1 is often lost[140]. This pattern aligns with an EMT transition: claudin-1 loss could free cells from strong adhesion, enabling dissemination. Consistently, lower claudin-1 in PDAC correlates with higher grade and worse outcomes in some studies. Conversely, claudin-2 and claudin-3 can be upregulated in PDAC, although data are variable. A unique source of insight is the study of pancreatic cystic neoplasms like intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), which can progress to cancer. In these lesions, claudin expression changes with dysplastic grade. For example, claudin-2 and claudin-4 are elevated in low-grade IPMN/MCN lesions and further increase with high-grade dysplasia, whereas claudin-1 tends to decrease with higher grade[141][142]. One

study found that the highest claudin-2 levels were in IPMN adenomas, but claudin-2 declined somewhat as lesions became invasive carcinoma[142]. Claudin-4 showed the opposite: relatively low in benign cysts and progressively higher in borderline, carcinoma in situ, and invasive carcinoma arising from IPMN[142]. Additionally, claudin-18 was detected strongly in the poorly differentiated components of IPMN-associated carcinomas, whereas mild dysplasia had weaker claudin-18[143]. These patterns again imply that claudin-4 and -18 are associated with the malignant transformation in the pancreas, whereas claudin-1 and -2 might be more involved in early neoplastic changes (or even play protective roles initially).

Clinically, claudins in PDAC have potential applications. Imaging agents that target claudin-4 are being explored to aid in the detection of pancreatic cancer, which is often challenging to visualize. For instance, radiolabeled peptides derived from the C-terminal fragment of CPE (cCPE) can bind claudin-4 in PDAC, allowing SPECT/PET imaging of tumors[144][145]. In a preclinical mouse model, a PET tracer targeting claudin-4 successfully highlighted PDAC lesions against background tissue[145]. Therapeutically, besides toxin-based approaches, claudin-4 could be used to selectively deliver drugs to PDAC (for example, coupling a chemotherapy payload to a claudin-4-binding moiety). Claudin-18.2 is already a target in trials; PDAC patients whose tumors express claudin-18.2 may benefit from monoclonal antibody therapy similar to gastric cancer patients[146][95]. The challenge is that PDAC is highly heterogeneous, and only a subset will express a given claudin strongly. Still, the near-universal presence of claudin-4 in PDAC is a strong rationale for claudin-4–directed strategies, which could include immunotherapy (if claudin-4 peptides can be presented by MHC, T cells might target claudin-4^high cells) or CAR-T cells engineered against a claudin-4-derived epitope (though specificity is a concern given normal tissue expression).

In summary, across pancreatic cancers, claudin-4 stands out as a consistently upregulated protein that contributes to the unique physiology of PDAC, claudin-18.2 appears as an aberrant but targetable molecule in a fraction of tumors, and loss of claudin-1 accompanies the EMT and invasiveness that make pancreatic cancer so deadly. These insights are driving innovative diagnostic and therapeutic approaches for this lethal disease.

Claudins in Inflammatory and Immune-Mediated GI Diseases

Tight junction defects are a well-recognized feature of inflammatory disorders of the GI tract. Dysregulation of claudins in these conditions often leads to a “leaky gut” barrier, which exacerbates inflammation by allowing luminal antigens and microbes to penetrate the epithelium[147][70]. At the same time, inflammatory cytokines released in the mucosa further modulate claudin expression in a vicious cycle. Here we discuss claudin alterations in key immune-mediated GI diseases, including inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), celiac disease, and eosinophilic esophagitis, and how these contribute to pathogenesis.

Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

Inflammatory bowel diseases (IBD) are chronic relapsing disorders characterized by intestinal inflammation – typically transmural and patchy in Crohn's disease (CD) and superficial continuous colitis in ulcerative colitis (UC). A central element in IBD pathogenesis is disruption of the intestinal epithelial barrier. Even in non-inflamed relatives of IBD patients, subtle barrier defects can exist, suggesting a predisposing trait. Claudin abnormalities represent a fundamental part of this barrier dysfunction. Both UC and CD patients have been documented to display altered expression and distribution of multiple claudins in the intestinal epithelium[148][28]. Biopsy studies show that during active inflammation, claudin-1, -2, -3, and -4 are upregulated in the colonic epithelium (particularly in ulcerative colitis) compared to healthy controls[96]. However, these claudins may not be correctly localized at the tight junction; for example, claudin-2 can mislocalize to the cytoplasm and claudin-3/4 can be discontinuous at cell borders under inflammatory stress[28][114]. Notably, claudin-8 and claudin-7 are conversely downregulated in active IBD. UC specimens show significantly reduced claudin-7 at TJs, which correlates with severity[149], and active CD is associated with loss of claudin-8 from the junctions (with remaining claudin-8 found in the cytoplasm)[30]. This shift – an increase in claudin-2 (pore-former) and decrease in claudin-7/8 (sealers) – leads to a net increase in intestinal permeability. Electron microscopy of IBD colon tissue confirms loosened tight junction strands and dilated intercellular spaces[150].

Functionally, claudin changes in IBD have direct consequences. Upregulated claudin-2 contributes to the "leaky gut" phenomenon by forming cation pores that allow Na^+ and water flux into the lumen, which can manifest as diarrhea. Indeed, claudin-2 is a mediator of the high paracellular water loss in active UC (excessive claudin-2 channels create small leaks that drive fluid secretion)[151][152]. Yet claudin-2's role is complex: beyond causing leakiness, it also triggers protective responses. As mentioned earlier, claudin-2 overexpression in mice dampened colitis severity by enhancing epithelial proliferation and inducing immune tolerance (increasing regulatory T-cells and anti-inflammatory cytokines)[103][153]. This suggests claudin-2 might be an acute-phase reactant of the epithelium – it opens the floodgates slightly, possibly to flush the lumen or to allow sampling of luminal content to immune cells, which paradoxically can help resolve inflammation by preventing deep bacterial invasion (a controlled leak might be better than uncontrolled breaches). In the long run, though, chronically high claudin-2 can promote dysplasia by facilitating continual epithelial turnover and pro-tumor signals[82][71].

Claudin-1 is consistently elevated in IBD epithelia, especially in UC. It localizes not only to TJs but also lateral membranes of crypt cells in IBD tissue[148]. An intriguing clinical correlate is that some patients with IBS (irritable bowel syndrome) with post-inflammatory features have reduced claudin-1 associated with increased

gut permeability and symptoms of diarrhea[148][154]. This underscores the link between claudins and intestinal functional integrity. In IBD, TNF-α is abundant and has been shown to increase claudin-1 expression via NF-κB activation[148][155]. While one might expect a tight junction protein to be beneficial, the timing and context of claudin-1 upregulation seem pathogenic: transgenic mice with intestinal claudin-1 overexpression suffered worse colitis with delayed mucosal healing[156]. The reason is that excess claudin-1 locked the epithelium in an inflamed, proliferative state by activating ERK and Notch, hindering goblet cell differentiation and proper barrier restoration[156][40]. Thus in IBD, claudin-1 is part of a feedback loop where inflammation boosts claudin-1, and claudin-1 in turn sustains pathways (like Wnt/β-catenin and Src) that perpetuate inflammation and even prime cells for neoplastic changes[11][99].

Claudin-3 and claudin-4 are moderately increased in IBD as well, but pro-inflammatory cytokines (like IL-1β, IFN-γ) cause their mislocalization and phosphorylation (via MLCK), so the functional tight junction pool is reduced[114][157]. Animal studies support their importance: claudin-3 knockout mice have more permeable colons and when challenged with inflammatory stimuli, they develop worse colitis and even faster tumorigenesis due to unrestrained STAT3/Wnt signaling in the epithelium[114][76]. This indicates claudin-3 normally acts to keep inflammatory signaling in check (perhaps by maintaining the spatial segregation of receptors or preventing bacterial intrusion). Meanwhile, claudin-7 loss, as occurs in active UC, directly causes enhanced uptake of luminal toxins and bacteria. Claudin-7–deficient mice demonstrate increased translocation of bacterial metabolites, which drives colonic inflammation through MMP activation and NF-κB signaling[149][158]. Additionally, the breakdown of the claudin-7/integrin complex in these mice impairs wound healing and barrier restitution[158][159]. Clinically, this could correspond to UC flares where mucosal healing is poor and ulcers persist. On the flip side, some research suggests that during remission, as inflammation subsides, claudin-7 levels are restored, helping re-establish the barrier.

In summary, IBD features a tight junction remodeling in which claudins are reprogrammed by the inflammatory milieu. The result is a barrier that is patchy and “leaky” in some places (from claudin-2 up, claudin-7/8 down) but compensatorily tighter in others (focal high claudin-1/3/4 that can lead to local epithelial stress). This dysregulation not only contributes to symptoms (diarrhea, increased gut permeability) but also sets the stage for chronic immune activation and even cancer development (CAC). Encouragingly, some treatments can normalize claudin expression: for instance, anti-TNF therapy in Crohn’s has been shown to restore claudin-8 and reduce claudin-2 levels in responders, correlating with improved barrier function. Probiotics have also been observed to increase claudin-3 and claudin-4 expression in experimental colitis, aiding barrier reinforcement[72][160]. Therefore, claudins are potential therapeutic targets or indicators in IBD – either directly (drugs to modulate claudin expression) or indirectly (using claudin levels as biomarkers of mucosal healing). For example, fecal miR-223 (which downregulates claudin-8) could be tracked as a

marker of active inflammation[69], or conversely, rising claudin-7 in biopsy might signal mucosal healing.

Celiac Disease

Celiac disease (CeD) is an autoimmune-mediated enteropathy triggered by gluten in genetically predisposed individuals. A hallmark of active celiac disease is increased intestinal permeability and villous atrophy. Biopsies from patients with active celiac show ultrastructural TJ abnormalities, including shortened TJ strands and greater paracellular space[161]. At the molecular level, several TJ proteins are altered: zonula occludens-1 (ZO-1) is downregulated (but can recover after a gluten-free diet), and claudins are dysregulated. Studies indicate that claudin-2 is upregulated in active celiac disease, whereas claudin-5 is downregulated[162]. Claudin-2's increase is consistent with a leaky, cation-permeable state, contributing to diarrhea and nutrient malabsorption by allowing ions and water to bypass the epithelial cells. Claudin-5, normally an endothelial TJ protein that also provides sealing in epithelia, being reduced suggests compromised tightness especially in the deeper layers of mucosa and perhaps subepithelial capillaries. Claudin-3 and -4 in standard (non-refractory) celiac disease are typically preserved or even slightly upregulated, indicating that the epithelial cells attempt to maintain barrier function via these claudins[162]. In fact, one study found that claudin-4 was "normally expressed" in celiac patients adhering to gluten-free diet, meaning it remained at the junctions as in healthy controls[162].

The situation changes in refractory celiac disease (RCD), a rare condition where the disease persists or recurs despite a strict gluten-free diet. In RCD, the mucosa is chronically inflamed and often undergoing clonal expansion of aberrant lymphocytes. Importantly, claudin-4 becomes downregulated in RCD, both at the protein level and via increased internalization[163]. So whereas regular celiac might have intact claudin-4, refractory celiac loses this key sealing claudin. This likely exacerbates barrier loss, creating a feed-forward loop of antigen permeation and immune stimulation. Additionally, RCD mucosa shows continued high claudin-2 and low claudin-5, indicating a persistent "leaky" profile[163]. The reduction of claudin-4 in RCD is attributed to two mechanisms: diminished synthesis (perhaps due to ongoing inflammation affecting transcription) and heightened endocytosis of claudin-4 from the membrane[163]. Interferon-gamma and IL-6, abundant in celiac lesions, may drive such changes. Another factor in celiac barrier dysfunction is zonulin, a protein that modulates tight junctions. Gluten ingestion triggers zonulin release, which acutely opens tight junctions; this likely affects claudin polymerization. Inhibitors of zonulin (like larazotide acetate) have been shown to prevent tight junction disassembly and are in trials to reduce celiac symptoms by keeping claudins in place.

Clinically, the persistent barrier defect in celiac disease correlates with symptom severity and histologic damage. After 6–12 months of gluten-free diet, most patients restore near-normal claudin distributions

(claudin-2 goes down, claudin-5 and ZO-1 go up, etc.), paralleling mucosal healing[162]. Those who do not normalize (like RCD patients) often continue to have malabsorption and are at risk for complications such as ulcerative jejunitis or lymphoma. Therefore, assessing claudin-2 or claudin-4 levels in follow-up biopsies could potentially serve as a biomarker of complete mucosal recovery or ongoing microscopic damage. From a mechanistic standpoint, therapies that could boost claudin-5 or claudin-4 expression in celiac enterocytes might improve barrier function and tolerance to minor dietary transgressions. For instance, some evidence suggests IL-10 and certain growth factors can strengthen tight junctions; these could be explored to see if they upregulate sealing claudins in celiac mucosa.

In essence, celiac disease underscores how a primary immune trigger (gluten) leads to cytokine cascades that alter claudin expression (more claudin-2, less claudin-5/ZO-1; claudin-4 intact unless refractory), resulting in a compromised barrier that furthers immune exposure to gluten peptides. Managing celiac might thus require not just immunosuppression or dietary exclusion, but potentially also barrier reinforcement strategies focusing on claudins.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is an allergic inflammatory condition of the esophagus characterized by eosinophil-predominant inflammation and Th2 cytokines (like IL-5, IL-13). Patients experience dysphagia and food impaction due to esophageal ring formation and strictures over time. A recurring theme in EoE pathogenesis is epithelial barrier dysfunction. Endoscopically, EoE can show mucosal friability and tears with minimal trauma, indicating a weak epithelial integrity. At the molecular level, allergic inflammation in EoE leads to changes in junctional proteins reminiscent of other atopic conditions (such as filaggrin loss in atopic dermatitis). Biopsies of active EoE have demonstrated marked decreases in claudin-1 and E-cadherin expression in the esophageal epithelium[67][164]. Claudin-1, which is normally present in the superficial squamous layers of the esophagus (as dots/lines in immunostaining[165]), becomes patchy or undetectable in many EoE patients. This reduction is partly driven by the cytokine milieu: IL-13, a signature Th2 cytokine elevated in EoE, was shown to directly reduce claudin-1 transcription in esophageal epithelial cells by mechanisms involving STAT6 signaling and possibly secondary mediators. One study identified HIF-1α (hypoxia-inducible factor) as an upstream regulator that normally helps maintain claudin-1; in EoE, HIF-1α can be dysregulated, leading to a drop in claudin-1 and impaired barrier[166][167].

Another prominent change is in claudin-7. TGF-β1, a fibrosis-related cytokine elevated in chronic EoE, can attenuate esophageal barrier function by specifically downregulating claudin-7[168]. In vitro, treating esophageal epithelial cells with TGF-β1 diminished claudin-7 levels and was associated with increased permeability, an effect reversible by TGF-β inhibitors[168]. Additionally, microRNA-155 (induced by IL-13

and perhaps by epithelial hypoxia in EoE) targets CLDN7 mRNA, further contributing to claudin-7 suppression[66][169]. The net effect is that the esophageal epithelium in EoE loses important tight junction components (claudin-1, claudin-7) and adhesion molecules, leading to dilated intercellular spaces. This has been observed on electron microscopy in EoE patients: intercellular space dilation is a histologic marker of barrier defect and correlates with symptoms like sensitivity to acid and food antigens.

Therapeutically, topical steroids (swallowed fluticasone or budesonide) used in EoE can help restore barrier proteins. A study comparing EoE patients before and after steroid treatment found that responders had increases in claudin-1 and filaggrin expression post-therapy[170][171]. This likely underlies the healing of mucosa and symptom improvement. Likewise, dietary therapy that removes food allergens reduces IL-13 levels in tissue and allows re-expression of claudin-1/7 over weeks to months.

A fascinating aspect of EoE is that barrier dysfunction can amplify allergic sensitization: a leaky esophagus may allow more allergen penetration, leading to localized IgE or Th2 responses, which then further worsen the barrier – a classic atopic cycle. Indeed, some propose using barrier protectants (like bioadhesive slurries containing sucralfate or novel tight junction enhancers) as adjuncts in EoE to break this cycle.

In summary, eosinophilic esophagitis exemplifies an immune-mediated disease where loss of claudin integrity (notably claudin-1 and -7) is central to pathophysiology. Restoring these claudins through anti-inflammatory treatments correlates with mucosal healing. EoE thereby reinforces the concept seen across GI inflammatory diseases: cytokine-driven claudin dysregulation leads to barrier defects that perpetuate disease, and interventions that normalize claudins can contribute to remission.

Claudins in Infectious and Metabolic GI Conditions

Infectious and metabolic disorders of the GI system often involve epithelial injury and fibrosis, with tight junction abnormalities playing contributory roles. We focus here on select examples: the role of claudins in viral infections (particularly hepatitis C in the liver), and in metabolic/fibrotic conditions such as non-alcoholic fatty liver disease (NAFLD) and GI fibrosis, as well as brief notes on how certain bacteria and parasites can target claudins.

Hepatitis C Virus (HCV) and Liver Fibrosis: HCV provides a textbook case of a pathogen exploiting claudins. As noted earlier, claudin-1 is an essential coreceptor for HCV entry into hepatocytes[42][43]. It forms a receptor complex with CD81, scavenger receptor-BI, and occludin on the hepatocyte surface. Interestingly, claudin-1 in this context is acting in a non-junctional capacity – it must be present in diffusely accessible membrane areas for the virus to dock, not locked away in tight junctions. HCV infection can increase the surface availability of claudin-1 by disrupting tight junctions: some HCV proteins (like NS5A) interact with TJ scaffolds and may cause mislocalization of claudin-1. This is believed to enhance viral spread within the liver lobule. Additionally, HCV can induce claudin-1 expression in hepatocytes and even in lymphocytes

(HCV can infect B cells, which interestingly express claudin-6 and -9 but not much claudin-1)[172][57]. Given claudin-1's crucial role, it has been a target for antiviral strategies. Monoclonal antibodies against claudin-1 have been shown to block HCV entry in cell culture and small animal models[173]. While direct anti-claudin therapy for HCV is not in clinical use (due to the success of direct-acting antivirals), these studies proved the concept that interfering with a tight junction protein can thwart a virus.

Chronic HCV infection leads to progressive liver fibrosis and cirrhosis. As part of this, the liver's epithelial cells (hepatocytes and cholangiocytes) and endothelial cells undergo changes, and the activation of stellate cells (myofibroblasts) drives scar deposition. Claudins are involved in this fibrotic response. In chronic hepatitis (whether HCV or other causes), claudin-1 and -7 are typically upregulated in the hepatocytes at the interface of fibrotic septa, as mentioned before[128]. This may reflect a partial EMT state or a regenerative change. More directly, a recent preclinical study identified that claudin-1 expressed in hepatic stellate cells (HSCs) is a driver of fibrosis: claudin-1 in HSCs can localize to the plasma membrane outside of junctions and form signaling hubs that activate the PDGF and TGF-β pathways, promoting HSC proliferation and matrix production[174][132]. When researchers treated fibrotic mice with an anti-claudin-1 antibody, they observed not only reduced fibrosis (less collagen deposition) but also a reprogramming of the tumor microenvironment that suppressed the emergence of HCC nodules[132][130]. This implies that claudin-1 is integral to the fibrosis-cancer axis in liver disease. Why would claudin-1 be on HSCs? It's thought that during transdifferentiation from a quiescent vitamin A-storing cell to a myofibroblast, HSCs start expressing epithelial markers, including claudins – possibly capturing signals from damaged epithelium or forming contacts with hepatocytes.

In metabolic liver disease like NAFLD/NASH (non-alcoholic steatohepatitis), there is less data on claudins, but one could extrapolate that similar patterns occur: as inflammation and ballooning degeneration of hepatocytes happen, tight junctions likely weaken. Occludin and claudin-5 might reduce in liver sinusoidal endothelial cells (contributing to the capillarization of sinusoids in NASH). If we consider gut-liver axis, increased intestinal permeability (with claudin-2 up, etc., in obesity and NASH) allows LPS and microbial products to reach the liver and trigger TLR-mediated inflammation – a recognized component of NASH pathogenesis[175]. Indeed, metabolic syndrome is associated with a "leaky gut," where Zonulin levels are high and claudin-1 expression may be patchy in the colon, linking metabolic changes to claudin dysfunction indirectly. Treatment of NASH with gut-targeted approaches (like probiotics or gut permeability reducers) is being researched, with claudins in mind as endpoints.

Other Infections: Many GI pathogens target tight junctions as part of their virulence strategy. For example, Clostridium perfringens (food poisoning bacterium) produces enterotoxin (CPE) that binds claudin-3 and -4 on enterocytes, causing cell lysis and leading to the symptoms of cramping and diarrhea[44]. In a way, CPE

uses claudins as a Trojan horse: claudin-4's normal role is to keep the gut epithelium tight, yet it becomes the channel for a toxin that blows the cells apart. Some enteric viruses (like coxsackievirus and reovirus) interact with JAM and claudin proteins to breach the gut lining, though claudins are less commonly their receptor compared to other molecules. Helicobacter pylori, in the stomach, doesn't directly bind claudins but leads to their dysregulation: H. pylori's CagA protein, once injected into gastric epithelial cells, can cause delocalization of ZO-1 and claudin-4, contributing to the disrupted gastric barrier in infection. This may be one reason why H. pylori gastritis can sometimes lead to increased transepithelial leak and contribute to peptic ulcer risk.

In the intestines, enteropathogenic E. coli (EPEC) attach to the apical surface and inject effectors that lead to dephosphorylation and removal of claudin-1 and occludin from TJs, increasing permeability and causing diarrhea. Vibrio cholerae produces zonula occludens toxin (ZOT) which, as the name suggests, targets the tight junction protein ZO-1 and indirectly affects claudins – this toxin loosens TJs to allow paracellular water efflux adding to secretory diarrhea. Although these pathogens may not specifically upregulate or downregulate a claudin gene, they manipulate claudin localization and thus function.

A unique parasite example: Giardia lamblia infection of the small intestine causes villous atrophy and barrier dysfunction; one mechanism is the parasite releasing proteases that cleave claudin-1 and claudin-4 extracellular domains, weakening the junctions. Similarly, Cryptosporidium adheres to the brush border and its presence correlates with reduced claudin-4 expression in infected intestinal segments.

Fibrosis and Strictures in the GI Tract

Apart from the liver, fibrosis can occur in Crohn's disease (intestinal strictures) and in radiation enteritis or systemic sclerosis affecting the gut. While fibroblasts create the collagen, epithelial-mesenchymal transition (EMT) of some epithelial cells can contribute. Claudin loss (especially claudin-1 and -7) is a signature of EMT. For instance, in Crohn's strictures, areas of active fibrogenesis have epithelial cells with low claudin-1 and -5, suggesting partial EMT might provide fibroblast-like cells that secrete matrix. Targeting claudins to prevent EMT (like preserving claudin-1 expression) might conceptually reduce fibrosis.

In summation, infectious and metabolic conditions exploit claudins in various ways: viruses use them as receptors, bacteria and parasites disable them to invade or cause disease, and chronic metabolic inflammation alters them, contributing to barrier defects that propagate disease.

Claudins in Barrier Dysfunction Disorders (e.g., GERD)

"Barrier-related" GI disorders refer to conditions where the primary issue is a compromised epithelial barrier without a singular infectious or immune cause. The classic example is gastroesophageal reflux disease

(GERD), where acid and bile from the stomach reflux into the esophagus, injuring the squamous epithelium. While GERD is mainly due to mechanical failure of the lower esophageal sphincter, the severity of mucosal damage and symptoms also depends on the integrity of the esophageal epithelial barrier. Recent research has highlighted that tight junctions in the esophagus are dynamic and can be impaired by acid exposure. Biopsies from GERD patients show ultrastructural evidence of widened intercellular spaces (dilated intercellular spaces are a microscopic hallmark of GERD-related esophagitis)[176][177], indicating TJ disruption. At the protein level, claudin-3 and claudin-4 normally present in superficial layers of squamous epithelium appear fragmented or reduced after repeated acid exposure[165][178]. A study by Kandulski et al. found that in patients with erosive reflux disease (ERD), claudin-1 and claudin-2 transcripts were upregulated 2–6 fold compared to controls[150][179]. Interestingly, this upregulation was significant in ERD (visible mucosal injury) but not in non-erosive reflux (NERD)[179]. On protein level, claudin-1 was detected more intensely in basal layers of ERD mucosa, and claudin-2 – which is usually not found in healthy esophageal squames – became expressed in GERD epithelium[180]. Despite this increase, the barrier remains weak, which is reflected by the lack of correlation between claudin expression and histological severity (basal cell hyperplasia, etc.)[179]. The authors concluded that while claudin-1/2 are upregulated (perhaps as a compensatory or inflammatory response), they alone do not prevent acid permeation.

More direct evidence of claudin involvement comes from interventional studies. An intriguing therapeutic trial is examining whether enhancing claudin-4 expression in the esophagus can improve GERD outcomes[181][126]. Quercetin, a flavonoid, was found in animal models to increase claudin-4 expression in the esophagus and improve barrier function. A clinical trial is underway to see if oral quercetin can raise esophageal claudin-4 levels and reduce GERD symptoms[181][182]. The rationale is that claudin-4 is selectively reduced in GERD patients, contributing to a “leaky” esophageal epithelium that permits acid diffusion and nerve activation[183]. By boosting claudin-4, the hope is to seal the tight junctions, making the epithelium more acid-resistant (similar to how claudin-18.2 makes gastric mucosa acid-resistant).

Another barrier component in GERD is claudin-7. Though not as studied as claudin-4, preliminary data suggest chronic reflux can decrease claudin-7 at esophageal cell borders, somewhat paralleling what is seen in EoE (since GERD can also have a minor inflammatory component). Also, E-cadherin (an adherens junction protein) is often cleaved in GERD; when E-cadherin is disrupted, tight junctions usually follow suit because the overall epithelial integrity is compromised. Indeed, treating GERD patients with proton pump inhibitors not only reduces acid but has been shown to partly restore E-cadherin and claudin localization, thereby improving the epithelial resistance.

Beyond GERD, conditions like non-erosive reflux disease (NERD) and functional heartburn might involve subtle claudin changes. NERD patients can have symptoms without visible erosions, and dilated intercellular

spaces are often their only finding. This suggests a mild drop in claudin function – enough to cause sensory nerve activation (heartburn) but not enough for gross injury. Possibly in NERD, claudin-4 is moderately reduced and claudin-1/2 changes are minimal, hence no erosions but heightened perception.

Finally, although not explicitly requested, one could consider irritable bowel syndrome (IBS) as a functional disorder with barrier aspects. Some IBS-D (diarrhea-predominant) patients have increased intestinal permeability and low-grade mucosal immune activation. They have been found to have lower colonic claudin-1 and occludin expression in some studies[148]. Restoring claudin-1 (for instance with probiotics or butyrate enemas) in such patients is speculated to help symptoms, though evidence is nascent.

In summary, GERD exemplifies a barrier disorder where no overt inflammation is initially present, but physical/chemical injury leads to tight junction disruption. Claudin-4 loss is a key event leading to increased paracellular acid leak which causes pain and mucosal damage[183]. Interventions that enhance barrier claudins are emerging as novel treatments to complement acid suppression. This highlights the principle that augmenting claudin function can be therapeutic, not just in GERD but potentially in any condition where barrier leak is part of the problem.

Clinical Implications of Claudins in GI Diseases

The growing understanding of claudins in GI pathology has begun to translate into clinical applications. Claudins are being explored as diagnostic and prognostic biomarkers and as therapeutic targets or tools in multiple GI conditions. Here we synthesize these implications, highlighting current evidence and future prospects.

The tissue-specific expression of certain claudins provides diagnostic utility in pathology. For instance, Claudin-18.2 is a highly specific marker of gastric lineage, and immunohistochemical staining for claudin-18 can help confirm a gastric origin of a carcinoma or distinguish gastric vs. esophageal vs. pancreatic primary tumors[146]. In diffuse gastric cancer (where traditional markers are scant), a positive claudin-18.2 stain strongly points to gastric signet-ring carcinoma cells. Similarly, claudin-4 is widely expressed by adenocarcinomas of the GI tract (esophageal, colorectal, pancreatic, etc.) but is absent in mesothelial cells – as a result, pathologists utilize claudin-4 staining to differentiate metastatic carcinoma (claudin-4 positive) from malignant mesothelioma in peritoneal biopsies[183][126]. In one series, claudin-4 had near 100% sensitivity for detecting adenocarcinoma cells in ascitic fluid, making it a valuable inclusion in immunocytochemistry panels.

Within tumors, claudin levels can carry prognostic information. For example, as noted, low claudin-1 expression in colon cancer was associated with higher recurrence and worse survival in stage II patients[100][101]. Thus, CLDN1 immunohistochemistry could potentially identify “high-risk” stage II

patients who might benefit from adjuvant therapy even in the absence of other risk factors. In HCC, there are conflicting reports: some indicate loss of claudin-1 portends poor prognosis (due to aggressive, dedifferentiated tumor phenotype)[134], while others suggest high claudin-1 might be worse (if claudin-1 is aiding invasiveness). Regardless, claudin expression profiles are increasingly part of molecular characterizations of tumors. As an example, comprehensive genomic studies of gastric cancer identified a "CLDN-low" subtype (enriched for diffuse type tumors with low claudin and E-cadherin, high immune infiltration), which had distinct outcomes and responses to therapy. In breast cancer too (though outside GI), a "claudin-low" molecular subtype corresponds to a particularly aggressive, EMT-heavy tumor group. These concepts may extend to GI malignancies: a subset of colon cancers could be "claudin-low" (loss of 3,4,7,8) correlating with an immune-rich microenvironment and potentially better response to immunotherapy, whereas "claudin-high" tumors (like many pancreatic and gastric adenocarcinomas that overexpress claudin-3,4,18) might have more immune exclusion but be targetable via those claudins.

In inflammatory diseases, claudins might serve as biomarkers of disease activity. For example, measuring claudin-2 levels in stool or biopsy could reflect intestinal inflammation (since claudin-2 is elevated in active IBD[184]). A study found that patients with UC in endoscopic remission but with persistently high biopsy claudin-2 had a higher chance of microscopic inflammation and earlier relapse[125]. Likewise, urinary excretion of claudin-3 (shed from intestinal cells) has been proposed as a noninvasive marker for gut permeability in GVHD and IBD. In celiac disease, antibody tests (anti-transglutaminase) are primary diagnostics, but in the future, assays that detect changes in claudin expression (or regulators like zonulin) might help monitor mucosal recovery on a gluten-free diet.

Perhaps the most exciting clinical application is the direct targeting of claudins for therapy. One success story is Claudin-18.2 in gastric cancer. Zolbetuximab (formerly known as IMAB362) is a chimeric IgG1 monoclonal antibody against claudin-18.2 that showed positive results in a Phase II trial for advanced gastric/gastroesophageal junction cancer. Patients whose tumors were claudin-18.2 positive and who received zolbetuximab plus chemotherapy had improved response rates, progression-free survival, and overall survival compared to chemo alone[95][185]. Notably, this benefit was significant in those with high claudin-18.2 expression on ≥70% of tumor cells. A subsequent Phase III trial (SPOTLIGHT, reported in late 2022) confirmed that adding zolbetuximab to first-line chemo in claudin-18.2-positive gastric/GEJ cancers significantly prolonged survival. This paves the way for regulatory approval and establishes claudin-18.2 as one of the first tight junction proteins to be successfully drugged in solid tumors. The mechanism of action is mainly antibody-dependent cellular cytotoxicity (ADCC) – immune cells are recruited to kill the claudin-18.2 expressing tumor cell. There is also evidence that binding of the antibody may directly interfere with claudin-18's interactions, but ADCC is primary.

Following on that, claudin-18.2 is being pursued in other GI cancers like pancreatic cancer, where ~20% of patients could benefit. A radiolabeled claudin-18.2 antibody is also being explored for imaging and radioimmunotherapy. Additionally, CAR T-cells targeting claudin-18.2 are in early trials for gastric and pancreatic tumors (the challenge is on-target off-tumor effects on normal gastric mucosa, but some strategies involve regional delivery to mitigate this).

Claudin-4 and claudin-3 are not far behind as targets. While a conventional antibody against claudin-4 might cause toxicity (since claudin-4 is widely expressed in normal tissues), researchers have cleverly leveraged Clostridium perfringens enterotoxin (CPE) which naturally and selectively homes to claudin-3/4. One approach is CPE-based therapy: using either the whole toxin or its binding domain to attack cancer cells. Native CPE is too potent and could cause intestinal perforations, but truncated versions (cCPE) that bind without full pore formation have been used to deliver liposomes or nanoparticles containing chemotherapeutics to claudin-4^+ tumors[139][186]. For example, scientists have conjugated cCPE to PEGylated nanoparticles loaded with drugs, achieving targeted release in pancreatic tumor xenografts with reduced systemic toxicity[139][187]. Another strategy is a CPE suicide gene – a gene therapy where the CPE gene is delivered under a tumor-specific promoter, causing claudin-4-expressing tumor cells to produce CPE and essentially kill themselves and neighboring tumor cells (a bit like a local bomb)[188]. Preclinical results in prostate cancer (claudin-4^+) showed significant tumor ablation with this method[189]. For GI use, one might see this applied in intratumoral injections for pancreatic cancer or peritoneal carcinomatosis where claudin-4 is abundant.

Monoclonal antibodies for other claudins are in development: anti-claudin-1 antibodies have shown promise in a murine HCC model by suppressing tumor growth and even fibrosis[132][130]. A company (Alentis) is developing anti-claudin-1 (called ALE-1 or B3) for liver cancer and fibrosis, with a Phase I trial anticipated. The rationale is that in fibrotic or cirrhotic tissue, claudin-1 is exposed on activated stellate cells and aggressive cancer cells, whereas normal hepatocytes have claudin-1 mostly hidden in tight junctions. The antibody might preferentially bind pathological cells. Early results indeed show it reprograms the tumor microenvironment and reduces collagen deposition[133][174].

In IBD and celiac disease, the therapeutic angle is different: enhancing claudin function to restore the barrier. While we don't yet have drugs that directly upregulate a specific claudin, there are indirect ways. For example, Larazotide acetate is a peptide that modulates tight junctions and prevents excessive opening (initially thought to antagonize zonulin's effect). In trials for celiac disease, larazotide modestly reduced symptoms on gluten exposure, presumably by keeping claudins like claudin-5 and occludin in place at the junction and limiting antigen entry. In IBD, probiotics (like Faecalibacterium prausnitzii) and certain diets (rich in fiber/butyrate) are known to increase claudin-4, -7, and -8 and decrease claudin-2, thereby reinforcing the barrier[175][69].

These could be considered "claudin therapies" in a broad sense. Also, IL-22 is a cytokine that promotes mucosal healing – one of its effects is increasing epithelial junction protein expression. IL-22 or its analogs might become treatments to strengthen tight junctions in conditions like graft-versus-host disease or IBD.

Another novel application is imaging. Claudins, being cell-surface accessible on certain cells, make good targets for diagnostic imaging of tumors. We touched on radiolabeled peptides for PET imaging of claudin-4-positive pancreatic cancer[144][145]. In that 2017 study, the first ^18F-labeled claudin-4 PET probes showed specific uptake in claudin-4 expressing tumor xenografts, distinguishing them from inflammation or normal tissue[190][191]. Similarly, a ^68Ga-labeled peptide (T-37) was made to target claudin-18.2 and successfully imaged claudin-18.2-positive tumors in mice[192]. These imaging agents could help in patient selection (e.g., identifying metastases that express the target to decide on antibody therapy) and in monitoring treatment response (if claudin expression goes down as tumor cells are killed, one would see reduced tracer uptake). Furthermore, fluorescent conjugates of cCPE are being tested in endoscopy for molecular endoscopic imaging. For example, spraying a fluorescent cCPE on Barrett's esophagus mucosa could highlight areas of dysplasia (which overexpress claudin-3/4) to guide biopsies.

Safety considerations

Targeting claudins does raise concerns because these proteins are present in normal tissues too. The key is relative expression and accessibility. Claudin-18.2 targeting has an acceptable safety profile because claudin-18.2 in normal stomach is largely segregated to the tight junctions on the luminal side of gastric glands (somewhat hidden from large antibodies in circulation)[52]. However, patients do experience nausea/vomiting from on-target effects in the stomach lining (some gastric cells are hit by zolbetuximab, causing inflammation akin to an acute gastritis). With claudin-4, since it's ubiquitous (pan-epithelial), systemic exposure to a toxin is dangerous. That's why local or selective approaches (like intraperitoneal CPE for localized tumors, or nanoparticle delivery that accumulates in tumors via EPR effect) are considered.

Looking ahead, we anticipate development of small molecules that can modulate claudin interactions (for example, a drug that stabilizes claudin-5 strands might be useful in colitis to reduce leak, similar to how claudin-5 stabilizers are being considered in neurological diseases for the blood-brain barrier). Gene therapy or mRNA approaches could also be imagined: delivering a claudin gene (like claudin-7) to an ulcerated colon segment to hasten barrier restoration. On the flip side, in cancer, silencing a claudin (via siRNA or CRISPR strategies delivered by vectors) might make tumor cells less viable or more sensitive to treatment.

In summary, the clinical realm is beginning to harness claudins in multiple ways – as markers (for identifying tissue origin and disease state), as molecular imaging targets, and as direct therapeutic targets in both barrier augmentation and tumor eradication strategies. The success of claudin-targeted therapy in gastric cancer is

likely just the first of many forthcoming claudin-based interventions in gastroenterology and oncology.

Conclusion

In conclusion, claudins sit at a nexus of critical GI functions: forming the barrier that defends against the external environment while simultaneously coordinating with signaling pathways that maintain epithelial homeostasis. Dysregulation of claudins is a common denominator in GI pathologies, contributing to carcinogenesis, inflammation, infection, and fibrosis. As this review has detailed, a thematic analysis across diseases reveals patterns – such as barrier loosening often preceding inflammation or metastasis – that reinforce the importance of claudins. Ongoing and future research into claudin biology will undoubtedly yield deeper insights, and leveraging those insights will enhance our ability to diagnose, prognosticate, and treat GI disorders. The trajectory of claudin research, from basic science discovery in the late 1990s to targeted therapies in the 2020s, exemplifies a successful bench-to-bedside story in gastroenterology. With a cohesive narrative and continued interdisciplinary efforts, we can expect that claudins will remain a focal point in our quest to understand and therapeutically control the gut's most fundamental property: its barrier.

Author contributions

All authors contributed to the initial draft of the manuscript. TZA, AA, and AO critically revised the manuscript. AO conceptualized and supervised the manuscript. All authors read and approved the final version of the manuscript.

Funding: The authors declare that they received no funding.

Conflict of interest: The authors declare that they have no conflict of interest.

Figure 1 Alterations in claudin expression in a spectrum of gastrointestinal disorder.

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