Targeting desmosomal adhesion and signalling for intestinal barrier stabilization in inflammatory bowel diseases—Lessons from experimental models and patients

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Abstract
Inflammatory bowel diseases (IBD) such as Crohn’s disease (CD) and Ulcerative colitis (UC) have a complex and multifactorial pathogenesis which is incompletely understood. A typical feature closely associated with clinical symptoms is impaired intestinal epithelial barrier function. Mounting evidence suggests that desmosomes, which together with tight junctions (TJ) and adherens junctions (AJ) form the intestinal epithelial barrier, play a distinct role in IBD pathogenesis. This is based on the finding that desmoglein (Dsg) 2, a cadherin-type adhesion molecule of desmosomes, is required for maintenance of intestinal barrier properties both in vitro and in vivo, presumably via Dsg2-mediated regulation of TJ. Mice deficient for intestinal Dsg2 show increased basal permeability and are highly susceptible to experimental colitis. In several cohorts of IBD patients, intestinal protein levels of Dsg2 are reduced and desmosome ultrastructure is altered suggesting that Dsg2 is involved in IBD pathogenesis. In addition to its adhesive function, Dsg2 contributes to enterocyte cohesion and intestinal barrier function. Dsg2 is also involved in enterocyte proliferation, barrier differentiation and induction of apoptosis, in part by regulation of p38MAPK and EGFR signalling. In IBD, the function of Dsg2 appears to be compromised via p38MAPK activation, which is a critical pathway for regulation of desmosomes and is associated with keratin phosphorylation in IBD patients. In this review, the current findings on the role of Dsg2 as a novel promising target to prevent loss of intestinal barrier function in IBD patients are discussed.

Keywords
adherens junctions, Crohn’s disease, desmocollin 2, desmoglein 2, desmosome, EGFR, GDNF, gut barrier, inflammatory bowel disease, intestinal epithelial barrier, paracellular permeability, pathophysiology, tight junctions, ulcerative colitis
Inflammatory bowel diseases (IBD) are broadly classified as either ulcerative colitis (UC), Crohn’s disease (CD) or IBD-unclassified (IBDU) when they share features of both UC or CD. While the incidence of IBD (especially CD) has stabilized following several decades of growth in North America and Europe, there appears to be a steady rise in its incidence in developing countries. The onset of IBD usually occurs during young adulthood irrespective of its subtype. CD can affect all parts of the gastrointestinal tract from the oral cavity to the anus, and is characterized by transmural inflammation and epithelioid granulomas within the gut wall. A typical primary manifestation site of CD is the terminal ileum. In contrast, UC always begins in the rectum and mainly affects the colon. In severe cases, however, inflammation can encroach onto the terminal ileum which is referred to as “backwash ileitis.” In UC, inflammation is restricted to the mucosal and submucosal part of the intestinal wall and characterized by cryptitis and crypt abscesses.

Despite intensive research efforts, details on the precise pathogenesis of IBD remain unclear although complex, molecular and cellular processes have been strongly implicated (Figure 1). Genome-wide association studies have also identified multiple risk-conferring gene loci for IBD. In addition, defects in local and systemic immune responses together with environmental factors are regarded as important triggers for IBD development. Another factor that contributes to the onset and perpetuation of intestinal inflammation is the composition of the gut microbiota. Although a cause-effect relationship between altered gut microbiota or dysbiosis and IBD is yet to be proven, the gut microbiota and its metabolome are thought to exert a large variety of local effects in the intestine that may contribute to the onset of IBD.

Loss of intestinal epithelial barrier function is increasingly recognized as a key event in the pathogenesis of IBD with genetically predisposed individuals being highly susceptible. In addition, loss of intestinal barrier function because of inflammatory stimuli is known to perpetuate and eventually worsen the condition of IBD patients. “Mucosal healing” is a term often used in the clinical setting to provide a macroscopic impression on the overall state of the mucosa including its intestinal barrier properties. As such, “mucosal healing” is one of the most important factors predicting IBD remission in patients and has been defined as an important future therapeutic focus in this context. Furthermore, restoration of intestinal epithelial barrier function in IBD patients critically contributes to their improved outcomes.
is considered to play a critical role. The intestinal epithelium is comprised of a single layer of cells that lines the gastrointestinal tract. The paracellular space between epithelial cells, which is commonly affected in inflammation, is usually sealed by the apical junctional complex composed of tight junctions (TJ), adherens junctions (AJ) and desmosomes.22,23 TJ and AJ are the best-characterized junctional complexes within the gut, while desmosomes in this organ have been largely neglected until relatively recently. However, increasing evidence points towards a critical role for desmosomal adhesion and signalling in maintaining the intestinal barrier in both health and disease states—especially in IBD.24-30

The aim of this review is to summarize recent findings on the role of desmosomes in intestinal epithelial barrier regulation, inflammation and IBD pathogenesis. In the first part, we briefly describe the most important players contributing to intestinal barrier integrity. In the second part, we then specifically focus on epithelial barrier regulation thereby highlighting the role of desmosomal adhesion and signalling for intestinal barrier regulation in health and disease especially in the context of IBD.

2 | OVERVIEW OF THE COMPOSITION OF THE INTESTINAL BARRIER

2.1 | The intestinal barrier has several major structural components

The intestinal barrier provides a physical and biochemical partition that enables the segregation of the gut lumen, which contains commensal bacteria, pathogens and dietary antigens, from the inner compartment of the body while allowing the selective absorption of nutrients, water and electrolytes. The intestinal barrier also allows a well-controlled presentation of luminal antigens to intestinal immune cells. According to a recent estimate, the intestinal barrier comprises a total surface area of 32 m² in humans, with 2 m² attributed to the large intestine alone.31 The intestinal barrier is not simply a static system, but is highly dynamic one that undergoes constant renewal from crypt stem cells to villi. Under normal conditions, the epithelial monolayer is renewed every 5-7 days.32

The intestinal barrier has several components (Figure 2A). The most superficial is the extracellular mucus layer lining...
the gut lumen. The next layers are the epithelium and lamina propria, respectively, both of which represent the cellular components of the intestinal barrier. Additionally, as mentioned above there is increasing evidence indicating that the intestinal microbiome shapes intestinal barrier function, making them an additional so-called “commensal component” of the intestinal barrier.33

2.2 Extracellular component of the intestinal barrier

The extracellular component of the intestinal barrier is the mucus layer, which is predominantly built around double-stranded and single-stranded mucin 2 polymers in the colon and in the small intestine respectively.34 While the outer mucus layer hosts microbes such as commensal bacteria, the inner mucus layer contains a comparably lower number of bacteria and forms an epithelium-protective zone.35 This protection can be attributed to the presence of antimicrobial proteins in the inner mucus layers. In addition to secreting mucus, Paneth cells release α-defensins, which play a critical role in local defence mechanisms, and thus, the integrity of cellular components of the intestinal barrier. Defects of α-defensin have amply been demonstrated to contribute to the pathogenesis of IBD, which is reviewed in detail elsewhere.36 In addition, dysregulated production of IgA, which controls the composition and density of intestinal commensal bacteria, has been observed in patients with CD.37 This can be explained by a disturbed interplay between dendritic cells and plasma cells in Peyer’s patches.

2.3 Commensal component of the intestinal barrier

The “commensal component” of the intestinal barrier is represented by the large number of bacteria that appear to closely interact with the intestinal epithelium.35 There is evidence that some of the interactions are mediated via the pattern recognition receptors (PRR) such as the Toll-like receptors (TLRs). Imbalance of physiologic and pathogenic bacteria—a condition known as dysbiosis—promotes aberrant TLR signalling and changes barrier function which contributes to IBD, colitis and irritable bowel syndrome.38 Moreover, hydrolytic enzymes secreted by intestinal microbiota indirectly contribute to the suppression of inflammation-induced cytokine secretion by fermentation products such as short fatty acids.12,39 Bacteria also regulate the expression and secretion of defensins via other PRR of the immune system.40

2.4 Cellular component of the intestinal barrier

The “cellular component” of the intestinal barrier consists of a single epithelial monolayer that lines the whole gastrointestinal tract. In addition, beneath the epithelial monolayer in the lamina propria exists a large variety of immune cells and cells of the enteric nervous system, which are in close contact with the epithelium. Both immune cells and the enteric nervous system are critically involved in the regulation of the intestinal epithelial barrier.

The enteric nervous system modulates inflammatory responses, regulates blood flow and peristalsis, thereby indirectly contributing to maintaining the intestinal barrier. Furthermore, among several factors secreted by the enteric nervous system, the Glial cell line-derived neurotrophic factor (GDNF) directly affects intestinal barrier function by targeting desmosomal adhesion of intestinal epithelial cells.41,42 Interestingly, GDNF is significantly reduced in patients with active inflammation in CD and UC.30 Furthermore, there is evidence that a toxic or autoimmune ablation of enteric glial cells leads to breakdown of IEB function followed by a spontaneous jejuno-ileitis comparable to the phenotype seen in CD.43,44 In line with this, enteric glial cells are reduced in healthy, non-inflamed parts of the intestine of patients suffering from IBD prior to the onset of inflammation.45,46

The immune cells of the lamina propria include those of the innate immune response such as macrophages, dendritic cells and neutrophils, as well as plasma and T cells of the adaptive immune response. One mechanism by which IECs direct adaptive immunity is by antigen sampling and presentation to immune cells of the lamina propria through highly specialized cells. These so-called M cells line the luminal surface of Peyer’s patches and take up antigens or microorganisms directly from the lumen to facilitate their transportation and presentation to underlying resident immune cells. Intestinal dendritic cells are a heterogeneous population of resident innate immune cells located in organized lymphoid tissue, such as Peyer’s patches and the lamina propria, with various functions ranging from antigen presentation, mediating oral tolerance and initiating immune responses.47 Recently, DCs have been found to regulate intestinal homoeostasis through TGF-β signalling by modulating mucus production and disease severity in Dextran Sulfate Sodium (DSS)-induced colitis through Notch signalling.48 Other myeloid cells, including macrophages and neutrophils, have also been identified as major contributors to IEC homoeostasis and inflammation. Resident macrophages not only affect IEC differentiation, but are also likely modulators of mucosal repair through IL-10 secretion and the subsequent upregulation of pro-repair molecules which induce IEC proliferation.49 Neutrophil infiltration of the intestine in so-called crypt abscesses is a hallmark
of UC, and while excessive neutrophil infiltration can be attributed to disease severity in UC patients, a lack of neutrophils in damaged intestinal mucosa leads to increased inflammation and perturbed mucus wound healing. This highlights a crucial balance of pro- and anti-inflammatory functions of various intestinal immune cell subsets, and their contribution to the regulation of intestinal homeostasis, inflammation and barrier function.

The intestinal epithelium as part of the cellular component is the first line of cells between the gut lumen and the inner compartment of the body. Therefore, a specific and important contribution to intestinal barrier function can be attributed to intestinal epithelial cells. As outlined above, intestinal epithelial cells undergo constant renewal within proliferative crypts as Lgr5-positive stem cells of the intestinal stem cell niche, and then, differentiate into enterocytes, Paneth cells, goblet cells. Paneth cells migrate to crypt bottoms thereby escaping crypt-villus flow. These cells contribute to the maintenance of the intestinal barrier by producing antimicrobial peptides such as defensins. In addition, secretion of antimicrobial peptides by Paneth cells reduces the secretion of mucus by goblet cells. Interestingly, genetic ablation of Paneth cells and Paneth-like cells in colonic crypts leads to a local reduction of Lgr5-positive stem cells, which demonstrates the requirement of this cell type to maintain cell proliferation and differentiation processes in the stem cell niche.

Enteroendocrine cells can be identified by their expression of the transcription factor Neurogenin 3 and constitute ~1% of the intestinal epithelial cell population. Nevertheless, this still renders the gastrointestinal tract the largest endocrine system of the body. Originally, enteroendocrine cells were thought to derive from the endoderm or the neural crest. However, it is now clear that they develop from the intestinal stem cell niche along with enterocytes, goblet cells and Paneth cells. Enteroendocrine cells are capable of luminal sensing and mediate local responses in a paracrine manner, on the one hand, and more distant effects in an endocrine manner on the other through secreting a variety of peptide hormones which are named and characterized by their specific function. Enteroendocrine cells are found throughout different parts of the gastrointestinal tract and were originally defined as L-cells, K-cells, I-cells, X-cells, M-cells, N-cells and S-cells based on their anatomical location and expression of specific peptide hormones. Accordingly, they are involved in a plethora of functional effects that regulate various aspects of digestive physiology such as postprandial digestion, insulin homeostasis, food intake and intestinal motility.

Goblet cells within the intestinal epithelium play an important role in the regulation of intestinal barrier function by producing and secreting mucus, that is, predominately MUC2 mucin. Furthermore, they also secrete antimicrobial proteins, chemokines and cytokines which points to an additional role in innate immunity. Goblet cells themselves are of several types that differ in function in the small intestine and in the colon. These differences stem on the fact that colonic surface goblet cells constitutively secrete mucus while mucus secretion in the small intestine is dependent on external stimuli such as acetylcholine or carbachol. Besides their secretory functions, goblet cells can present antigens to dendritic cells in the lamina propria which underscores their contribution to host defence.

Finally, the majority comprising ~80% of the population of intestinal epithelial cells are enterocytes. As described for the other intestinal epithelial cells, enterocytes differentiate from the stem cell niche within the crypts. During their migration along the crypt-villus axis, they undergo differentiation which induces changes of their phenotypes. In this context, the expression of TJ proteins in particular change significantly during the course of differentiation. As a result, a leakier barrier, which permeates macromolecules, exists in the crypts, whereas a tight barrier, which permeates only small molecules, exists at the villi. Enterocytes are responsible for nutrient absorption. Fully differentiated enterocytes are characterized by an apical brush border which serves to increase the surface area of the lumen by 9-16-fold in the small intestine. Enterocytes significantly contribute to epithelial barrier integrity as will be described in detail below. In addition, enterocytes secrete a large number of antimicrobial proteins as well as immunoglobulins and produce cytokines that allow them to participate in immune cell responses underscoring their important contribution to intestinal immunity.

### 3 | THE APICAL JUNCTIONAL COMPLEX BETWEEN ENTEROCYTES REGULATES PARACELLULAR PERMEABILITY

The intestinal epithelial barrier can be traversed by transcellular transport, which is the physiologic route for nutrients. The intercellular space, also referred to as the paracellular way, is most commonly affected in diseases such as IBD. Therefore, regulation of the components sealing the paracellular cleft is vital to maintain the intestinal barrier in good shape. The paracellular cleft is sealed by the apical junctional complex or “terminal bar” that is comprised of TJs, AJs and desmosomes (Figure 2B). All of these junctions are critically involved in the regulation of the intestinal barrier and have specific functions. While TJ and AJ have been extensively characterized, the role of desmosomes in the context of intestinal barrier stabilization has received far less attention. Here, we briefly sum-up the most important aspects of TJ and AJ structure and regulation before we focus on the increasing evidence for a significant role of desmosomes in the regulation of intestinal epithelial barrier function.
4  |  TJ AND AJ IN THE INTESTINE

Alterations of TJ integrity induce a number of pathophysiological conditions including some of those typically observed in patients with IBD. TJ form a circumferential belt around intestinal epithelia cells thereby polarizing them into apical and basolateral sides. TJs comprise claudins, the IgG-like junctional adhesion molecules (JAMs) and the tight junction-associated MARVEL proteins (TAMPs) such as occludin, tricellulin and marvelD3. All these proteins are typically located at the most apical part of the junctional complex.

With 27 members, claudins are the major structural and functional components of TJ. Depending on their type, claudins can either contribute to the sealing of the intercellular space or form pores that allow the paracellular passage of water and ions. The sealing claudins 1, 3, 5, 4, 8, 15 and 20 are present in different parts of the intestine. In contrast, pore-forming or “leaky” claudins such as claudins 2, 10 and 15 are usually concentrated in crypts and, when upregulated, contribute to intestinal inflammation by increasing intestinal permeability. This is especially the case for claudin 2 in IBD.

JAMs have a dual role in intestinal barrier regulation. In the intestine, the presence of JAM-A at the cell border regulates the intestinal barrier as a signalling hub for Rap2, afadin and ZO-2 that in turn affect cytoskeletal dynamics. Moreover, the presence of JAM-A in enterocytes is critical for the normal regulation of intestinal transepithelial leucocyte migration. The significance of occludin in maintaining intestinal barrier integrity first appeared to be minor since TJ strands and barrier function were still present in epithelial tissues deficient for occludin. Instead, a role for occludin in regulating apoptosis was proposed. On the contrary, it has been repeatedly shown that occludin is required for intact intestinal barrier function in various models, thus complicating our understanding of the specific role for occludin in IEB stability.

Tricellulin, as its name suggests, is found where three or more cells meet and has also been implicated in the regulation of macromolecule flux. Tricellulin is downregulated by Interleukin 13 receptor α2 in patients with UC, but not CD underlining its importance for intestinal barrier dysfunction at least for UC.

TJ are all linked to the actin cytoskeleton via TJ-associated proteins ZO-1-3, making cytoskeletal dynamics important for the regulation of TJ integrity. Importantly, at their intracellular domains, TJ are also recognized as important signalling hubs. Beside this, TJ integrity is dependent on proper intercellular adhesion by AJ and desmosomes.

AJs provide mechanical strength between cells to facilitate cell-cell adhesion and cell polarization. AJs are formed by members of the cadherin superfamily, most prominently E-cadherin in epithelial cells. E-cadherin is a transmembrane glycoprotein which mediates cell-cell adhesion via cis- and trans-dimerization of its extracellular domains in the intercellular cleft. The cytoplasmic C-terminus of E-cadherin binds to adaptor proteins such as α-catenin, β-catenin and p120 catenin. The cadherin-catenin complex interacts with the underlying actin cytoskeleton which may regulate cell structural integrity.

In 1995, Hermiston et al showed that the proper assembly of AJs was essential to maintain intestinal barrier function, as disruption of AJs led to characteristics which closely resembled IBD. Underscoring this association with IBD, genome-wide association studies have linked CDH1 and CHD3, genes encoding E-cadherin and p-cadherin, with CD and CU. The underlying molecular mechanisms associated with IBD have been studied intensively in vivo and in vitro. While total knockout of E-cadherin in murine embryos was lethal, conditional E-cadherin knockout specifically in the intestinal epithelium of murine embryos led to a severe disruption of intestinal morphogenesis and death within 24 hours. Deletion of E-cadherin in adult mice resulted in bloody diarrhoea and increased cell shedding, as well as impaired cell maturation. In vitro experiments, which simulated inflammation through IFNγ treatment, demonstrated a reduction in E-cadherin expression and increased epithelial instability. Furthermore, a major signalling pathway in the intestinal mucosa is the Wnt/β-catenin pathway. As E-cadherin and β-catenin have been implicated in both tumourigenesis of colorectal cancer as well as IBD, the Wnt signalling pathway seems to affect epithelial homoeostasis and tissue regeneration.

5  |  THE INTEGRITY OF DESMOSOMES IS CRUCIAL TO MAINTAIN INTESTINAL BARRIER FUNCTION UNDER BASAL CONDITIONS

Desmosomes were previously the least understood part of the apical junctional complex. They represent robust intercellular adhesive structures that are also abundant in tissues of high mechanical stress such as the heart and skin. Similar to the structure of AJs, adhesive forces in desmosomes are mediated by desmosomal cadherins which are tethered to the intermediate filament system. In humans, the major isoforms of desmosomal cadherins, that is, desmogleins (Dsg 1-4) and desmocollins (Dsc 1-3), are expressed in a tissue-specific manner. Notably, the intestinal epithelium expresses Dsg2 and Dsc2 only. On the cytoplasmic side, Dsg2 and Dsc interact with members of the armadillo repeat protein family plakoglobin and plakphlin, which subsequently associate with desmoplakin and anchor the desmosomal complex to the intermediate filaments. While the morphological description in 1963...
led to the assumption that desmosomes are important to maintain the intestinal barrier,\textsuperscript{22} it took until 2010 to prove this on a functional level. It was observed that an inhibitory Dsg2 antibody targeting the Dsg2 extracellular domain, thereby reducing homophilic Dsg2 interactions, caused a profound alteration in TJ component distribution.\textsuperscript{27} Similarly, in a Dsg-deficient mouse model, the ultrastructure of desmosomes was altered, claudin 1 and occludin levels were reduced and intestinal permeability was increased in vivo.\textsuperscript{29} As levels of Dsc2 were upregulated and levels of E-cadherin were normal, these data demonstrate that Dsg2 plays a particularly important role in regulating intestinal epithelial barrier function under basal conditions.

Conflicting data have been reported on the role of Dsc2. Interestingly, mice with permanent enterocyte-specific knock-out of Dsc2 did not show increased susceptibility to barrier dysfunction in DSS-induced colitis. In contrast, in a model with an inducible conditional knockout of Dsc2 in enterocytes, mice exhibited impaired mucosal repair after biopsy-induced colonic wounding and attenuated recovery from DSS-induced colitis.\textsuperscript{78} Therefore, it appears that in contrast to Dsg2, permanent loss of Dsc2 can be well compensated for, while acute loss of Dsc2 affects intestinal barrier function and especially mucosal wound healing. In vitro analyses using human intestinal cell lines after knockdown of Dsc2 demonstrated delayed epithelial cell migration and repair after scratch wounding. This was associated with reduced cell-matrix traction forces, decreased levels of integrin $\beta_1$ and $\beta_4$ and altered activity of the small GTPase Rap1.\textsuperscript{78}

### 6 ALTERATIONS OF DSG2 LEVELS AND DESMOSOME ULTRASTRUCTURE IN IBD

Based on the finding that Dsg2 is required for maintenance of enterocyte cohesion and intestinal epithelial barrier properties in vitro,\textsuperscript{27,28,97} alterations of Dsg2 protein levels as well as Dsg2 localization in samples from IBD patients were studied. In a first cohort of 14 patients, who underwent surgery because of conservative refractory CD, 13 patients showed altered Dsg2 distribution patterns as revealed by immunostaining. Claudin-1 was affected similarly in all of these patients.\textsuperscript{28} Moreover, 11 patients’ samples displayed alterations in occludin staining, whereas E-cadherin distribution was similar to controls. These data indicated that the structure of desmosomes and TJs was compromised, while AJs were intact, suggesting that these alterations were not caused by a complete loss of epithelium. Western blot analysis confirmed that Dsg2 levels were reduced to about 63% of controls in 11 patient samples, which was similarly the case for claudin-1, but not for E-cadherin.

This was confirmed in a second cohort of 12 CD patients, in which protein levels and distribution of both Dsg2 and Dsc2, but not of E-cadherin, were altered.\textsuperscript{29} In two patients’ biopsies, we characterized the ultrastructure of the junctional complex in detail by transmission electron microscopy (TEM). Controls displayed a regular sequence and morphology of TJ, AJ and desmosomes along the apical part of the basolateral membrane (Figure 3), similar to the description of Farquhar and Palade.\textsuperscript{22} In contrast, in CD patients’ samples, the ultrastructure of TJs as well as of desmosomes was altered, whereas AJs appeared normal. Desmosomes were sometimes missing or composed of asymmetric and irregular plaques.\textsuperscript{29} In a third cohort, Dsg2 was reduced in nine patients with CD and nine patients with CU, respectively, categorically indicating that the integrity of desmosomes is compromised in IBD patients, at least when the course of the disease is severe.\textsuperscript{30} The resultant loss of Dsg2 impairs TJ integrity and function, which leads to disruption of barrier properties and increased susceptibility to infections similar to the situation in mice deficient for intestinal Dsg2.\textsuperscript{29} Finally, in a cohort of 17 patients with CD loss of Dsg2 was also described, especially in severe inflammation. Interestingly, when enteroids from the same CD patients were generated from crypts that contain the intestinal stem cell niche, loss of Dsg2 was maintained under culture conditions. This phenomenon was observed without cytokine stimulation and was present over several passages of enteroid culture.\textsuperscript{98} This indicated that loss of Dsg2 in CD is maintained in the intestinal regeneration niche or on a stem level respectively. In this study loss of Dsg2 was present on a protein level, whereas Dsg2 mRNA was unaltered indicating a posttranscriptional mechanism leading to loss of Dsg2 in CD.\textsuperscript{98} While the detailed mechanisms underlying this observation remain to be elucidated this may support the view that inflammation-induced barrier defects in CD are not just a secondary phenomenon because of an inappropriate immune response but play a primary role in the pathogenesis of CD.\textsuperscript{99} This may be established on the level of intestinal stem cells.

The importance of desmosomes during disease pathogenesis is not limited to IBD, as it also plays a critical role in enteropathogenic Escherichia coli (EPEC) infection.\textsuperscript{100,101} Infection of enterocytes with EPEC reduced Dsg2 and Dsc2 levels in vitro and disruption of desmosomes even preceded ultrastructural alterations of TJs in mice in vivo. In this scenario, the proposed mechanism was a Rho GTPase- and actin-mediated dysregulation of desmosomes via the EHEC toxin EspH, which can sequester p115-RhoGEF and thereby reduce RhoA activity. This is in line with the findings that RhoA is critical for desmosomal adhesion and stabilizes desmosomal adhesion in keratinocytes\textsuperscript{102-104} and is required for proper epithelial barrier function in enterocytes.\textsuperscript{105}
Interestingly, Liu et al reported that krüppel-like factor 5 (KLF5)-deficient mice show increased epithelial permeability and demonstrated that KLF5 is an important transcription factor for Dsg2. This observation further underlines the significant role for Dsg2 in maintaining intestinal epithelial function. In support of this, mice with intestinal-specific loss of Dsg2 showed increased epithelial permeability but no inflammation under basal conditions. They were, however, highly susceptible when subjected to DSS resulting in more severe colitis when compared to WT mice. Comparable to the observations made in patients when Dsg2 was lost, the TJ proteins occludin and claudin 1 were reduced in Dsg2-deficient mice, with normal levels of other claudins and E-cadherin. Following DSS-induced colitis in Dsg2-deficient mice, molecular analysis demonstrated increased levels of pro-inflammatory cytokines and activation of the STAT3 signalling pathway, but no relevant activation of EGFR or p38MAPK. Interestingly, proteomic analyses showed decreased levels of HSP70 heat shock proteins, which had previously been established as protective factors in IBD pathophysiology.

**FIGURE 3** Electron microscopy of a healthy patient and a patient with Crohn’s Disease. Electron microscopy picture to exemplify that desmosomes are not only reduced, but also have an altered structure in patients with IBD: While controls (healthy patients) display a regular sequence and morphology of TI, AJ and desmosomes along the apical part of the basolateral membrane, the ultrastructure of TJs as well as of desmosomes is altered in samples from patients with CD, whereas AJ's appear normal. Desmosomes are sometimes missing or composed of asymmetric and irregular plaques. This picture was taken and modified from Gross et al 2018 after Copyright approval from Mucosal Immunology.
More recently, it was shown that barrier dysfunction after TNF-α treatment was not only paralleled by activation of p38MAPK, but also associated with phosphorylation of cytokeratins 8 and 18 and by loss of Dsg2 in vitro and in vivo.\textsuperscript{30} In this context, GDNF specifically targeted Dsg2 and thereby induced barrier maturation by preventing p38MAPK activation (Figure 4). In DSS-colitis, inflammation-induced loss of Dsg2, p38MAPK and cytokeratin phosphorylation were attenuated by intraperitoneal GDNF treatment. Strikingly, loss of Dsg2 in patients with IBD was accompanied by a significant reduction of GDNF which led to the conclusion that GDNF is critically involved in inflammation-induced loss of intestinal barrier function in IBD.\textsuperscript{30} These data not only show the importance of GDNF in the context of intestinal barrier regulation, but also underline the therapeutic potential of targeting Dsg2 to improve intestinal epithelial barrier function in IBD.

### 8 | MECHANISMS UNDERLYING DS2-MEDIATED INTESTINAL BARRIER REGULATION

The data discussed above indicate that loss of Dsg2 in IBD contributes to disease pathogenesis by impairing intestinal barrier function. To test whether Dsg2 adhesion modulates...
barrier properties, we used a tandem peptide (TP) designed to cross-link Dsg molecules, which did not modulate homophilic binding of classical cadherins such as E-cadherin or N-cadherin.\textsuperscript{28,109,110} Previously, TP was shown to prevent loss of Dsg binding in an in vivo model of the autoimmune blistering skin disease pemphigus.\textsuperscript{97} In enterocytes in vitro, TP blocked TNF-\(\alpha\)-induced loss of enterocyte cohesion. It also blocked an increase in permeability, as well as claudin-1 disruption and the upregulation of the pore-forming TJ component claudin 2.\textsuperscript{28} Together, these results demonstrate that Dsg2 is important for intestinal epithelial barrier regulation (see Figure 4).

Prompted by these findings, the adhesive and signalling functions of Dsg2 in enterocytes were characterized in more detail. First, by structured illumination microscopy (SIM) and stimulated emission depletion microscopy (STED), extra-desmosomal Dsg2 was detected both on the free surface of differentiated cultured enterocytes as well as along the apical segment of the basolateral membrane.\textsuperscript{26} Single molecule atomic force microscopy (AFM) revealed that Dsg2 on the surface of living enterocytes undergoes binding events with a mean unbinding force of 30.4 pN, which is in the range of other desmosomal cadherins tested by this method.\textsuperscript{96,104,111,112} Importantly, Dsg2 interactions were blocked significantly by an inhibitory antibody and were reduced to the same extent as under cell-free conditions, where recombinant Dsg2 was coupled to the AFM plate and the tip of the cantilever. This indicated that adhesion in enterocytes was most likely homophilic.\textsuperscript{26} As the same antibody reduced enterocyte cohesion, Dsg2 is apparently required for intestinal epithelial cell adhesion. This function is enhanced by direct interaction with galectin-3, which stabilizes Dsg2 at the membrane and protects Dsg2 from internalization and proteasomal degradation.\textsuperscript{113} Since Transepithelial electrical resistance (TER) was significantly lower in enterocytes depleted for Dsg2 but over-expressing Dsc2, it can be concluded that the effect of Dsg2 on cell adhesion is relevant for intestinal epithelial barrier maintenance.\textsuperscript{26}

It is well established that besides their adhesive properties, Dsg molecules serve as signalling hubs.\textsuperscript{114,115} We therefore asked whether Dsg2 in enterocytes contributes to barrier regulation via cellular signalling pathways. The involvement of Dsg2 in cell signalling was shown previously by its regulation of apoptosis in enterocytes.\textsuperscript{116,117} In keratinocytes, p38MAPK forms a signalling complex with Dsg3 and it participates in the regulation of desmosome number, size and keratin filament insertion as revealed by TEM.\textsuperscript{97,114,118} Therefore, the role of p38MAPK regulation by Dsg2 was investigated but in contrast to Dsg3, direct interaction of p38MAPK with Dsg2 was not detected neither in keratinocytes\textsuperscript{114} nor in enterocytes (unpublished observation). To provide a functional link between Dsg2 and p38MAPK, an inhibitory Dsg2 antibody was acutely applied under conditions where it was not sufficient to reduce cell cohesion. This incubation activated p38MAPK indicating that Dsg2 regulates p38MAPK in enterocytes. To demonstrate the role of Dsg2 in p38MAPK regulation more directly, enterocytes deficient for Dsg2 and Dsc2 or for Dsg2 only were used. Interestingly, cells missing Dsg2 but overexpressing Dsc2 had lower levels of activated but not total p38MAPK, indicating that Dsg2 but not Dsc2 controls p38MAPK activity.\textsuperscript{26}

However, in contrast to keratinocytes where Dsg3 clearly destabilizes desmosomal adhesion to render desmosomes more dynamic in pemphigus or under conditions of wound healing,\textsuperscript{28,118} the function of p38MAPK in enterocytes is more complex. This can be concluded from experiments where both pharmacologic inhibition and activation of p38MAPK reduced enterocyte cohesion.\textsuperscript{26} In the same vein, p38MAPK downstream of Dsg2 appears to have both positive and negative effects on epithelial barrier regulation. To test this under standardized conditions, Ca\textsuperscript{2+} switch assays, in which depletion of Ca\textsuperscript{2+}-induced loss of Dsg2 and E-cadherin from cell junctions, were performed. This was accompanied by TJ disruption and barrier breakdown. Repletion of Ca\textsuperscript{2+} restored both junctional integrity and barrier function. Importantly, the inhibitory Dsg2 antibody did not interfere with barrier restoration in contrast to an antibody targeting E-cadherin, indicating that the adhesive function of Dsg2 may not be crucial for this process. However, since this antibody activated p38MAPK, we studied the effect of a p38MAPK inhibitor on barrier restoration. The p38MAPK inhibitor blunted barrier restoration.\textsuperscript{26} In line with this, pharmacologic activation of p38MAPK enhanced barrier recovery in enterocytes deficient for Dsg2 and Dsc2 up to a level observed in wild-type enterocytes. However, long-term activation of p38MAPK compromised barrier function. Taken together, these data indicate that Dsg2-mediated p38MAPK regulation is required for intestinal epithelial barrier restoration—especially under conditions where desmosomes are more dynamic.

Another pathway studied in detail in the context of Dsg2 adhesion is EGFR signalling. Dsg2 at least in part colocalizes with EGFR in enterocytes in human colon and enteroids.\textsuperscript{29} In addition, EGFR cooperates with ADAM family members 10 and 17 to induce Dsg2 shedding and thereby regulate Dsg2 availability at enterocyte and keratinocyte cell junctions.\textsuperscript{119-122} Moreover, Dsg2 ectodomain fragments were shown to compromise intestinal barrier functions and to promote enterocyte proliferation via EGFR.\textsuperscript{123} The opposite was also demonstrated as Dsg2 regulated the function of EGFR. In enterocytes deficient for Dsg2 but not in cells deficient for Dsc2, EGFR was absent from cell junctions and phosphorylation of EGFR on Y845 was reduced as well.\textsuperscript{29} The recruitment of EGFR to cell junctions can be explained by a direct interaction of Dsg2 and EGFR via their extracellular domains, which was detectable by specific AFM interaction studies on living enterocytes and under cell-free conditions as well as by pull-down of EGFR with an antibody.
targeting Dsg2 and by a Dsg2-Fc construct.\textsuperscript{29} This interaction was reduced sterically by EGF even under cell-free conditions. As Y845 phosphorylation of EGFR is controlled by Src, binding of Src to the Dsg2/EGFR complex was studied. Src interacted with EGFR but not with Dsg2 and controlled junctional localization of the Dsg2/EGFR complex. Since, similar to inhibition of p38MAPK as outlined above, the inhibition of Src or of EGFR impaired barrier restoration, it can be concluded that Dsg2 facilitates Src-mediated EGFR activation at cell junctions which participates in intestinal epithelial barrier regulation. In cells not expressing Dsg2, EGFR promoted enterocyte proliferation.\textsuperscript{29,113} Taken together, these results suggest that Dsg2 shapes EGFR function from cell proliferation towards cell cohesion in a manner dependent on Src transactivation of EGFR (Figure 4). However, since in colon cancer Dsg2 was shown to be upregulated,\textsuperscript{113} it is possible that this mechanism is set-off in cancer cells where desmosomes may be less mature.

9 ROLE OF DSG2 IN COLORECTAL CANCER

Chronic intestinal inflammation, as seen in CD and UC, is associated with an increased risk of colorectal cancer. Duration and severity of the respective IBD can further increase the risk of colorectal cancer.\textsuperscript{124} The role of Dsg2 and Dsc2 on tumourigenesis has been studied in multiple cancers including colon cancer. In addition to the association of Dsg2 with progressive disease in skin, prostate and cervical cancer,\textsuperscript{78} analyses of human colon cancer samples revealed increased Dsg2 protein expression levels. The upregulation of Dsg2 in colorectal cancer was dependent on the tumour-related upregulation of Pinin, a desmosome-associated protein.\textsuperscript{125} For Dsc2, a downregulation in colon carcinomas has been reported.\textsuperscript{126,127} In this context downregulation of Dsc2 directly contributed to tumour progression through activation of Akt/β-catenin signalling—a signalling pathway that is commonly affected in the pathogenesis of colorectal cancer.\textsuperscript{128} Overall this suggests that overexpression of Dsg2 and loss of Dsc2 may both contribute to colorectal cancer development and/or progression. This also underscores their importance in the regulation of intestinal homeostasis and creates an additional link between IBD and potentially the onset of inflammation-induced colorectal cancer. This link, however, will have to be elucidated in future studies.

10 SUMMARY AND FUTURE PERSPECTIVE

Collectively, several lines of evidence show that desmosomes are important for maintenance of intestinal epithelial barrier function. Specifically, the desmosomal cadherin Dsg2 appears to be critical for cell-cell adhesion and regulation of signalling pathways such as p38MAPK and EGFR, both of which are required for re-establishment of barrier properties, a scenario important for mucosal healing and barrier restoration in IBD. Since GDNF was found to stabilize Dsg2 binding and to be reduced in IBD mucosa, whereas TNF-α was found to reduce cell adhesion, it is tempting to speculate that dysregulation of desmosomal adhesion contributes to pathogenesis of IBD by impairing intestinal epithelial barrier properties. This evidence contributes to the knowledge that pathogenesis of IBD is complex and further characterization of underlying mechanisms is required to establish new therapeutic approaches for patients. Therefore, it remains to be investigated how desmosomes are involved in the stabilization of TJ integrity. Given that Dsg2 represents an important signalling hub, it will have to be tested whether this is involved in signalling pathways directly regulating TJ. In this context, the precise contribution of the desmosomal plaque proteins plakoglobin, plakophilins and desmoplakin remain to be elucidated in the intestine. The mechanism underlying conserved loss of Dsg2 in enteroids generated from CD patients will have to be elucidated which will enhance the understanding of the mechanisms underlying loss of intestinal barrier function in IBD. Furthermore, the promising in vitro data using the Dsg2-linking tandem peptide (TP) to stabilize intestinal barrier function remains to be tested in vivo. In the event of beneficial effects on intestinal barrier stabilization in inflammation, therapeutic application of the peptide, for example, by enteric coated capsules could be envisioned. Nonetheless, further evidence obtained from patient material systematically collected at different stages of IBD will be required to support the novel concept that desmosomes may be a promising target for stabilization of intestinal barrier function in IBD.

CONFLICT OF INTEREST
None of the authors has conflicts of interest to declare.

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REFERENCES
1. Abraham C, Cho JH. Inflammatory bowel disease. New Engl J Med. 2009;361(21):2066-2078.
2. D’Arcangelo G, Aloi M. Inflammatory Bowel disease-unclassified in children: diagnosis and pharmacological management. Paediatr Drugs. 2017;19(2):113-120.
3. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19(suppl A):5a-36a.
24. Spindler V, Meir M, Vigh B, et al. Loss of desmoglein 2 contributes to the pathogenesis of Crohn’s disease. *Inflamm Bowel Dis*. 2015;21(10):2349-2359.

25. Ungewiss H, Rotzer V, Meir M, et al. Dsg2 via Src-mediated transactivation shapes EGFR signaling towards cell adhesion. *Cell Mol Life Sci*. 2018;75(22):4251-4268.

26. Ungewiss H, Vielmuth F, Suzuki ST, et al. Desmoglein 2 regulates the intestinal epithelial barrier via p38 mitogen-activated protein kinase. *Sci Rep*. 2017;7(1):6329.

27. Schlegel N, Meir M, Heupel WM, Holthöfer B, Leube RE, Waschke J. Desmoglein 2-mediated adhesion is required for intestinal epithelial barrier integrity. *Am J Physiol Gastrointest Liver Physiol*. 2010;298(5):G774-G783.

28. Rotzer V, Hartlieb E, Winkler J, et al. Desmoglein 3-dependent signaling regulates keratinocyte migration and wound healing. *J Invest Dermatol*. 2016;136(1):301-310.

29. Gross A, Pack LAP, Schacht GM, et al. Desmoglein 2, but not desmocollin 2, protects intestinal epithelia from injury. *Mucosal Immunol*. 2018;11(6):1630-1639.

30. Meir M, Burkard N, Ungewiss H, et al. Neurotrophic factor GDNF regulates intestinal barrier function in inflammatory bowel disease. *J Clin Investig*. 2019;130:2824-2840.

31. Hélander HF, Fandriks L. Surface area of the digestive tract—revisited. *Scand J Gastroenterol*. 2014;49(6):681-689.

32. Sato T, Vries RG, Snippert HJ, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*. 2009;459(7244):262-265.

33. König J, Wells J, Cani PD, et al. Human intestinal barrier function in health and disease. *Clin Transl Gastroenterol*. 2016;7(10):e196.

34. Birchennough GM, Johansson ME, Gustafsson JK, Bergstrom JH, Hansson GC. New developments in goblet cell mucus secretion and function. *Mucosal Immunol*. 2015;8(4):712-719.

35. Deplancke B, Gaskins HR. Microbial modulation of innate defense: goblet cells and the intestinal mucus layer. *Am J Clin Nutr*. 2001;73(6):1131s-1141s.

36. Gersemann M, Wehkamp J, Stange EF. Inmate immune dysfunction in inflammatory bowel disease. *J Intern Med*. 2012;271(5):421-428.

37. Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. *Nat Rev Immunol*. 2012;12(7):503-516.

38. Frosali S, Pagliari D, Gambassi G, Landolfi R, Pandolfi F, Cianci R. How the intricate interaction among toll-like receptors, microbiota, and intestinal immunity can influence gastrointestinal pathology. *J Immunol Res*. 2015;2015:489821.

39. Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. *World J Gastroenterol*. 2007;13(20):2826-2832.

40. Coretti L, Natale A, Cuomo M, et al. The interplay between defenses and microbiota in Crohn’s disease. *Mediators Inflamm*. 2017;2017:8392523.

41. Meir M, Flemming S, Burkard N, et al. Glial cell line-derived neurotrophic factor promotes barrier maturation and wound healing in intestinal epithelial cells in vitro. *Am J Physiol Gastrointest Liver Physiol*. 2015;309(8):G613-G624.

42. Meir M, Flemming S, Burkard N, Wagner J, Germer CT, Schlegel N. The glial cell-line derived neurotrophic factor: a novel regulator of intestinal barrier function in health and disease. *Am J Physiol Gastrointest Liver Physiol*. 2016;310(11):G1118-G1127.
44. Bush TG, Savidge TC, Freeman TC, et al. Fulminant jejuno-ileitis following ablation of enteric glia in adult transgenic mice. *Cell*. 1998;93(2):189-201.

45. von Boyen GB, Schulte N, Pflugcr C, Spaniol U, Hartmann C, Steinkamp M. Distribution of enteric glia and GDNF during gut inflammation. *BMC Gastroenterol*. 2011;11:3.

46. Pochard C, Coquenlorge S, Freyssinet M, et al. The multiple faces of inflammatory enteric glial cells: is Crohn’s disease a glialopathy? *Am J Physiol Gastrointest Liver Physiol*. 2018;315(1):G1-G11.

47. Sun T, Nguyen A, Gommerman JL. Dendritic cell subsets in intestinal immunity and inflammation. *J Immunol*. 2020;204(5):1075-1083.

48. Ihara S, Hirata Y, Serizawa T, et al. TGF-beta signaling in dendritic cells governs colonic homeostasis by controlling epithelial differentiation and the luminal microbiota. *J Immunol*. 2016;196(11):4603-4613.

49. Quiro M, Nishio H, Neumann PA, et al. Macrophage-derived IL-10 mediates mucosal repair by epithelial WISP-1 signaling. *J Clin Investig*. 2017;127(9):3510-3520.

50. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic properties, and thickness in human colonic biopsies and mouse small and large intestinal explants. *Int J Exp Pathol*. 2011;92(4):219-231.

51. Brazil JC, Quiro M, Nusrat A, Parkos CA. Innate immune cell-epithelial crosstalk during wound repair. *J Clin Investig*. 2019;129(8):2983-2993.

52. van der Flier LG, van Gijn ME, Hatzis P, et al. Transcription factor achaete scute-like 2 controls intestinal stem cell fate. *Cell*. 2009;136(5):903-912.

53. Thachil É, Hugot J, Arbeille B, et al. Abnormal activation of autophagy-induced crinophagy in Paneth cells from patients with Crohn’s disease. *Gastroenterology*. 2012;142(5):1097-1099.e1094.

54. Sato T, van Es JH, Snippert HJ, et al. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. *Nature*. 2011;469(7330):415-418.

55. Sternini C, Anselmi L, Rozengurt E. Enteroendocrine cells: a site of ‘taste’ in gastrointestinal chemosensing. *Curr Opin Endocrinol Diabetes Obes*. 2008;15(1):73-78.

56. van Es JH, Snippert HJ, et al. The multi-organ system in humans. *Endocr Dev*. 2017;32:20-37.

57. Gordon JI. Understanding gastrointestinal epithelial cell biology: lessons from mice with help from worms and flies. *Gastroenterology*. 1993;105(2):315-324.

58. Gunawardene AR, Corfe BM, Staton CA. Classification and functions of enteroendocrine cells of the lower gastrointestinal tract. *Int J Exp Pathol*. 2011;92(4):219-231.

59. Gustafsson JK, Ermund A, Johansson ME, Schutte A, Hansson GC, Sjovall H. An ex vivo method for studying mucus formation, properties, and thickness in human colonic biopsies and mouse small and large intestinal explants. *Am J Physiol Gastrointest Liver Physiol*. 2012;302(4):G430-G438.

60. McDole JR, Wheeler LW, McDonald KG, et al. Goblet cells deliver luminal antigen to CD103+ dendritic cells in the small intestine. *Nature*. 2012;483(7389):345-349.

61. Turner JR, Buschmann MM, Romero-Cálo I, Sailer A, Shen L. The role of molecular remodeling in differential regulation of tight junction permeability. *Semin Cell Dev Biol*. 2014;36:204-212.
14. Krug SM, Bojarski C, Fromm A, et al. Tricellulin is regulated via interleukin-13-receptor alpha2, affects macromolecule uptake, and is decreased in ulcerative colitis. *Mucosal Immunol*. 2018;11(2):345-356.

15. Takeichi M. Dynamic contacts: rearranging adherens junctions to drive epithelial remodelling. *Nat Rev Mol Cell Biol*. 2014;15(6):397-410.

16. Campbell HK, Maiers JL, DeMali KA. Interplay between tight junctions & adherens junctions. *Exp Cell Res*. 2017;358(1):39-44.

17. Daulagala AC, Bridges MC, Kourtidis A. E-cadherin beyond desmosomes. *J Biol Chem*. 2009;284(13):8589-8595.

18. Serafino A, Moroni N, Zonfrillo M, et al. WNT-pathway components as predictive markers useful for diagnosis, prevention and treatment in inflammatory bowel disease. *Mucosal Immunol*. 2018;11(2):3055-3064.

19. Vlad-Fiegen A, Langerak A, Eberth S, Muller O. The Wnt pathway destabilizes adherens junctions and promotes cell migration via beta-catenin and its target gene cyclin D1. *FEBS Open Bio*. 2012;2:26-31.

20. Serafino A, Moroni N, Zoﬁrollo M, et al. WNT-pathway components as predictive markers useful for diagnosis, prevention and therapy in inflammatory bowel disease and sporadic colorectal cancer. *Oncotarget*. 2014;5(4):978-992.

21. Kowalczyk AP, Green KJ. Structure, function, and regulation of desmosomes. *Prog Mol Biol Transl Sci*. 2013;116:95-118.

22. Holthofer B, Windoffer R, Troyanovsky S, Leube RE. Structure and function of desmosomes. *Int Rev Cytol*. 2007;264:65-163.

23. Heupel WM, Zillikens D, Drenckhahn D, Waschke J. Pemphigus vulgaris IgG directly inhibits desmoglein 3-mediated transinteractions. *J Immunol*. 2008;181(3):1825-1834.

24. Hartlieb E, Kempf B, Partilla M, Vigh B, Spindler V, Waschke J. Desmoglein 2 is less important than desmoglein 3 for keratinocyte cohesion. *PLoS ONE*. 2013;8(1):e53739.

25. Meir M, Salm J, Fey C, et al. Enteroid generation from patients with severe inﬂammation in Crohn’s disease maintains altered junctional proteins. *J Crohn’s Colitis*. 2020;https://doi.org/10.1093/ecco-jcc/jja085.

26. Keita AV, Lindqvist CM, Ost A, Magana CDL, Scholutz I, Halfvarson J. Gut barrier dysfunction—a primary defect in twins with Crohn’s disease predominantly caused by genetic predisposition. *J Crohns Colitis*. 2018;12(10):1200-1209.
118. Egu DT, Walter E, Spindler V, Waschke J. Inhibition of p38MAPK signalling prevents epidermal blistering and alterations of desmosome structure induced by pemphigus autoantibodies in human epidermis. Br J Dermatol. 2017;177(6):1612-1618.

119. Lorch JH, Klessner J, Park JK, et al. Epidermal growth factor receptor inhibition promotes desmosome assembly and strengthens intercellular adhesion in squamous cell carcinoma cells. J Biol Chem. 2004;279(35):37191-37200.

120. Bech-Serra JJ, Santiago-Josefat Belén, Esselens C, et al. Proteomic identification of desmoglein 2 and activated leukocyte cell adhesion molecule as substrates of ADAM17 and ADAM10 by difference gel electrophoresis. Mol Cell Biol. 2006;26(13):5086-5095.

121. Klessner JL, Desai BV, Amargo EV, Getsios S, Green KJ. EGFR and ADAMs cooperate to regulate shedding and endocytic trafficking of the desmosomal cadherin desmoglein 2. Mol Biol Cell. 2009;20(1):328-337.

122. Blaydon DC, Biancheri P, Di WL, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. New Engl J Med. 2011;365(16):1502-1508.

123. Kamekura R, Nava P, Feng M, et al. Inflammation-induced desmoglein-2 ectodomain shedding compromises the mucosal barrier. Mol Biol Cell. 2015;26(18):3165-3177.

124. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. New Engl J Med. 2015;372(15):1441-1452.

125. Wei Z, Ma W, Qi X, et al. Pinin facilitated proliferation and metastasis of colorectal cancer through activating EGFR/ERK signaling pathway. Oncotarget. 2016;7(20):29429-29439.

126. Khan K, Hardy R, Haq A, Ogunbiyi O, Morton D, Chidgey M. Desmocollin switching in colorectal cancer. Br J Cancer. 2006;95(10):1367-1370.

127. Funakoshi S, Ezaki T, Kong J, Guo RJ, Lynch JP. Repression of the desmocollin 2 gene expression in human colon cancer cells is relieved by the homeodomain transcription factors Cdx1 and Cdx2. Mol Cancer Res. 2008;6(9):1478-1490.

128. Kolegraff K, Nava P, Helms MN, Parkos CA, Nusrat A. Loss of desmocollin-2 confers a tumorigenic phenotype to colonic epithelial cells through activation of Akt/beta-catenin signaling. Mol Biol Cell. 2011;22(8):1121-1134.

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