Chapter 13
The Epithelial Barrier

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Abstract The intestinal epithelium is the body's first line of defense against harmful contents of the gut, and defects in the epithelial barrier are thought to contribute to the initiation and perpetuation of inflammatory bowel diseases. Recent genome-wide association studies have identified a number of mutations in genes implicated in the regulation of the intestinal epithelium, which may result in barrier dysfunction and thereby predispose to the development of IBD. In this chapter, we will review the role of the epithelial barrier in the pathogenesis of intestinal inflammation and introduce relevant animal models that link epithelial barrier defects to increased colitis susceptibility and IBD susceptibility genes that are associated with epithelial barrier regulation.

The intestinal epithelium consists of a cohesive monolayer of epithelial cells that separate the content of the gut lumen from underlying tissues. The epithelium has two major functions; it absorbs nutrients and water from the digestive tract, while at the same time acting as an impermeable barrier for potentially harmful foreign materials, such as bacteria and viruses. To maintain stringent barrier function despite continuous antigen exposure and mechanical stress, intestinal epithelial cells (IEC) are constantly being replenished by a small pool of highly proliferative stem cells at the base of epithelial crypts. The progeny of these intestinal stem cells differentiates

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into specialized epithelial cells as cells migrate along the crypt-surface axis, and senescent IEC at the surface tip are ultimately shed into the gut lumen. Thus, the intestinal epithelium undergoes complete renewal every 5–7 days, without compromising barrier integrity.

Structure and Function of the Epithelial Tight Junction Complex

IEC are anchored to one another and to the surrounding connective tissue through various transmembrane proteins, which are clustered in distinct cell–cell and cell-matrix adhesion structures and connect to the cytoskeleton of the cell (see Fig. 13.1). Among these, the apical junctional complex—consisting of the tight junction at the apex of the lateral cell membrane and the more basally located adherens junction—is of critical importance for the regulation of paracellular solute flux and cell migration [1, 2]. In particular, claudin proteins in the epithelial tight junction form a belt-like continuous barrier around the cell, which restricts water and small molecule movement from the tissue into the lumen and vice versa. To date, 27 claudin protein family members have been identified [3]. Based on their preference to promote or restrict paracellular permeability, several claudins have been separated into "leaky" or "tight" functional groups, and their respective expression pattern is thought to confer tissue-specific barrier properties (e.g., low permeability in the epidermis and high permeability in the kidney). Consequently, genetic deletion of individual claudins in transgenic mice is typically associated with epithelial barrier dysfunction and—in some cases—chronic inflammation, although functionally related claudins can often compensate the loss of just one family member [4].

Epithelial Barrier Defects in IBD Pathogenesis

Considering the crucial importance of the epithelial barrier in the regulation of intestinal homeostasis, it would be expected that preexisting barrier dysfunction can result in a pronounced inflammatory response caused by increased antigen translocation across the epithelium. Indeed, numerous studies have demonstrated increased intestinal permeability in IBD patients [5–8], which suggests that epithelial barrier function is severely compromised in intestinal inflammation. The results present a chicken-and-egg problem, however: is intestinal inflammation triggered by increased transepithelial antigen translocation caused by a congenital barrier defect, or is barrier function in IBD patients secondary to mucosal leukocyte infiltration and cytokine secretion (see Fig. 13.2)? The answer, more likely than not, is "both." On the one hand, it is well known that various inflammatory mediators increase transepithelial permeability and disrupt epithelial homeostasis. For example, the prominent pro-inflammatory cytokines interleukin IL-4, interferon IFN-γ, and tumor necrosis factor TNF-α, whose expression is upregulated in the intestinal mucosa of

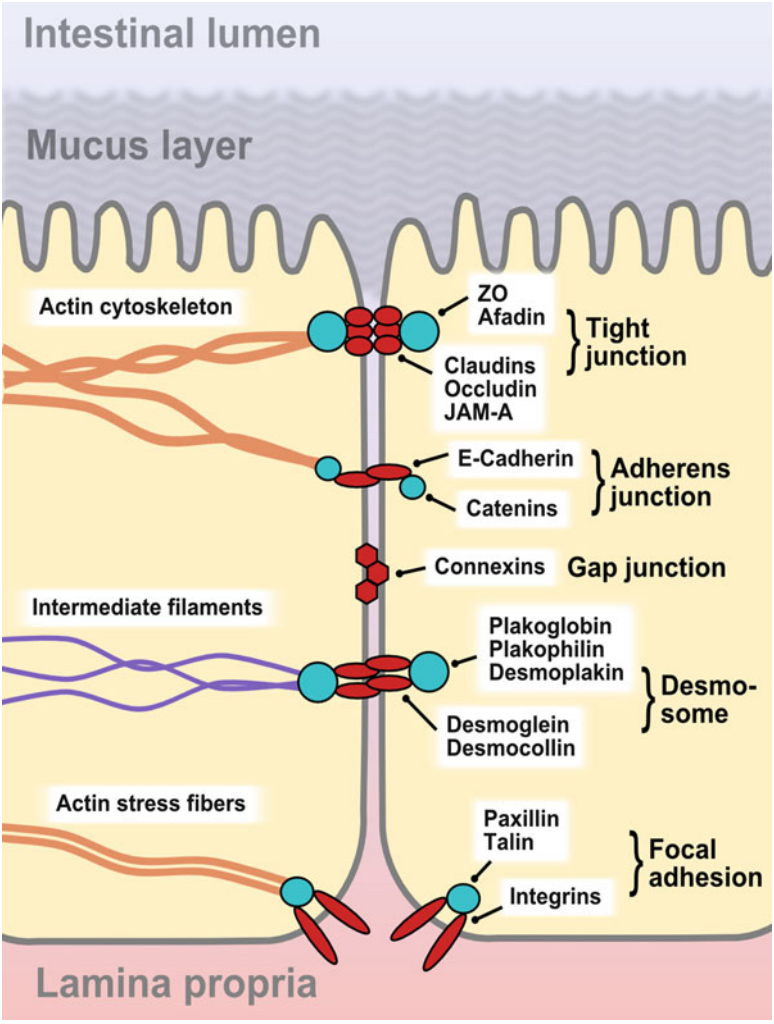

Fig. 13.1 Schematic representation of epithelial junctional complexes. Transmembrane adhesion molecules are shown in *red*; intracellular scaffold proteins are represented in *blue*

persons with IBD, impair barrier function both by inducing aberrant IEC apoptosis and by disassembling the apical junctional complex [9]. Studies from our laboratory and others have shown that key tight junction and adherens junction molecules, including E-cadherin, JAM-A, and occludin, are internalized or degraded during active intestinal inflammation [2]. In addition, it is thought that chronic IBD is associated with a switch from a "tight" to a "leaky" claudin expression profile in epithelial cells, which exacerbates barrier dysfunction and perpetuates inflammation. For example, it has been shown that in active Crohn's disease (CD) mucosa the pore-forming claudin-2 is upregulated, whereas the sealing claudin-5 and claudin-8 are downregulated and removed from epithelial tight junctions [10].

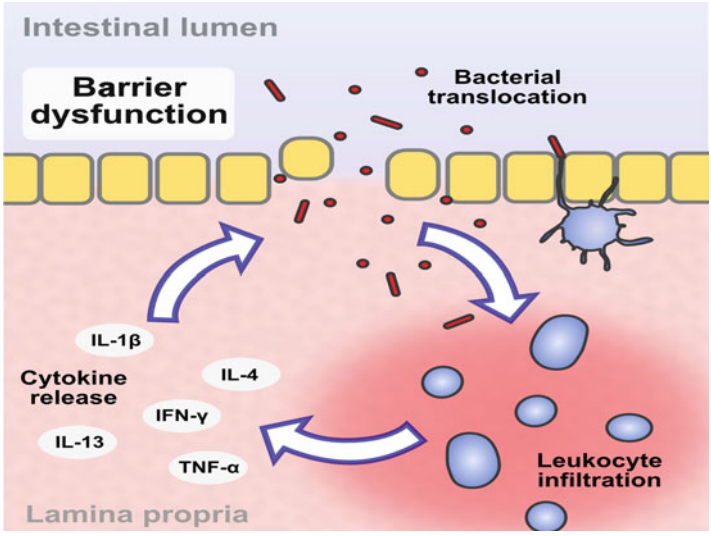

Fig. 13.2 Epithelial barrier defects contribute to the pathogenesis of intestinal inflammation. Breaches in the epithelial barrier result in bacterial translocation into the lamina propria, which causes leukocytes infiltration and the release of inflammatory cytokines. Many cytokines, including IL-1β, IL-4, and IFN-γ increase epithelial permeability, thereby perpetuating the cycle of inflammation

On the other hand, there is evidence that at least in some cases, barrier defects may precede leukocyte infiltration and overt inflammation. Daniel Hollander and colleagues [11] found that healthy relatives of CD patients had increased transepithelial small molecule permeability, which was much higher than in controls. Although this observation raises the possibility that an inherited barrier defect may increase IBD susceptibility, the findings have remained controversial because no such effect was observed in subsequent studies [12–14]. Interestingly, however, Soderholm et al. [15] reported that baseline intestinal permeability was elevated in CD patients and their spouses, rather than their first-degree relatives. In contrast, after acetylsalicylic acid administration, small molecule flux was strongly increased in patients and relatives, whereas spouses responded like healthy controls. It is thus possible that normal transepithelial permeability is determined by environmental factors such as nutrition and that genetic predisposition alters the response of the intestinal epithelium to luminal or mucosal stimuli. However, this intriguing hypothesis remains to be further investigated in future studies.

Animal Models of Intestinal Epithelial Barrier Dysfunction

The remarkable clinical heterogeneity of chronic intestinal inflammation and the limited tools to study epithelial permeability defects in the human gut make it challenging to evaluate the contribution of barrier dysregulation to IBD etiology.

Table 13.1 Select transgenic mouse models of epithelial barrier dysfunction and intestinal inflammation

Model	Intestinal phenotype	AJC molecular changes	Reference(s)
SAMP1/YitFc	Spontaneous chronic ileitis preceded by increased intestinal permeability	Claudin-2 ↑; occludin ↓	[16, 17]
Il10$^{-/-}$	Spontaneous severe enterocolitis preceded by increased intestinal permeability	Not determined	[19, 20]
p120-catenin$^{-/-\,a}$	Spontaneous severe enterocolitis caused by epithelial barrier disruption	E-cadherin ↓; α-catenin ↓; β-catenin ↓	[21]
JAM-A$^{-/-}$	Enlarged lymphoid follicles and enhanced susceptibility to experimental colitis associated with intestinal barrier defect	Claudin-10 ↑; claudin-15 ↑	[24]
Muc2$^{-/-}$	Spontaneous chronic colitis associated with epithelial barrier dysfunction	Claudin-10 ↑; claudin-1 ↓; claudin-5 ↓	[29]
Hnf4α$^{-/-\,a}$	Enhanced susceptibility to experimental colitis associated with intestinal barrier defect	Claudin-2 ↑; claudin-7 ↓; ZO-1 ↓	[35, 36]
Mlck transgene[a]	Enhanced susceptibility to experimental colitis associated with intestinal barrier defect	None detected	[38]

AJC apical junctional complex
[a]Intestine-specific

Considerable interest has been paid to animal models of barrier dysfunction, and there is growing evidence that innate defects in the epithelial barrier increase susceptibility to intestinal inflammation. Although no perfect in vivo model for human IBD has been described to date, results from multiple lines of investigation (summarized in Table 13.1 and discussed below) point toward a common pathological phenotype resulting from diverse genetic defects in IEC homeostatic pathways.

SAMP1/YitFc Mice

One of the most intriguing rodent models of intestinal inflammation is the SAMP1/YitFc (SAMP) mouse, which was derived by repeated brother–sister mating of senescence-accelerated mice (SAM). Matsumoto and colleagues [16] observed that in addition to frequent skin ulceration described in earlier studies, SAMP mice develop spontaneous inflammatory skip lesions in the ileum and cecum, with striking similarities to CD. Disease onset was dependent on the enteric microflora, as germfree mice showed no signs of inflammation, whereas enteritis was inducible by colonization with commensals. More recently, work from Theresa Pizzaro's laboratory showed that SAMP mice exhibit a pronounced intestinal epithelial barrier defect, which precedes the development of overt intestinal inflammation [17].

When compared to the founder AKR mouse strain, SAMP mice have a significantly higher mRNA expression of the "leaky" claudin-2 and, conversely, reduced expression of occludin. Interestingly, barrier dysfunction was also observed in germfree mice, which strongly suggests that the primary epithelial barrier defect is causally linked to the development of intestinal inflammation in these animals. Although the underlying reason for barrier dysfunction in SAMP mice remains to be determined, genetic analyses have implicated mutations in several apical junctional complex-associated genes, including *Cldn2* (claudin-2), *Cdh1* (E-cadherin), and *Mllt4* (afadin), which alone or in combination may compromise junction integrity [18].

Il10-Deficient Mice

Similar to SAMP mice, mice with targeted deletion of the *Il10* gene spontaneously develop intestinal inflammation at around 10 weeks after birth [19]. However, inflammation in these animals extends throughout most of the intestinal tract, and local inflammation restricted to the proximal colon can also be observed in germfree mice, indicative of a more severe disease phenotype. Importantly, mutations in the IL10 pathway are strongly associated with increased susceptibility to IBD in humans, consistent with reduced anti-inflammatory signaling. Although IL10 deficiency primarily affects the function of the innate immune system, there is evidence that loss of IL10 also results in a pronounced epithelial barrier defect. Madsen et al. [20] reported that *Il10*-deficient mice have microbiota-dependent, increased intestinal permeability which was observed weeks before the onset of inflammation. Taken together, these data suggest that barrier dysfunction contributes to disease development in animals with compromised immune homeostasis.

p120-Catenin-Deficient Mice

The stability of epithelial adherens junctions is in part regulated by the catenin protein family, which are intracellular binding partners of E-cadherin. As reported recently, mice deficient for p120-catenin in IEC suffer from early-onset, wasting enterocolitis, with notable fragility of the epithelial monolayer [21]. Structural analysis revealed increased intestinal permeability and neutrophil recruitment in transgenic mice, which was caused by a loss of E-cadherin, as well as α-catenin and β-catenin from the IEC lateral membrane. Thus, genetic impairment of adherens junction integrity results in a breakdown of the epithelial barrier and catastrophic inflammation.

JAM-A-Deficient Mice

Junctional adhesion molecule JAM-A is a tight junction-associated adhesion molecule with important roles in mediating cell–cell contacts, cell migration, and epithelial cell proliferation [22, 23]. Studies from our laboratory have shown that mice with genomic

deletion of the JAM-A coding gene (*F11r*) exhibit increased intestinal permeability and bacterial translocation across the epithelium [24]. Unlike the transgenic animals introduced above, *F11r*$^{-/-}$ mice do not develop spontaneous colitis; however, we observed that JAM-A-deficient mice show signs of subclinical mucosal immune activation, as indicated by enlarged lymphoid follicles and higher myeloperoxidase activity resulting from an increased number of lamina propria neutrophils. In addition, JAM-A-deficient mice were found to be more susceptible to chemically induced colitis, with an earlier disease onset, more severe tissue damage, and increased mortality compared to wild-type controls. Structurally, we observed that IEC from JAM-A-deficient mice had increased expression of claudin-10 and claudin-15, indicative of a leaky epithelial barrier.

Of importance to human pathology, although no JAM-A (*F11R*) defect has been observed in IBD patients, it has been shown that mutations in the *MAGI2* gene are associated with the development of ulcerative colitis [25]. MAGI proteins are PDZ domain-containing scaffold proteins that localize to the tight junction and promote the formation of intracellular signaling complexes, which are at least in part stabilized by JAM family members. It is thus feasible that loss of JAM-associated proteins may compromise the epithelial barrier and increase IBD susceptibility.

Mouse Models of Mucus Layer Defects

The intestinal epithelial barrier is itself protected by a layer of mucus secreted by a specialized type of IEC, the goblet cell. The mucus gel physically limits access of bacteria to surface IEC and stores antimicrobial peptides mainly derived from small intestinal Paneth cells, thereby creating a comparatively germfree environment in the immediate vicinity of the intestinal epithelium. It is thus feasible that alterations in the mucus layer may contribute to IBD pathogenesis, and indeed, changes in mucin deposition and glycosylation have been observed in CD and ulcerative colitis (UC) patients, as well as in some of their healthy relatives [26]. Importantly, a recent study additionally identified goblet cells as an interface for immune cell education [27]. McDole et al. observed that goblet cells in the small intestine act as passages for luminal antigens, which are processed by tolerogenic dendritic cells in the lamina propria.

In agreement with these reports, several recent studies have shown that mice with various genetic defects in goblet cell function and mucus secretion or assembly are prone to intestinal inflammation. For example, mice deficient for mucin 2, the major component of the intestinal mucus layer, spontaneously develop mild colitis and are exceptionally susceptible to chemically induced inflammation [28]. Loss of mucus integrity in these animals was found to be associated with a pronounced epithelial barrier defect, as evidenced by increased claudin-10 mRNA expression and decreased claudin-1 and claudin-5 message levels [29]. Interestingly, aberrant mucin 2 production was also observed in *Il10*$^{-/-}$ mice, suggesting that loss of IL-10 signaling results in a multifactorial imbalance in mucosal homeostasis [30]. Similar to *Muc2* gene-deficient animals, mice lacking core-1- and core-3-derived O-glycans

(i.e., mucin-bound oligosaccharide side chains), or the mucin 2-modifying enzyme AGR2, exhibit varying degrees of colitis susceptibility [31–33]. Although the exact nature of the barrier defect in these animal models remains to be determined, collectively the studies suggest that multiple genetic defects converging on mucus secretion and modification can compromise epithelial barrier function, resulting in enhanced bacterial translocation and increased intestinal inflammation.

HNF4α-Deficient Mice

A somewhat unexpected candidate gene for the development of IBD, *HNF4A*, coding for the transcription factor hepatocyte nuclear factor (HNF)-4α, was recently identified in genome-wide association scans (GWASs) [34]. HNF-4α is strongly expressed in the intestinal epithelium and has been implicated in downregulation of epithelial cell proliferation pathways controlled by Wnt/β-catenin signaling. In particular, it has been shown that IEC-specific deletion of HNF-4α increases epithelial turnover and IEC differentiation into goblet cells [35, 36]. In parallel, Cattin et al. [36] reported that *Hnf4α*-deficient mice exhibit increased intestinal permeability, which is associated with increased claudin-2 expression and reduced claudin-7 and zonula occludens [37] -1 levels. HNF-4α may thus indirectly control intestinal permeability, through transcriptional regulation of epithelial differentiation pathways.

MLCK Transgenic Mice

Additional support for the hypothesis that an innate barrier defect promotes intestinal inflammation comes from a report on mice with IEC-specific over-expression of a constitutively active myosin light chain kinase construct (CA-MLCK) [38]. Myosin-dependent contractility of the perijunctional actin belt is an important mechanism regulating tight junction integrity and, consequently, activation of MLCK results in partial disassembly of the apical junctional complex [2]. Similar to *F11r* and *Hnf4α*-deficient animals, CA-MLCK transgenic mice do not spontaneously develop colitis, but show signs of heightened immune activation in the mucosa and are susceptible to experimental colitis.

IBD Susceptibility Genes Implicated in Epithelial Barrier Regulation

As we have seen, a multitude of studies on transgenic animals suggest that single genetic mutations are sufficient to upset fine-tuning of homeostatic regulation of the intestinal epithelial barrier that may promote development and perpetuation of

Table 13.2 Select susceptibility loci and candidate genes for IBD with a possible role in epithelial barrier regulation, identified in genome-wide association scans (GWAS)

Locus	Candidate gene (protein)	Function in intestinal epithelial cells	Reference(s)
16q22	*CDH1* (E-cadherin)	Principal cell adhesion molecule of the epithelial adherens junction	[34]
1q21	*ECM1* (extracellular matrix protein 1)	Secreted glycoprotein that contributes to cell proliferation	[41, 43]
7p22	*GNA12* (guanine nucleotide-binding protein α12)	Inhibits tight junction assembly by phosphorylation of ZO proteins through Src and HSP90	[37, 44]
20q13	*HNF4A* (hepatocyte nuclear factor 4α)	Transcription factor that regulates differentiation along the intestinal crypt-surface axis	[34, 36]
1q23	*ITLN1* (intelectin-1)	Lectin thought to protect the brush border membrane	[54, 55]
7q31	*LAMB1* (laminin β1)	Secreted protein involved in enterocyte differentiation	[34, 59]
18p11	*PTPN2* (protein tyrosine phosphatase N2)	Inhibits IFN-γ-induced expression of claudin-2	[56, 57]
7q22	*MUC3A* (mucin 3A)	Essential glycoprotein in the protective mucus layer	[52, 60]
12q12	*MUC19* (mucin 19)	Essential glycoprotein in the protective mucus layer	[51]

chronic intestinal inflammation. The obvious questions, of course, are if and how these findings translate to human disease and what lessons we can learn from the animal models. We further discuss here possible roles of recently identified IBD susceptibility genes—summarized in Table 13.2—in the regulation of intestinal epithelial homeostasis and barrier function. Notably, many of the mutations found in humans result in similar phenotypes observed in transgenic mice and suggest that animal models are valuable aids in studies of IBD pathobiology.

CDH1 (E-cadherin)

E-cadherin is the main adhesion molecule in the epithelial adherens junction. Loss of E-cadherin expression results in catastrophic failure of the epithelial barrier, and downregulation of E-cadherin can be seen in active IBD mucosa [39]. A recent GWAS identified a new UC susceptibility region harboring, among others, the *CDH1* gene encoding E-cadherin [34]. Although complete loss of function is unlikely because deletion of E-cadherin is incompatible with life, it is possible that genomic mutations of *CDH1* result in a functionally restricted form of the protein that compromises epithelial barrier function. Indeed, Muise and colleagues [40] reported that a common polymorphism in *CDH1* results in a truncated E-cadherin isoform that does not correctly localize to the plasma membrane. Importantly, these authors additionally found that this mutation is a risk allele for CD, but

interestingly, it was not observed for UC. Nevertheless, these findings indicate that functional changes in E-cadherin impair the epithelial barrier and promote intestinal inflammation.

Extracellular Matrix Protein 1

Extracellular matrix protein 1 (ECM1) is a secreted glycoprotein implicated in number of biological processes, including endothelial cell proliferation and angiogenesis; however, its function in epithelial homeostasis is less well understood. It has been reported that expression of ECM1 is enhanced in epithelial cancers and that it promotes tumor growth through as yet unknown mechanisms [41, 42]. The genomic cluster containing the *ECM1* gene has been identified as an UC susceptibility region, and it has been suggested that mutations in *ECM1* may impair epithelial homeostasis, potentially by reduced activation of NF-κB signaling pathways [43]. Considering that NF-κB is a major regulator of the mucosal immune response and cell survival pathways, it is thus possible that loss of ECM1 may increase cytokine-induced epithelial cell apoptosis and, conversely, reduce proliferation; however, this hypothesis remains to be addressed.

GNA12 (Guanine Nucleotide-Binding Protein α12)

Another recently discovered UC-risk gene is *GNA12*, encoding the heterotrimeric G protein α12 (Gα12) [37]. G proteins are crucial signaling mediators, which relay signals from cell surface receptors to intracellular molecules, but little is known about how Gα12 may regulate epithelial cell homeostasis. It has been shown that Gα12 associates with the tight junction scaffold protein ZO-1 and that it inhibits tight junction integrity in kidney epithelial cells by activation of tyrosine kinase Src, which in turn disrupts the interaction of ZO-1 with claudin-1 and occludin [44]. Interestingly, the authors found that Gα12 itself is activated by heat shock protein (HSP) 90, a stress response chaperone whose expression is increased during inflammation. Recently, these authors reported that reactive oxygen species, which have been shown to accelerate epithelial regeneration [45], activate Gα12 and disrupt the barrier function of kidney epithelial cells [46]. In light of these observations, it appears counterintuitive that *GNA12* mutations might confer susceptibility for chronic colitis. However, it is possible that Gα12 may have different functions in IEC or that the polymorphisms in UC patients increase its activity.

HNF4A (Hepatocyte Nuclear Factor-4α)

As we have discussed in the previous section, HNF-4α is a transcription factor that regulates epithelial homeostasis and barrier function in the intestine. The specific function of HNF-4α in the human remains enigmatic at this time; however, studies

using inducible gene-deficient mice revealed that HNF-4α regulates IEC homeostasis by Wnt/β-catenin signaling-dependent modulation of cell proliferation and differentiation [36], which may—directly or indirectly—have potent effects on regulation of barrier function.

MUC3A and MUC19 (Mucin 3A and 19)

Considering the strong evidence from animal models that defective goblet cell differentiation and epithelial mucin secretion may predispose to the development of chronic intestinal inflammation, it would be expected that impaired goblet cell function may similarly contribute to human IBD. Indeed, it has been noted that mucin composition changes during inflammation, with increased secretion of mucins 1, 2, and 5 and reduced expression of mucins 9 and 17 [47–50]. Recent genome-wide association studies identified rare coding mutation in *MUC19* as a risk factor for Crohn's disease and ulcerative colitis [51]. In addition, Kyo et al. discovered multiple single-nucleotide polymorphisms in the *MUC3A* gene that are weakly associated with the development of Crohn's disease and ulcerative colitis [52, 53]. The specific function and expression of these mucins has not been investigated to date; however, considering the critical role of the mucus layer in the protection of the intestinal epithelium, it is not surprising that even minor alterations in goblet cell function may contribute to IBD pathobiology.

Intelectin-1, Laminin β1, and Protein Tyrosine Phosphatase N2

Multiple additional risk factors identified in genome-wide association studies are thought to protect the intestinal epithelial barrier; however, their specific roles are somewhat enigmatic. Intelectin-1 (ITLN1) is a D-galactosyl-specific lectin expressed in Paneth and goblet cells [54] that was recently found to increase susceptibility for Crohn's disease [55]. Although intelectin-1 has been suggested to promote epithelial barrier function, how this is achieved is poorly understood. Most likely intelectin-1 binds bacteria at the brush border membrane and thus restricts access of potential pathogens to IEC. Alternatively, it is possible that intelectin-1 physically stabilizes the apical membrane of enterocytes, which prevents the release of digestive enzymes into the gut lumen. Laminins are integral structural proteins in the extracellular matrix, and *LAMB1* mutations are associated with increased risk of ulcerative colitis [34]. The effect of loss of function of laminin β1 (LAMB1) in the intestine has not been investigated at this point. Considering the function of laminins as anchoring proteins for epithelial cells, it is conceivable that *LAMB1* mutations weaken the attachment of the epithelium to the basal lamina and thereby drive sloughing off of the mucosa in inflamed tissue. Finally, *PTPN2* has been identified as a risk allele for Crohn's disease [56]. Scharl et al. [57] found that protein tyrosine phosphatase N2 (PTPN2) is induced by IFN-γ and that it attenuates IFN-γ-mediated activation of STAT 1 and 2. Consequently, loss of *PTPN2* results in increased transepithelial permeability and may be involved in the perpetuation of intestinal inflammation.

Concluding Remarks

Taken together, the above observations strongly support a model in which genetic alterations of proteins involved in the regulation of the epithelial barrier promote the activation of the mucosal immune system, most likely by allowing more luminal antigens to cross into the lamina propria. It is interesting to note that these proteins encompass a wide spectrum of functions, ranging from cell–cell adhesion molecules to cytokines and transcription factors, and that their loss results in a remarkably similar intestinal phenotype (see Fig. 13.3). Not all of the mutations investigated in transgenic animal models are associated with overt inflammation, but rather

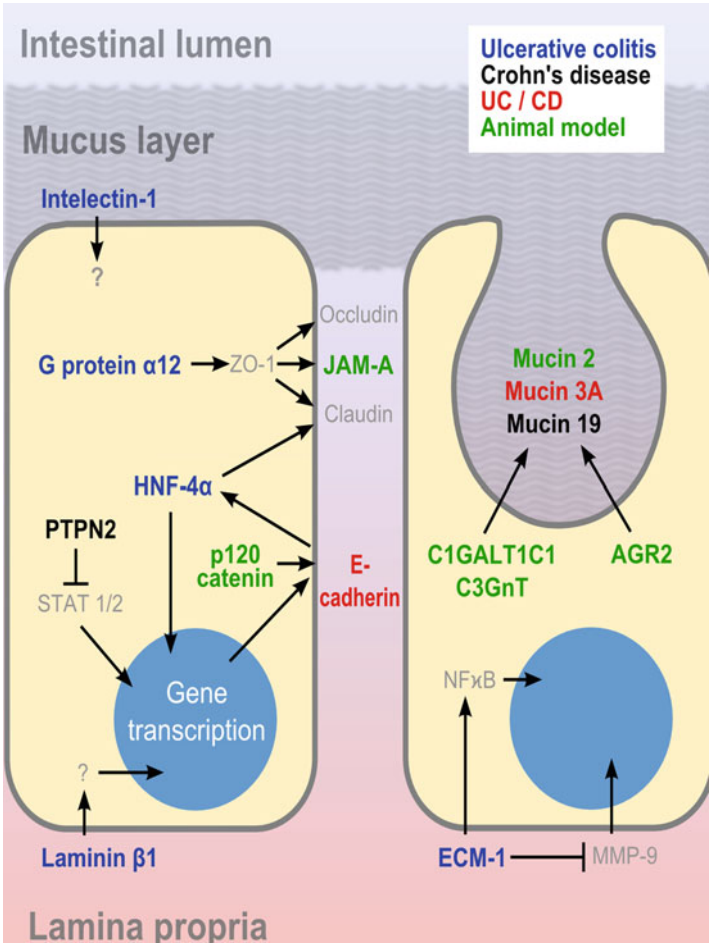

Fig. 13.3 Schematic representation of IBD susceptibility genes, implicated in regulating the epithelial barrier. *Arrows* indicate potential functional connections to intracellular signaling pathways and other structural proteins

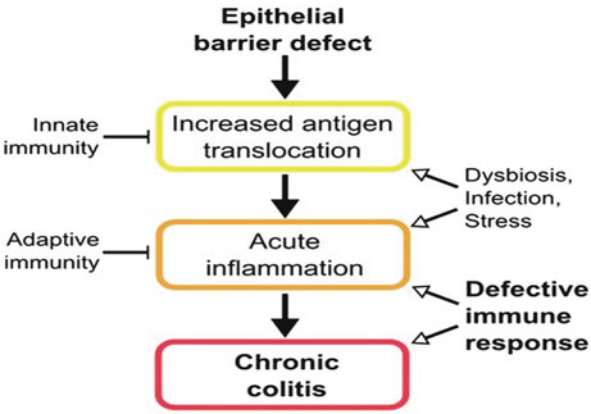

Fig. 13.4 Proposed model of the progression from primary intestinal barrier dysfunction to chronic colitis. Innate and adaptive immunity dampen the pathological response to increased mucosal antigen translocation. Additional defects in the immune system result in chronic inflammation

appear to universally increase the susceptibility to colitis. This observation is compatible with the hypothesis that in most cases, the development of IBD requires two "hits," for example, a host immune defect in conjunction with intestinal dysbiosis [58]. It appears that even when the integrity of the epithelial barrier is impaired, both innate and adaptive immunities are able to suppress inflammation (see Fig. 13.4). Like man, mice may thus be able to compensate to some extent for the loss of barrier-promoting proteins, but will be afflicted with intestinal inflammation if mucosal homeostasis is compromised further.

Also of note is the fact that most of the known susceptibility genes related to epithelial barrier function appear to increase the risk for developing ulcerative colitis, but are not associated with Crohn's disease. It is therefore feasible to speculate that a primary barrier defect can initiate the extensive crypt erosion and superficial inflammation seen in UC, but may not contribute to the striking transmural inflammatory phenotype found in CD. If this is the case, treatment aimed specifically at restoring epithelial barrier function may emerge as a valuable tool for inducing and sustaining remission in ulcerative colitis patients.

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