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REVIEW

The role of mucosal barriers in human gut health

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Abstract The intestinal mucosa is continuously exposed to a large number of commensal or pathogenic microbiota and foreign food antigens. The intestinal epithelium forms a dynamic physicochemical barrier to maintain immune homeostasis. To efficiently absorb nutrients from food, the epithelium in the small intestine has thin, permeable layers spread over a vast surface area. Epithelial cells are renewed from the crypt toward the villi, accompanying epithelial cell death and shedding, to control bacterial colonization. Tight junction and adherens junction proteins provide epithelial cell–cell integrity. Microbial signals are recognized by epithelial cells via toll-like receptors. Environmental signals from short-chain fatty acids derived from commensal microbiota metabolites, aryl hydrocarbon receptors, and hypoxia-induced factors fortify gut barrier function. Here we summarize recent findings regarding various environmental factors for gut barrier function. Further, we discuss the role of gut barriers in the pathogenesis of human intestinal disease and the challenges of therapeutic strategies targeting gut barrier restoration.

Keywords Gut · Epithelial cell · Barrier function · Inflammatory bowel disease · Inflammation

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Introduction

A well-structured network of epithelial and stromal cells in the gut facilitates efficient and selective nutrient absorption while providing a physical barrier against noxious agents. The intestine is covered by a single layer of epithelial cells which are differentiated from pluripotent intestinal epithelial stem cells (IESCs) at the base of the crypt (Santos et al. 2018). The small intestine and colon differ in the gross organ structure and composition/distribution of intestinal epithelial cells (IECs) (Fig. 1). In the small intestine, thin and long villi increase the mucosal surface area for efficient nutrient absorption. In contrast, villi are absent in the colon, but extended crypts efficiently absorb water and metabolic products produced by the microbiome (Allaire et al. 2019).

The small intestine has fewer goblet cells than the colon, but both Paneth cells and M cells are located here. In particular, Peyer's patches and Paneth cells are mostly found in the ileum and are closely associated with a high bacterial density (Ramanan and Cadwell 2016). As there are no Paneth cells in the colon, the expression of antimicrobial molecules is lower here than in the small intestine (Cunliffe and Mahida 2004). However, there are more goblet cells in the colon than in the small intestine and the colon has a thick double mucus layer, firm inner layer, and loose outer layer. As the inner layer is anchored to the intestinal epithelium, which has polymerized mucin 2 (MUC2), microorganisms cannot easily invade the intestinal epithelium. Therefore, there are no microorganisms in the inner mucus layer (Johansson et al. 2008). The inner mucus layer is converted to the outer layer by a MUC2 proteolytic process by the host or bacteria. As a result, the loosened mucus of the outer layer contains microorganisms (Atuma et al. 2001; Johansson et al. 2008).

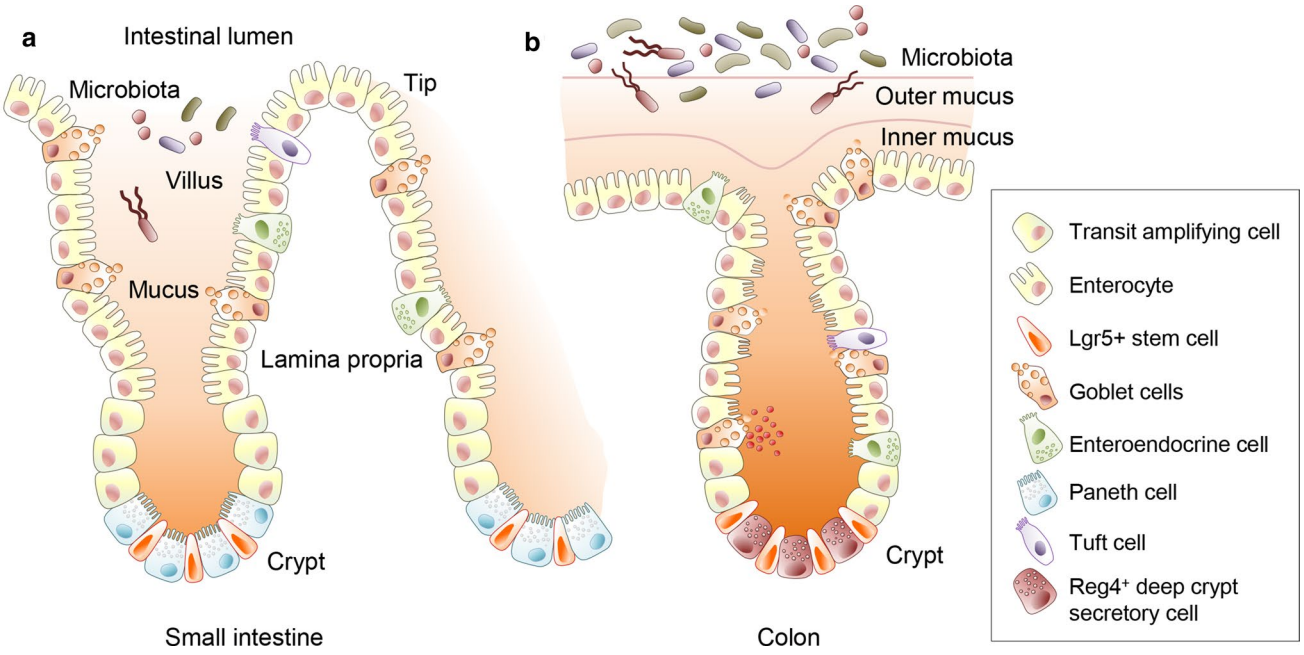

Fig. 1 The difference in epithelial cell composition between the small intestine and colon. Gross features of the small intestine (**a**) and colon (**b**). There are several differences between the two. First, thin and long villi extend from the luminal surface area for nutrient absorption in the small intestine but are absent in the colon. Second, antimicrobial peptide (AMP) producing Paneth cells are in the small intestinal crypt but not the colon. Instead, Reg4$^+$ deep crypt secretory cells in the colon play the same role as the Paneth cells. Third, the colon has a more abundant bilayer mucus than the small intestine due to a larger number of goblet cells. Therefore, the small intestine absorbs nutrients better than the colon. The small intestine and colon both have Lgr5$^+$ stem, TA, enteroendocrine, and tuft cells. Lgr5$^+$ stem cells can self-renew and differentiate into TA cells, which move from the crypt to the villi and can differentiate into tuft, enteroendocrine, and goblet cells

Regarding physicochemical barriers, the gut mucosa has multiple layers to maintain tissue homeostasis (Fig. 2) (Allaire et al. 2019). The outer layer is a microbial ecosystem that competes for and represses pathogens. The next layer is a mucous barrier containing antimicrobial peptides produced by secretory epithelial cells. The third layer is a monolayer epithelium tightly interconnected with tight and adherens junctions, including claudins, occludin, zonula occludens (ZO), and E-cadherin. The final barrier is an immunological surveillance system that controls for and combats external invaders. These multi-layered gut barriers sustain sterile conditions in most organs within the body. In the low-oxygen microenvironment of the gut, fermented short-chain fatty acid (SCFA) metabolites from dietary fibers or other signals help epithelial cells fortify barrier functions in the epithelium. Here we discuss the crucial environmental sensors maintaining the gut barrier, focusing on regulation of the epithelial barrier and its relationship with inflammatory intestinal diseases.

Gut epithelium

The repertoire of intestinal epithelial cells

The most prominent subtypes of intestinal epithelial cells are enterocytes, which absorb water and nutrients (Kong et al. 2018; Serra et al. 2019). Secretory subtypes of IECs include enteroendocrine cells, goblet cells, and Paneth cells (Table 1). Enteroendocrine cells regulate digestive function and the immune and nervous systems via hormone secretion and are divided into at least eight subsets according to their secretory hormones. For example, enterochromaffin cells secrete 5-hydroxy-tryptamine (5-HT, also called serotonin), D cells secrete somatostatin (SST), G cells secrete gastrin, I cells secrete cholecystokinin (CCK), and K cells secrete gastric inhibitory peptide (GIP). Enterochromaffin-like cells secrete histamine, L cells secrete glucagon-like peptide (GLP) and peptide YY (PYY), Mo cells secrete motilin, N

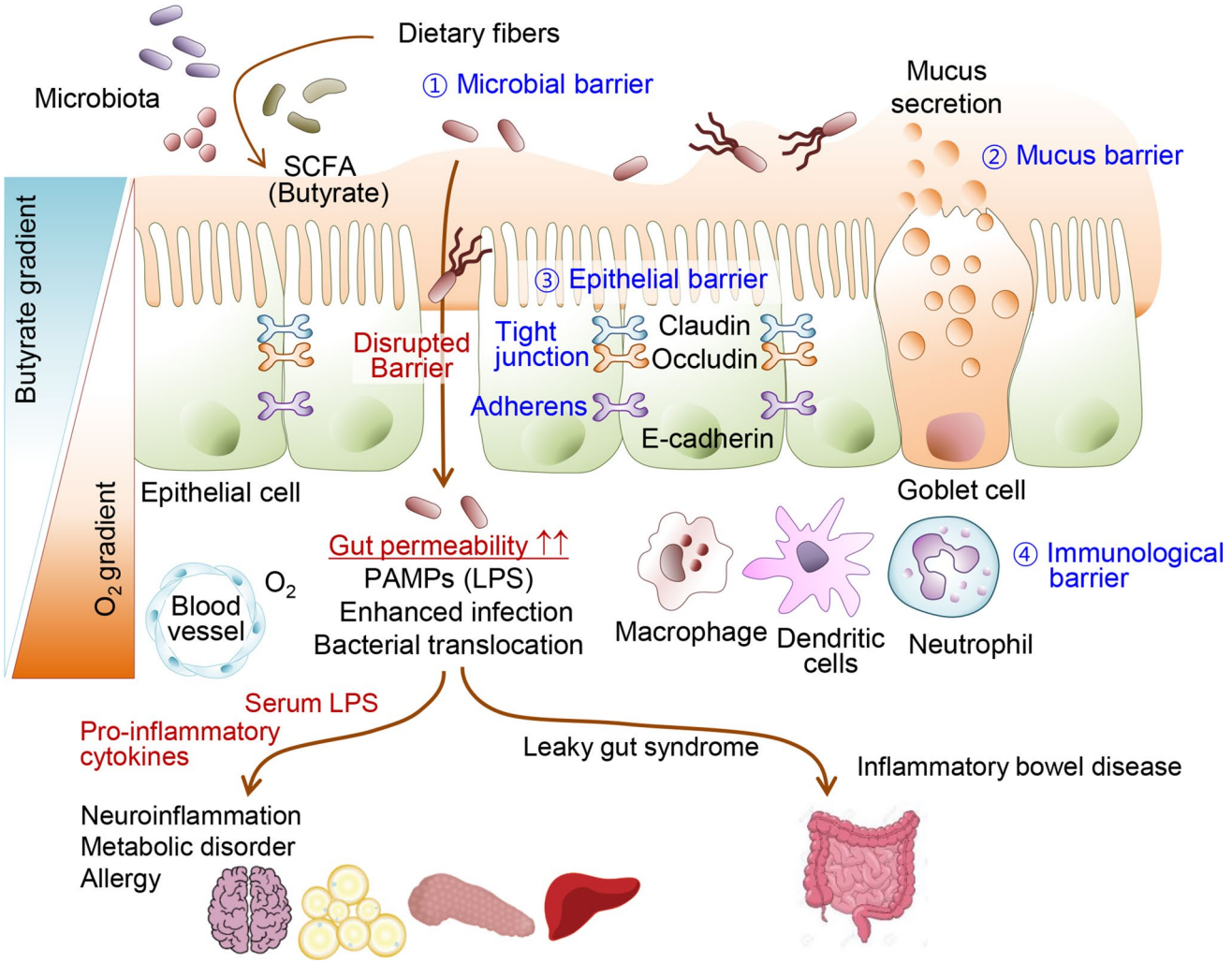

Fig. 2 Disrupted gut barriers induce inflammation and an IBD outbreak. There are three physicochemical barriers in the gut other than the commensal microbiome that protect against pathogens in the gut. First, antimicrobial peptides produced by Paneth cells can disrupt microbial cell walls and membranes by forming pores that induce cell lysis. Second, the mucus layer produced by goblet cells can prevent pathogen invasion. The third barrier is a physical barrier composed of epithelial cells connected by tight and adherens junctions. Gut barrier integrity failures increase gut permeability and bacterial translocation, which lead to an inflammatory response induced by innate immune cells. IBD is induced if these responses lead to chronicity. In the lumen, short-chain fatty acids (SCFAs) produced by anaerobes also contribute to the intestinal barrier integrity

cells secrete neurotensin (NTS), and S cells secrete secretin (SCT) (Helander and Fandriks 2012; Gribble and Reimann 2016). Goblet cells secrete mucins and Paneth cells secrete antimicrobial molecules to form physical and biochemical barriers (Ma et al. 2018; Lueschow and McElroy 2020). Goblet cells secrete glycosylated mucins into the intestinal lumen, forming a mucus layer through the disulfide bond between glycosylated mucins (Fu et al. 2011).

The most abundant MUC2 plays an important role in mucus layer organization on the epithelial surface of the colon but also binds to the glycan receptors of dendritic cells to maintain gut homeostasis and induce anti-inflammatory signaling (Heazlewood et al. 2008; Shan et al. 2013). Mucin secretion by goblet cells can be regulated by gut microbes or their metabolites (SCFAs or cytokines) (Shimotoyodome et al. 2000; Fallon et al. 2002). Goblet cell-derived products such as intestinal trefoil factor (ITF) and resistin-like molecule-β (RELM-β) also regulate intestinal physical barriers. ITF regulates tight junctions and cell apoptosis and promotes epithelial repair. RELM-β controls T_H2-mediated responses (Artis et al. 2004; Aihara et al. 2017). Antimicrobial peptides (AMPs) secreted by IECs are small and basic amino acid-rich proteins. Epithelial cells produce AMPs, such as regenerating islet-derived protein IIIγ (REGIIIγ), in the small intestine, and β-defensin and cathelicidin in the colon (Hase et al. 2002; Cunliffe and Mahida 2004; Vaishnava et al. 2008, 2011).

Table 1 Subtypes of intestinal epithelial cells

Types	Subtypes	Functions	Marker	References
Enterocyte	–	Absorb water and nutrients	AldolaseB	(Kong et al. 2018; Serra et al. 2019)
Enteroendocrine cell	Enterochromaffin cell	Aid intestinal motility reflexes and secretion	5-HT	(Helander and Fandriks 2012; Gribble and Reimann 2016)
	Enterochromaffin like cell	Stimulate gastric acid secretion	Histamine	
	D cell	Inhibit gastrin release	SST	
	G cell	Stimulate gastric acid secretion	Gastrin	
	I cell	Stimulate pancreatic enzyme secretion	CCK	
	K cell	Stimulate insulin release	GIP	
	L cell	Aid carbohydrate uptake, mucosal enterocyte proliferation, and insulin release	GLP-1, GLP-2, PYY	
	Mo cell	Initiate migrating myoelectric complex	Motilin	
	N cell	Inhibit intestinal contractions	NTS	
	S cell	Reduce acid in the upper small intestine	SCT	
M cell	–	Antigen uptake and delivery to APC	GP2	(Mabbott et al. 2013)
Tuft cell	–	Aid initiation of immune response to parasite	DCLK1	(Gerbe et al. 2016; Howitt et al. 2016; Middelhoff et al. 2017)
Goblet cell	–	Mucin production and secretion	MUC2, ITF, RELM β	(Artis et al. 2004; Linden et al. 2008; Aihara et al. 2017)
Paneth cell	–	AMP production and secretion	α-defensin, cathelicidin, REGIIIγ	Porter et al. 2002; Bevins and Salzman 2011; Lueschow and McElroy 2020)

5-HT 5-hydroxy-tryptamine; *SST* somatostatin; *CCK* cholecystokinin; *GIP* gastric inhibitory peptide; *GLP* glucagon like peptide; *PYY* peptide YY; *NTS* neurotensin; *SCT* secretin; *GP2* glycoprotein2; *DCLK1* Doublecortin-like kinase 1 protein; *MUC2* mucin2; *MUC3* mucin3; *ITF* intestinal trefoil factor; *RELM β* resistin-like molecule-β; *REGIIIγ* regenerating islet-derived protein IIIγ

Paneth cells in the crypts of the small intestine secrete lysozymes and a variety of AMPs, such as α-defensin, cathelicidin, REGIIIγ, and sPLA2 (Bevins and Salzman 2011). Defensins and cathelicidin interact with the negatively charged microbial cell membrane to form a pore-like structure, causing cell membrane disruption (Lai and Gallo 2009). REGIIIγ binds to the cell wall peptidoglycans of gram-positive bacteria and catalyzes the formation of pores, inducing bacterial cell lysis (Cash et al. 2006; Mukherjee et al. 2014). Paneth cells are also an important cellular niche for $Lgr5^+$ stem cells via molecules such as Wnt3, EGF, and Notch ligands (Sato et al. 2011). However, there are no typical Paneth cells located in the colon. Instead, $Reg4^+$ deep crypt secretory cells function as the colon equivalent of Paneth cells (Sasaki et al. 2016). Microfold cells (M cells) found in the follicle-associated epithelium specialize in the uptake of luminal antigens and delivery to antigen-presenting cells (APCs) (Mabbott et al. 2013). Cup cells are wine-like cells, accounting for 6 % of ileum epithelial cells, but their function is unknown (Madara 1982). Tuft cells (taste-chemosensory epithelial cells) secrete cytokines to initiate an immune response to parasites (Gerbe et al. 2016; Howitt et al. 2016; Middelhoff et al. 2017).

Homeostasis of intestinal epithelium from stem cells

Intestinal epithelial cells are some of the most proliferative cells in the body. To maintain the integrity and homeostasis of the intestinal barrier against pathogen and xenobiotic attack, epithelial cells constantly regenerate from the crypt region's intestinal stem cells (ISC) (Fig. 3a) (Volk and Lacy 2017). Self-renewal and differentiation of intestinal epithelial cells are associated with the leucine-rich repeat-containing G-protein coupled receptor (GPR) 5 (LGR5). LGR5 is expressed in various body tissues and is a member of the Wnt signaling pathway which plays an essential role

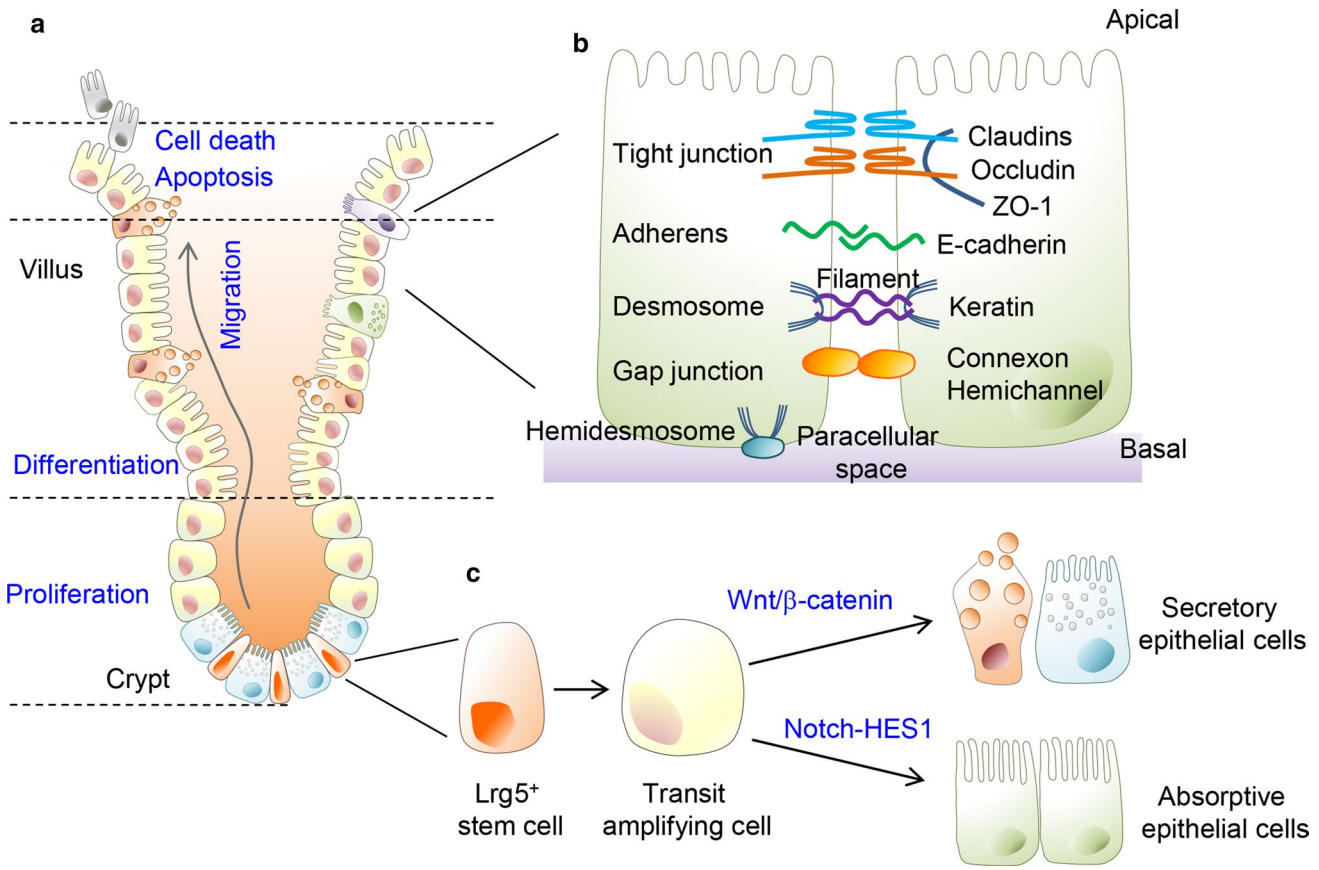

Fig. 3 Dynamic homeostasis of the gut epithelium. **a** Proliferation and differentiation of Lgr5$^+$ stem cells into TA cells simultaneously occur in the intestinal crypt. TA cells are differentiated into secretory and absorptive epithelial lineages during migration from the crypt to villi. When these differentiated cells reach the villi tips, apoptosis occurs via cell signaling. **b** There are various junctions in the paracellular spaces between adjacent cells. The tight junction is composed of claudin, occludin, and ZO-1, and the adherens junction is composed of E-cadherin. There are also desmosomes, gap junctions, and hemidesmosomes in the paracellular space that are involved in transporting nutrients and forming the physical intestinal barrier. **c** TA cells derived from Lgr5$^+$ stem cells can differentiate into secretory or absorptive epithelial lineages. Math1 activation by Wnt/β-catenin signaling, ATOH1, and DLL1 can induce TA cell differentiation into secretory epithelial progenitors. HES 1 activation by Notch signaling can induce TA cell differentiation into absorptive epithelial progenitors

in recovering intestinal epithelium (Hsu et al. 1998; Cordero and Sansom 2012). LGR5 is a representative marker of ISCs, especially in adult tissue, and cancers, as differentiation of the epithelial cells is mediated by multipotent LGR5$^+$ ISCs (Barker et al. 2007; Beumer and Clevers 2016). ISCs divide to proliferate at the bottom of the crypt, and their daughter cells climb to the upper villi, much like a conveyer belt. These rapidly dividing daughter cells, called transit-amplifying (TA) cells, then differentiate into an absorptive progenitor or a secretory progenitor (Hsu et al. 2014).

TA cell plasticity and differentiation are strictly controlled by three major signaling pathways: Wnt, Notch, and bone morphogenetic protein (BMP) (Fig. 3c). Notch-HES1 signaling promotes the TA cells' absorptive lineage (Demitrack and Samuelson 2016; Kim and Jang 2020) post-differentiation to an absorptive enterocyte (Gui et al. 2017). The Wnt-Math1 signaling pathway leads the TA cells to differentiate into a secretory lineage (Yang et al. 2001; Gui et al. 2017). ATOH1 and DLL1 coordinate to form a secretory progenitor (van Es et al. 2012; Tomic et al. 2018). The differentiation process then forms the enteroendocrine cells, goblet cells, and Paneth cells, which are regulated by NEUROG3, GHI1, SPDEF, SOX9, and EPHB3. BMP is critical for balancing Wnt-driven homeostatic proliferation (Medema and Vermeulen 2011). At the crypt domain, Wnt concentration is more dominant than BMP although both Wnt and BMP signals are important for axis between self-renewal and differentiation. In contrast, at the villi domain, BMP concentration is more dominant than Wnt which mediates proliferation versus differentiation (Spit et al. 2018). The strict, rapid differentiation and proliferation of epithelial cells promote intestinal homeostasis. Impaired or damaged cells can be removed or replaced by newly differentiated cells (Gu et al. 2011; Bischoff et al. 2014). Increased epithelial proliferation removes parasitized or infected epithelial cells (MacDonald 1992), while crowding of epithelial cells extrudes the villi,

preventing excessive epithelial cell accumulation and tumor formation (Eisenhoffer et al. 2012).

Intestinal organoid is one of useful in vitro models for patient specific investigation of the intestinal epithelium hereafter the first establishment in 2009 for self-organizing 'mini-guts' (Sato et al. 2009). Single Lgr5$^+$ ISCs or isolated crypt containing ISCs are seeded into a supporting Matrigel matrix which provides stem cell niche. The isolated ISCs have the ability to survive, proliferate, self-organize into 3-dimensional structures in vitro. They require Wnt/Notch for self-renewal and differentiation (Angus et al. 2019). Wnt in the small intestine can be provided by mesenchymal cells and Paneth cells. Unlike intestinal organoid originated from small intestine, colonic organoid does not contain Wnt-producing Paneth cell, which therefore require more exogenous Wnt supplement (Takahashi and Shiraishi 2020). Patient-derived gut organoids can be utilized for investigating infectious disease, whole-genome sequencing, drug screening and regenerative medicine.

Epithelial cell junctions

Cell-cell junctions are a well-organized, structural continuum of the extracellular connection between adjacent cells. They are composed of different cytoskeleton elements (Fig. 3b). These junctions maintain homeostasis by regulating tissue integrity and ion, solute, and microbe diffusion across the tissue.

Tight junction

Mammals have tight junctions in the apex of the lateral plasma membranes between adjacent cells. Tight junctions surround each cell form a proteinaceous film that regulates ion and solute diffusion via a paracellular pathway. Tight junctions maintain the division of apical and basolateral membrane proteins and lipids (Zihni et al. 2016). Tight junctions are composed of transmembrane protein families, including claudin, occludin, and the peripheral membrane adaptor protein ZO (Van Itallie and Anderson 2014; Lee et al. 2018a). In human studies, claudin 1, 2, 3, 4, 5, 7, 8, 12, and 15 are expressed in the small intestine (Lu et al. 2013). Claudin and occludin form homotypic complexes between cells. ZO-1, 2, and 3 connect occludin and claudin to the actin cytoskeleton, which maintains the tight junction formation. The mutual assembly of tight junction proteins forms different pore-sized networks, mediating the differential diffusion of ions and solutes (Zihni et al. 2016). Since the permeability of ions of different sizes and charges is determined according to the amino acids in the claudins, diffusion varies with the expressed claudin type (Van Itallie and Anderson 2006). While the precise mechanism of action remains elusive, occludin regulates tight junction stability, permeability, and barrier function through phosphorylation and a ZO-1 interaction (Lee et al. 2018a).

Adherens junction

Adherens junctions are protein complexes that are usually more basal than the tight junction (Guo et al. 2007). The adherens junction plays a role in cell-cell adhesion, actin cytoskeleton regulation, cell signaling, and gene transcription (Takeichi 2014). Cadherin, such as E-cadherin, is the main type of transmembrane protein comprising the adherens junction. The cadherins connect to adjacent cadherins in a calcium-dependent manner. These cadherins indirectly bind α-catenin via β-catenin, and in turn α-catenin links to the actin cytoskeleton (Knudsen et al. 1995). P120-catenin linked with the cadherin ternary complex is associated with the cadherin juxtamembrane domain, which suppresses cadherin endocytosis (Davis et al. 2003). E-cadherin adhesion can be intensified through the protein vinculin's link to a force-dependent conformation of α-catenin (le Duc et al. 2010). Nectins bind to afadins which are involved in Ca^{2+}-independent cellular adhesion (Takai and Nakanishi 2003). These nectin-based adhesions make the first cell-cell junction, which then recruit the cadherin-catenin complex to form the adherens junction (Tachibana et al. 2000; Honda et al. 2003).

Environmental sensors for gut barriers

Epithelial cells are the primary cellular determinant of the epithelial barrier function in the gut. Epithelial cells express toll-like receptors (TLRs), which are essential for the recognition of conserved microbial factors. There are several environmental sensors involved in maintaining the gut epithelial barrier, such as hypoxia-induced factor (HIF), aryl hydrocarbon receptor (AhR), and SCFAs. Here, we will focus on the cellular mechanism and relationship of these environmental sensor signals for gut barrier integrity.

Short-chain fatty acids (SCFAs)

SCFAs are microbiota-derived metabolites, such as acetate, propionate, butyrate, and valerate, which are produced from dietary fibers through the fermentation of anaerobic flora (Fig. 4). SCFAs are passively diffused from the lumen to the cell and then transported into the cells via carrier proteins, such as proton-coupled monocarboxylate transporter 1 (MCT1) and sodium-coupled monocarboxylate transporter 1 (SMCT1) (Sivaprakasam et al. 2017; Parada Venegas et al. 2019). These are agonists for the G-protein coupled receptors (GPR) 41/FFAR3, GPR43/FFAR2, and GPR109A/NIACR1, leading to various immune responses

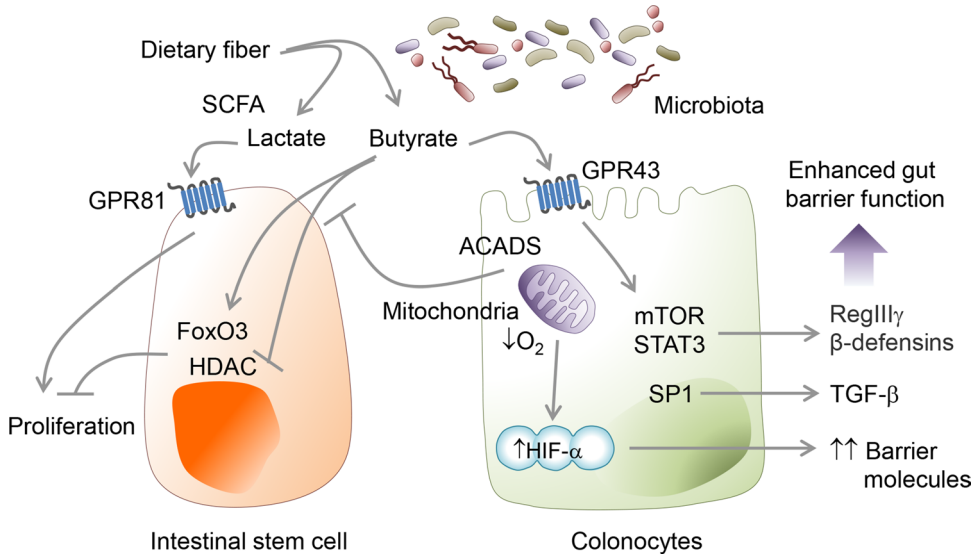

Fig. 4 The role of SCFAs in gut barrier function. SCFAs produced by the microbiota after anaerobic fermentation of dietary fiber can be recognized by G-protein coupled receptors such as GPR41, 43, 81, and 109 A. When butyrate is recognized by GPR43, STAT3 expression is induced by the mTOR pathway and STAT3 can induce REGIIIγ and β-defensin expression. This can induce SP1 expression, the transcription factor for TGF-β expression in colonocytes that inhibits ISC proliferation by HDAC inhibition and FoxO3 expression. Lactate, which is recognized by GPR81, can induce ISC proliferation. Mitochondrial oxygen consumption during butyrate metabolism can indirectly stabilize HIF-α

in IECs, dendritic cells, and macrophages (Priyadarshini et al. 2018). Butyrate can facilitate differentiation of IL-10 producing Tregs and reduce the pro-inflammatory cytokine TNF-α from macrophages, which promotes inflammation by recruiting neutrophils in the gut (Vinolo et al. 2009; Lee and Hase 2014). SCFAs enhance antimicrobial peptides such as REGIIIγ and β-defensin via activation of mTOR and STAT3 in the epithelium barrier. (Zhao et al. 2018; Chen and Vitetta 2020). In ISCs of colon crypt, butyrate can suppress cell proliferation by inhibiting histone deacetylases (HDAC) and enhancing promoter activity for the negative cell-cycle regulator FoxO3. Fully differentiated colonocytes metabolize and reduce butyrate levels through Acyl-CoA dehydrogenase (ACADS) (Kaiko et al. 2016; Xiao et al. 2018). However, lactate accelerates stem cell proliferation dependent on GPR81 (Lee et al. 2018b). Butyrate can promote TGF-β expression through HDAC inhibition and SP1 (Martin-Gallausiaux et al. 2018). In association with other environmental signals, butyrate can stabilize HIF as O_2 consumption for its metabolic process causes cellular hypoxic conditions (Kelly et al. 2015). These findings suggest that crosstalk between microbiota-derived SCFAs and intestinal epithelial HIF augments gut barrier function.

Toll-like receptor (TLR)

TLRs are representative pattern recognition receptors (PRR) with a transmembrane protein form that can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Kawasaki and Kawai 2014). TLRs are identified from TLR1 to TLR13, with TLR1 to TLR10 found in human cells. Each TLR is combined in a heterodimer or homodimer that can recognize various ligands according to its combination. If TLR ligands are recognized, two major types of adaptor proteins, such as Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF) and myeloid differentiation factor 88 (MyD88), can mediate downstream signals (Kamdar et al. 2018). NF-κB is a transcription factor that expresses pro-inflammatory cytokines such as IL-1, IL-6, IL-12, and TNF-α (Mukherjee et al. 2016).

In both Crohn's disease and ulcerative colitis (UC) patients, expression of TLR1, TLR2, TLR6, TLR8, and TLR9 remains unchanged, while expression of TLR4 and TLR5 is increased compared to healthy controls (Kordjazy et al. 2018). In immunocompetent cells, TLR signaling generally induces innate immune responses. In chronic inflammation, it mediates intestinal barrier breakdown via inflammatory mediators, such as TNF-α (Peterson et al. 2010). However, activation of TLRs by the commensal microflora controls intestinal epithelial homeostasis and protects against injury (Rakoff-Nahoum et al. 2004). In intestinal epithelial cells, TLR2 stimulation efficiently preserves ZO-1-associated barrier integrity against stress-induced damage, which is controlled by PI3K/AKT and conventional protein kinase C (PKC) isoforms via MyD88 (Cario 2008). TLR1-deficient mice have increased permeability and reduced transmucosal resistance followed by

increased bacterial translocation to systemic organs (Kamdar et al. 2018). These findings suggest that TLR1–TLR2 signaling sustains epithelial integrity through the tightening of intercellular junctions. Conversely, TLR4 activation induces enhanced barrier permeability and leaky gut through upregulation of myosin light chain kinase (MLCK), which mediates the opening of tight junctions by promoting actin-myosin filament contraction(Nighot et al. 2017). In indirect association with other environmental sensors, TLR3 and TLR4 activation can upregulate HIF-1α gene expression at the mRNA level via the NF-κB pathway (Han et al. 2016). LPS induces TLR4 signaling, which drives ferritin-mediated iron sequestration and results in deprivation of an essential PHD cofactor, free iron, followed by HIF-1α stabilization (Siegert et al. 2015). These findings demonstrate that different TLR signals are associated with the differential control of the intercellular barrier integrity by enhancing or disrupting intestinal epithelial barrier junction molecules. This depends on the type of microbe.

Aryl hydrocarbon receptor (AhR)

AhR is a ligand-dependent intracellular transcription factor (Rothhammer and Quintana 2019). AhR is usually combined with the heat shock protein 90 (HSP90) dimer and X-associated protein 2 (XAP2) in the cytoplasm (Fig. 5). AhR contains two regions, the Per-Arnt-Sim (PAS) domain and the basic Helix/Loop/Helix (bHLH) domain. The PAS domain is located in AhR's C-terminal, which plays a role in maintaining the cytosolic AhR complex in the absence of ligands. The bHLH domain is in AhR's N-terminal, which contains a nuclear localization sequence (NLS) dependent on AhR ligands and a nuclear export sequence (NES) (Hao and Whitelaw 2013). Once AhR ligands such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 6-Formyl indolo[3,2-b]carbazole (FICZ), and 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) are bound to the AhR-HSP90 dimer-XAP2 complex, AhR NLS is exposed and the ligand-AhR complex is transported into the nucleus (Ikuta et al. 1998;

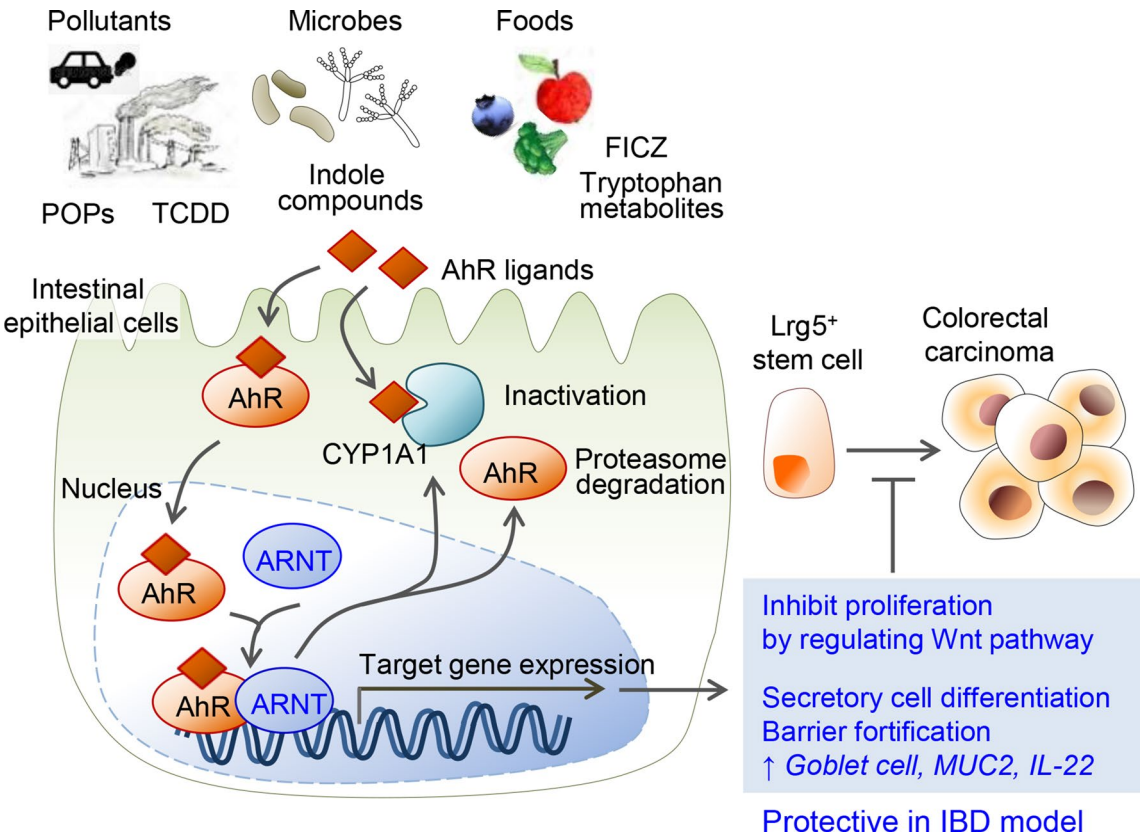

Fig. 5 The role of AhR signaling in gut barrier function. Ligands such as TCDD, FICZ, and ITE are essential for AhR activation. When ligands bind to the AhR/Hsp90/XAP2 complex, it moves from the cytoplasm to the nucleus and binds to ARNT. This complex acts as the transcription factor for XRE, which is involved in CYP1A1 and AhRR expression. If the AhR-ARNT complex is not formed by AhRR, AhR moves from the nucleus to the cytoplasm and it is degraded by the proteasome. CYP1A1 can also metabolize the AhR ligand, inactivating AhR signaling. AhR activation can induce tight junction component expression and goblet cell differentiation and inhibit $Lgr5^+$ stem cell proliferation by regulating Wnt/β-catenin signaling

Ehrlich et al. 2018). In the nucleus, the AhR-ligand complex that has dissociated from the HSP 90 dimer-XAP2 combines with the AhR nuclear translocator (ARNT, also known as HIF-1β). The AhR-ARNT complex is recruited to the xenobiotic response element (XRE) and acts as a transcription factor for the expression of molecules such as cytochrome P450 family-1 subfamily-A polypeptide-1 (CYP1A1), CYP1B1, and AhR repressor (AhRR) (Zhu et al. 2019). CYP1A1 is a representative metabolizing enzyme in the cytoplasm that can reduce AhR signaling via ligand consumption (Schiering et al. 2017). AhRR also competes with the AhR-ligand complex for ARNT. When ARNT is combined with AhRR, exposure to AhR NES mediates the relocation of the AhR-ligand complex from the nucleus to the cytoplasm. It is then finally degraded by proteosomes in the cytoplasm (Ikuta et al. 1998; Rothhammer and Quintana 2019).

AhR is expressed in epithelial and immune cells in the gut and plays a role in the intestinal barrier's homeostatic and inflammatory conditions. AhR promotes anti-inflammatory DC and induces Th17 differentiation and Treg stabilization. In a 2, 4, 6-trinitrobenzenesulphonic acid (TNBS) colitis model, activation of AhR by FICZ reduced inflammatory cytokines and induced IL-22 expression in DCs and $CD4^+$ T cells, which triggers AMP production and reinforces the mucus barrier (Monteleone et al. 2011). In dextran sulfate sodium (DSS)-induced colitis, AhR activation by FICZ enhanced the expression of tight junction proteins such as ZO-1, claudin-1, and occludin to reduce barrier permeability (Yu et al. 2018). AhR-deficient IECs abnormally function in the Wnt/β-catenin and ubiquitin E3 ligase signaling pathways (Metidji et al. 2018). AhR controls IEC self-renewal by limiting ISC proliferation and promoting its differentiation. AhR in IECs enhances IL-10 receptor expression to boost their responsiveness to IL-10 and enhance epithelial barrier function (Lanis et al. 2017). In the IECs of a Crohn's disease patient, miRNA-124 induced pro-inflammatory transcriptional programs by targeting AhR (Zhao et al. 2016). In contrast with AhR's barrier protection, dietary and microbial oxazoles activate indoleamine 2, 3-dioxygenase 1(IDO-1) to generate tryptophan metabolites, which inhibited IL-10 production and induced intestinal inflammation (Iyer et al. 2018). SCFAs, especially butyrate, enhance the AhR pathway and AhR-dependent genes in IECs, which suggests that butyrate may be a potential AhR ligand (Marinelli et al. 2019). In association with other environmental sensors, AhR competes with HIF-1α to interact with ARNT (HIF-1β) (Chan et al. 1999). This integration of HIF-1α and AhR might lead to interference between the two signaling pathways in a variety of cellular responses. AhR promotes HIF-1α degradation in Tr1 cells (Mascanfroni et al. 2015). Research must examine the crosstalk between HIF-1α and AhR in IECs and its effect on gut barrier function.

Hypoxia-inducible factor (HIF)

HIF is an oxygen-sensitive transcription factor and a cellular survival mechanism for hypoxic stress that is related to cellular metabolism, the intestinal barrier, erythropoiesis, and angiogenesis (Glover and Colgan 2011). Receptor tyrosine kinase (RTK) in the plasma membrane recognizes growth factors and activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of the rapamycin (mTOR) signaling pathway. Activated mTOR can induce production of the HIF-α molecule as a transcription factor (Guo et al. 2015). These factors consist of three oxygen-sensitive α-subunits of HIF molecules called HIF-1α, HIF-2α, and HIF-3α and a conserved β-subunit, HIF-1β, also known as aryl hydrocarbon receptor nuclear translocator (ARNT) (Rankin and Giaccia 2008).

In normoxia, HIF-α is hydroxylated at the proline or asparagine residues by prolyl hydroxylase (PHD) and asparaginyl hydroxylase factor inhibiting HIF (FIH) (Fig. 6). Hydroxylated HIF-α in the cytoplasm is ubiquitinated by the von Hippel-Lindau protein (pVHL), leading to their proteasomal degradation. In hypoxia, HIF-α accumulates in stable condition and translocates from the cytoplasm to the nucleus, where it binds to HIF-1β and 300-kilodalton coactivator protein (p300)/CREB binding protein (CBP). This complex acts as a transcription factor for hypoxia response element (HRE), expressing genes that allow for adaptation or survival under hypoxic conditions (Cavadas et al. 2013). HIF's hypoxia-induced responses can induce or regulate inflammation according to different cells in the gut. Hypoxia may represent an environmental cause for inflammatory bowel disease (IBD) pathogenesis. Both HIF-1α and HIF-2α are found in high levels in IECs in active UC or Crohn's disease patients (Xue et al. 2013).

Hypoxia promotes IECs to produce TNF, leading to an increase in epithelial barrier permeability (Taylor et al. 1998). HIF signals in the innate immune cells, including neutrophils, macrophages, and dendritic cells, enhance pro-inflammatory cytokine production (Bosco et al. 2011). In contrast, hypoxia-exposed IECs in the physiological gut lumen induce barrier-preservative factors to reduce the inflammatory burden of ITF, MUC3, and CD73 expression. Even transmigrating neutrophils rapidly deplete microenvironmental oxygen, which leads to the stabilization of HIF molecules in the gut epithelium (Campbell et al. 2014). In experimental animal models of oxazolone and TNBS-induced colitis, HIF-1α isoform expression was beneficial in ameliorating inflammation via induction of barrier-protective genes (Karhausen et al. 2004). In experimental murine DSS-induced colitis, HIF-2α augmented intestinal inflammation via increased inflammatory responses (Shah et al. 2008). The PHDs consist of three isoforms, PHD1, PHD2, and PHD3, which mediate diverse functions in

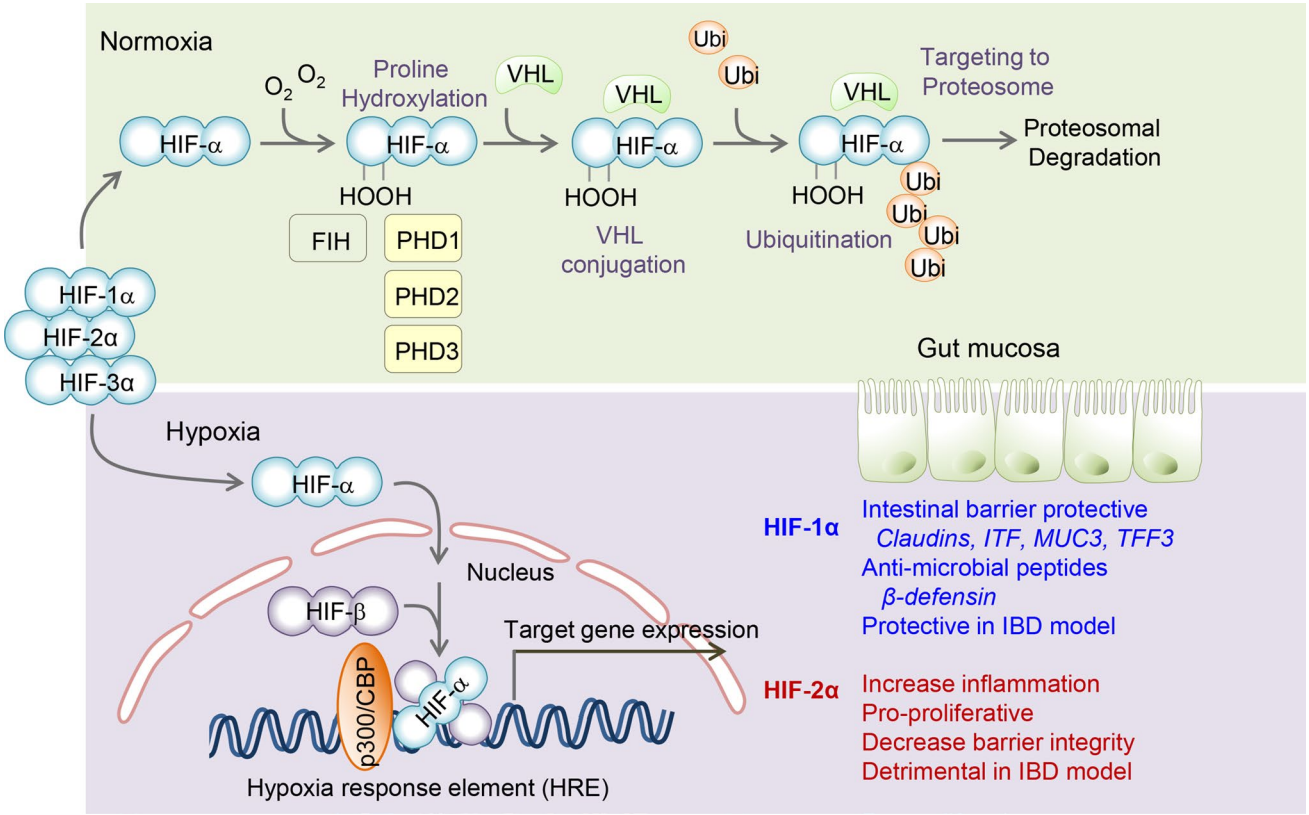

Fig. 6 The role of HIF signaling in gut barrier function. In normoxia, proline or asparagine hydroxylation occurs in HIF-α by PHD or FIH. pVHL is also conjugated into hydroxylated HIF-α, leading to ubiquitination and proteasomal degradation. In hypoxia, HIF-α are stabilized and accumulate without hydroxylation. They move from the cytoplasm to the nucleus and bind to p300/CBP and HIF-β, forming a heterodimer. This acts as the transcription factor for HRE, with the gene expression depending on subtype. HIF-1α induces the expression of genes involved in enhancing intestinal barrier function, such as β-defensin, MUC3, and ITF. HIF-2α induces pro-proliferative and pro-inflammatory gene expression, which decreases barrier integrity in the IBD model

immunocompetent and non-immune cells. Deficiency of PHD1 or PHD3 protects intestinal epithelial barrier integrity in mice (Tambuwala et al. 2010; Chen et al. 2015). These results suggest differential effects of HIF isoforms in gut homeostasis.

Relation with human IBD and therapeutic strategies

Gut barriers in IBD

Defects in the gut barrier are associated with a broad range of human diseases, such as IBD, and extra-intestinal diseases, such as non-alcoholic fatty liver disease and neurologic brain diseases (Fig. 2) (Vancamelbeke and Vermeire 2017). IBD is a chronic inflammatory disease in the gastrointestinal tract comprising uncreative colitis and Crohn's diseases. Possible causes include combined host genetic alterations and environmental factors. IBD is thought to be closely related to immune function alterations caused by commensal microbiota (Zhang and Li 2014). In a healthy adult gut, Firmicutes, Bacteroidetes, Proteobacteria, and Actinomycetes co-exist in balance. Patients with IBD, especially UC patients, have decreased Firmicutes and Bacteroidetes and increased Proteobacteria and Actinomycetes (Machiels et al. 2014). This dysbiosis disrupts the balanced microbial composition and accumulates bacterial toxins such as LPS. IBD patients have higher intestinal permeability than healthy groups (Michielan and D'Inca 2015). Occludin expression systemically decreases at the mRNA and protein levels in patients with uncreative colitis and Crohn's diseases. Expression of tight junction and adherens junction components such as ZO-1, claudin, E-cadherin, and β-catenin decreases in epithelial cells in inflammatory regions. This is mainly caused by circulating pro-inflammatory cytokines, such as IFN-γ, TNF-α, and IL-13 (Fries et al. 2013). TNF-α increases epithelial permeability through alterations in tight junction function, structure, and dynamics upon infection (Capaldo and Nusrat 2015).

Gut barrier fortification as a target of IBD therapeutics

Current novel IBD drugs have mainly focused on controlling inflammation, as this is the most important disease symptom (Neurath 2017). Recently, biologics to block key mediators of pathogenic inflammation, such as TNFs or integrin, have been increasingly used in IBD patients. TNF-α blockers can reduce the excessive inflammatory response and gut permeability (Suenaert et al. 2002). In addition, therapies that block cytokine signaling have been developed, such as Janus kinases (JAKs) inhibitors and tofacitinib (Danese et al. 2016). Fecal microbiota transplant involves feces from healthy donors being transplanted into IBD patients. The changes in intestinal bacterial composition are expected to have beneficial effects in IBD patients (Lopez and Grinspan 2016). However, novel fundamental modulators need to be further investigated.

One current IBD therapeutic strategy is to restore the gut barrier function (Fig. 7). The protective role of HIF-1α during gut inflammation has led to the investigation of PHD inhibitors as a potential therapeutic strategy. Pan-PHD inhibitors, such as dimethyloxalylglycine (DMOG) and FG-4497, can reduce the symptoms of experimental murine colitis (Cummins et al. 2008; Robinson et al. 2008). Oral administration of AKB-4924 or TRC160334 protects against murine colitis and reduces systemic off-target effects in extra-intestinal organs (Gupta et al. 2014; Marks et al. 2015). Several pan-PHD inhibitors are currently being examined for the treatment of various diseases, including IBD (Marks et al. 2015). Further, local treatment of AKB-4924 is currently under phase I clinical trials (NCT02914262).

Based on the beneficial effect of SCFA on the gut barrier, Phase 2 clinical trials with GLPG0974, a GPR43-specific antagonist, in individuals with mild-to-moderate UC did not change clinical outcomes over a short period (Bolognini et al. 2016).While SCFAs have presented beneficial effects in experimental systems of intestinal inflammation, clinical effects remain controversial (Galvez et al. 2005).

Oral treatment with the microbial metabolite Urolithin A (UroA) derived from polyphenolics in berries and pomegranate fruits and its analog UAS03 significantly enhanced gut barrier function and inhibited gut inflammation, suggesting a potential therapeutic application for the IBD treatment (Singh et al. 2019). AhR ligands such as indigo from plants can promote mucosal healing by inducing IL-22 production from type 3 innate lymphocytes cells (ILC3) (Zelante et al.

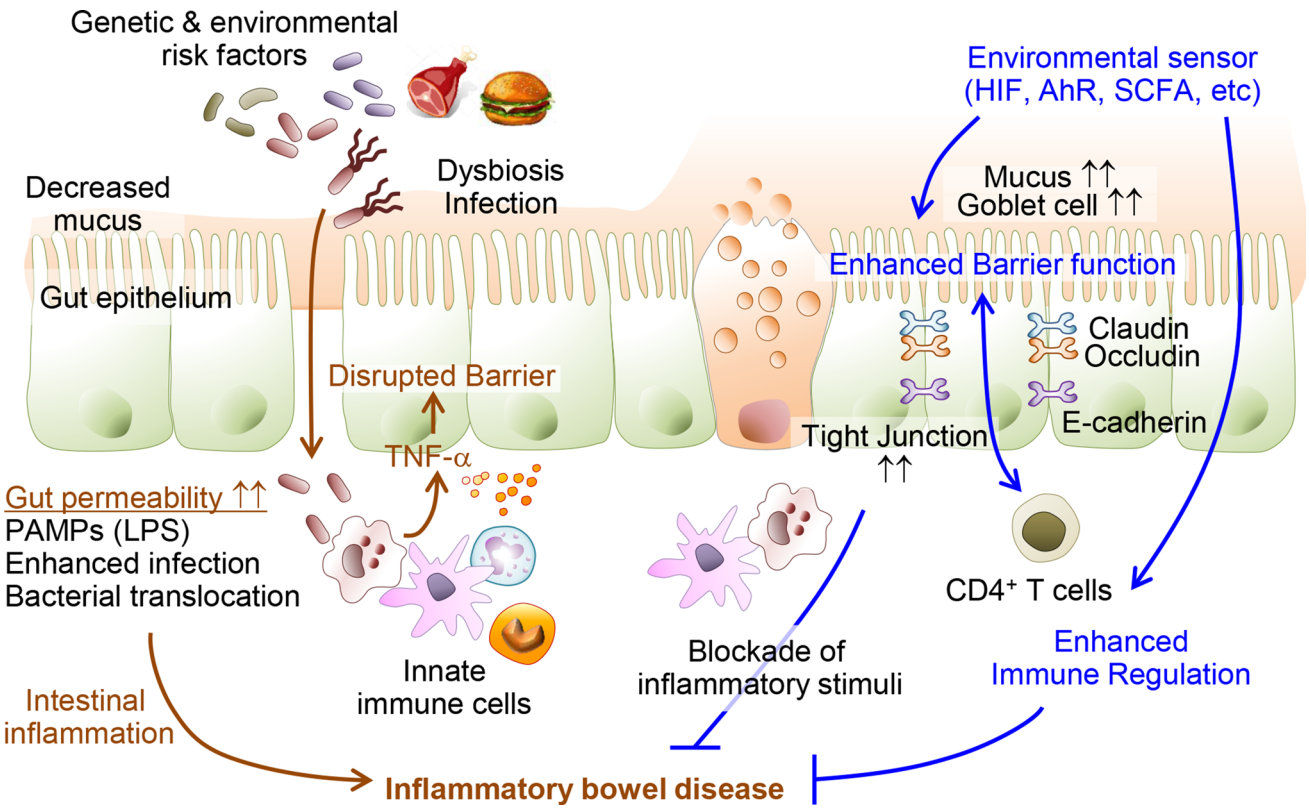

Fig. 7 Overview of IBD and therapeutic approaches. IBD, a chronic inflammatory disease in the lower gastrointestinal tract, has complex genetic and environmental reasons. On a cellular level, decreased mucus, dysbiosis in the lumen, infection, and a severe inflammatory response via innate immune cells are related to IBD pathogenesis. Recent research regarding the role of gut environmental sensors in reducing inflammation via fortification of the gut barrier has shed light on the development of novel IBD therapeutics

2013). In a prospective, randomized, double-blind, placebo-controlled trial, indigo naturalis effectively induced a clinical response in UC patients. However, its safety has not been established because of potential adverse effects, including pulmonary arterial hypertension (Naganuma et al. 2018). TLR2-p treatment significantly reduced colitis-associated conditions, suggesting that the TLR2 signaling pathways are promising therapeutic targets (Laroui et al. 2012). TLR9 activation improved mucosal healing and symptomatic remission in UC patients (Atreya et al. 2016). Palmitoylethanolammide (PEA) improves the acute phase of the intestinal inflammation that occurs in UC through enteric glia/toll-like receptor 4-dependent PPAR-α activation (Esposito et al. 2014). MLCK is a potential therapeutic target as epithelial MLCK–dependent barrier dysfunction following TLR signaling mediates intestinal inflammation (Clayburgh et al. 2005). Divertin blocks MLCK1 recruitment without inhibiting enzymatic function, which corrects barrier dysfunction and prevents intestinal inflammation (Graham et al. 2019).

Concluding remarks

Biological barrier homeostasis is critical for protecting against infection. In the gut mucosa, barrier integrity is critical since the gut has a unique environment consisting of nutritional and microbial factors. Barrier function breakdown initiates local inflammation in luminal products followed by the onset of intestinal inflammatory disease. Research indicates that epithelial cells utilize gut environmental sensors to maintain these barriers. Currently, novel therapeutic targets for barrier modulation via environmental sensors have been studied in animal models and human trials. Barrier and anti-inflammatory modulators are a promising therapeutic option for treating IBD.

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Declarations

Conflict of interest The authors declare they have no conflict of interests.

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