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REVIEW

The diet-microbiota axis: a key regulator of intestinal permeability in human health and disease

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ABSTRACT

The intestinal barrier orchestrates selective permeability to nutrients and metabolites while excluding noxious stimuli. Recent scientific advances establishing a causal role for the gut microbiota in human health outcomes have generated a resurgent interest toward intestinal permeability. Considering the well-established role of the gut barrier in protection against foreign antigens, there is mounting evidence for a causal link between gut permeability and the microbiome in regulating human health. However, an understanding of the dynamic host–microbiota interactions that govern intestinal barrier functions remains poorly defined. Furthermore, the system-level mechanisms by which microbiome-targeted therapies, such as probiotics and prebiotics, simultaneously promote intestinal barrier function and host health remain an area of active investigation. This review summarizes the recent advances in understanding the dynamics of intestinal permeability in human health and its integration with gut microbiota. We further summarize mechanisms by which probiotics/prebiotics influence the gut microbiota and intestinal barrier functions.

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Introduction

There is a growing appreciation for the role of gut permeability in human health. "Google" and "PubMed" searches for the term "gut permeability" returned 19,200,000 and 53,660 results, respectively, as of March 2022. Despite being frequently used analogous to the terms "leaky gut" and "gut barrier dysfunction", intestinal permeability is a normal functional feature of the gastrointestinal (GI) barrier in a healthy individual that is measured by the flux rates of micro- and macro-molecules across the gut epithelium.[1] In contrast, terms like "leaky gut" and "barrier dysfunction" more accurately describe states of "abnormal intestinal permeability" where disturbances in intestinal permeability arise due to functional impairments and diseases.

As with intestinal permeability, there is a growing appreciation of the role of gut microbiota (the collective bacterial, archaeal, viral, and eukaryotic microorganisms occupying the GI tract) in maintaining normal human physiology and pathobiology. Considering the well-established role of the gut barrier in protecting the body from foreign antigens, including those derived from the gut microbiota, there is mounting evidence for a causal link between gut permeability and the microbiome in regulating human health and disease. A comprehensive understanding of the relationships among gut barrier biology, intestinal permeability, and the gut microbiome can therefore provide novel insights into the dynamic balance between human health and disease, which is the focus of this review article.

The intestinal barrier: greater than the sum of its parts

The term "intestinal barrier" traditionally refers to a complex multilayer system consisting of physiochemical, structural, and immunological compartments. The physiochemical and structural

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compartments consist of a mucus layer and a single layer of epithelium, which cover a surface area of about 400 m^2 and require 40% of the body's energy for their maintenance.[2] Importantly, these components combine to serve as a fence that limits the entry of bacteria, luminal antigens, toxins, and metabolites into the underlying mucosa.[3] Should this physiochemical barrier be breached, the immunological component – consisting primarily of innate immune cells including macrophages and dendritic cells – senses luminally derived molecular patterns and initiates inflammatory signals to promote antigen destruction and restitution of the intestinal barrier.[4]

In addition to these structural and immunological compartments, the gut microbiota is now being recognized for its critical contribution to homeostatic regulation and pathogenic disruption of the intestinal barrier. In this capacity, the gut microbiota provides energy to colonocytes, safeguards epithelial integrity by producing bacteriocins (antibacterial molecules), and regulates mucosal immune responses.[5] Collectively, these GI compartments create a functional intestinal barrier that facilitates the exchange of nutrients and metabolites between the host and its environment, and simultaneously manages the entry of pathogens, toxins, and foreign antigens into the body (Figure 1). Unfortunately, there is a general lack of appreciation for the nuances and dynamic nature of gut permeability in health and disease, particularly with respect to the host–microbiota interactions that govern permeability; hence, our focus is on those details in this review.

Intestinal mucus: the frontline of the gut barrier

The entire length of the GI tract is coated with a viscous, thick, and jelly-like substance referred to as mucus that is continuously secreted into the intestinal lumen at a rate of ~10 liters/day.[6] As an interface between luminal contents and the intestinal epithelium, mucus not only serves as a physical barrier to protect the intestinal epithelial cell (IEC)

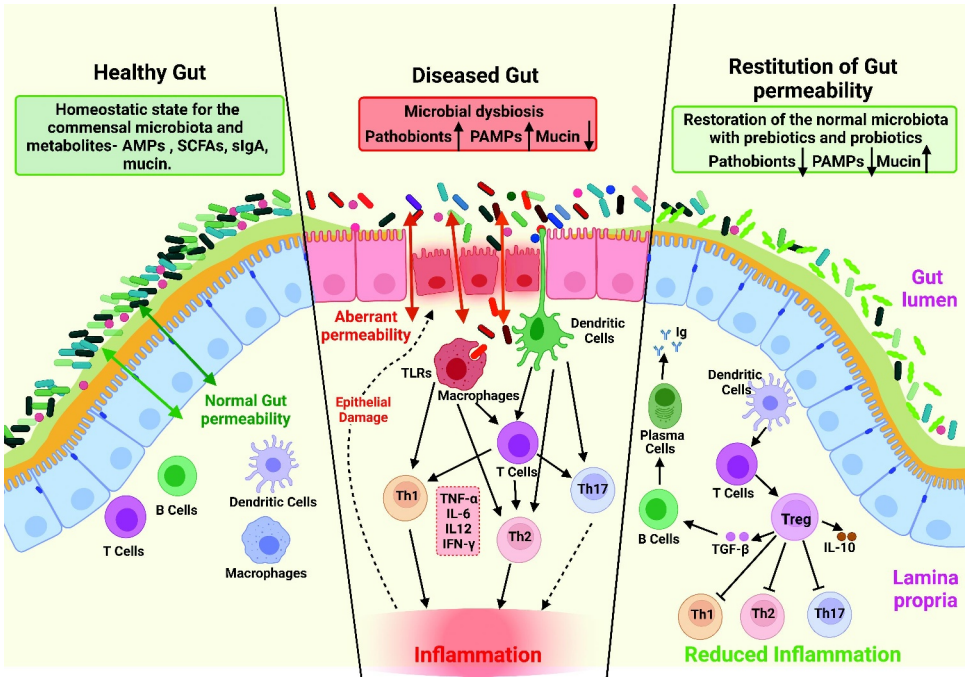

Figure 1. Changes in intestinal homeostasis under different conditions.
Left: A representation of a healthy gut where the intestinal epithelial cells are joined together with tight junction proteins and covered by thick mucus layers that do not allow commensal bacteria to make contact with intestinal epithelial cells. Normal commensal bacteria are free-living on the luminal surface of the mucus surface. Highly coordinated and well-governed paracellular permeability occurs.
Middle: A representation of a diseased gut where there is disruption of the tight junction proteins and epithelial barrier integrity. Infiltration of the luminal microbiota into the lamina propria induces a pro-inflammatory signaling cascade that can lead to severe pathological outcomes.
Right: A representation of a restored gut with a normal microbiota and gut barrier function. Intake of prebiotics and probiotics may augment gut integrity by replenishing the commensal bacteria and reducing inflammation.

monolayer from luminal contents but also aids in nutrient digestion and maintaining a homeostatic relationship with the gut microbiota.[7,8]

Extensive discussions regarding the composition, regulation, and function of the intestinal mucus layer are the subject of multiple excellent reviews[8–10] and will not be covered in detail here. However, the present discussion necessitates a succinct overview of mucus biochemistry to better illustrate the extent of host–microbiota interactions at the mucus interface. In brief, mucus is composed of glycosylated proteins called mucins. Goblet cells, a type of specialized intestinal epithelial cell, are principally responsible for the synthesis and secretion of mucin.[10] Mucin consists of a protein core containing three crucial amino acid residues (proline, threonine, and serine) commonly referred to as a PTS domain.[11] The serine and threonine residues substantially undergo O-glycosylation, while the proline facilitates the O-glycosylation process in the Golgi complex.[12] O-glycosylation is critical for preservation of the protein core from endogenous protease-dependent degradation and enhances the ability of mucin to bind with water molecules to form a gel.[13] Mucins can be broadly classified into either gel-forming or transmembrane mucins based on their architectural and operative characteristics. The secreted gel-forming mucins MUC2, MUC5AC, MUC5B, and MUC6 are the key constituents of intestinal mucus, whereas MUC2 is the predominant mucin of the mucus barrier. MUC1, MUC3, MUC4, MUC13, and MUC17 are the key transmembrane mucins of the intestine expressed on the apical surface of epithelial cells and are responsible for creating a protective barrier between the secreted mucins and the underlying epithelial cells.[14,15]

The mucus layer plays a critical role in defending against microbial infections by working synergistically with commensal organisms.[16] The components of mucus not only form a passive physical barrier and act as adhesion decoys for pathogens, but they also actively produce antimicrobial molecules. For example, α-1-4-linked N-acetylglucosamine, a mucin O-glycan, protects the host from *Helicobacter pylori* infection by inhibiting its cell wall biosynthesis.[17] Similarly, MUC7 has inherent direct candidacidal activity that protects it from oral candidiasis.[18] Host-derived antimicrobial molecules such as secretory α-defensins, secretory enzymes (i.e., lysozyme), and immunoglobulin A (IgA) are also an integral part of the mucus layer.[19] However, if mucin synthesis is aberrant and/or secreted mucins are degraded, then the activity of the antimicrobial molecules is impaired. Consequently, their ability to protect against exposure to luminal antigens is limited and disease may ensue.[20–23] Indeed, aberrant mucin expression is a hallmark of multiple human intestinal diseases, including inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), Celiac Disease (CD), and colorectal cancer (CRC), all of which are also associated with changes in the gut microbiota.[24–26]

Tight junctions: guardians of intestinal barrier function

Underlying the mucus layer is the intestinal epithelial barrier, a single layer of epithelial cells linked by cell–cell adhesions, including tight junctions (TJs). Owing to their physical location, tight junctions, the most apical cell–cell adhesion complex, are considered key regulators of the epithelial barrier function.[27] Overall, the TJ is a complex entity composed of a myriad of proteins, including claudins, occludin, zonula occludens (ZO-1, 2, 3), and junctional adhesion molecules (JAM).[28]

Many excellent reviews have focused on the details of TJ structure/composition.[29–32] In brief, ZO proteins are peripheral membrane phosphoproteins with a molecular mass of 220 KDa[33] that are expressed in all epithelial and endothelial cells as well as in cell types lacking TJs.[34,35] Thus, while ZO proteins are not integral proteins of the TJ, a complex interdependence among these proteins and other TJ proteins, including claudins and barrier integrity, has been reported.[36] Similarly, JAM proteins are also involved in the maintenance of intestinal barrier homeostasis, and JAM-A knockout (KO) mice present with increased barrier permeability, increased bacterial translocation into the mucosa, and elevated numbers of colonic lymphocytes.[37] Occludin is another integral TJ protein found in both epithelial and endothelial cells that contributes to TJ stabilization and optimal barrier functions. However, occludin KO mice possess intact TJs but display complex histological

phenotypes, thus suggesting that occludin could be involved in TJ maturity and possibly indispensable for TJ formation.[38] Notably, a recent study provided evidence that occludin may also help regulate apoptosis in intestinal epithelial cells under inflammatory conditions.[39] Yet another study has also demonstrated that occludin is required for apoptosis when claudin–claudin interactions are disrupted.[40] Such findings point to a complex role for occludin in maintaining the intestinal barrier by promoting cell survival.

Recent studies, including those from our laboratory, have revealed an integral function for the claudin family of proteins in the regulation of TJ structure and function.[41–43] Studies manipulating claudin protein expression both in cell culture and *in vivo* have shown that these proteins are expressed in a cell- and tissue-specific manner and also regulate cellular functions distinct from their role in barrier function. For example, claudin-1 KO mice die postnatally due to the dysregulation of dermal barrier function.[44] In contrast, forced claudin-1 overexpression in the intestinal epithelium results in remarkable changes in epithelial cell homeostasis, including goblet cell loss and susceptibility to colitis and colitis-associated cancer.[45,46] Together, these findings suggest that optimal expression of claudin-1 is essential for normal mammalian homeostasis and barrier function.

In contrast to the effects of deletion and overexpression of claudin-1, genetic manipulation of the pore-forming claudin protein family member claudin-2, alters trans-epithelial resistance and paracellular permeability of cations, especially Na^+ and Ca^{++} ions.[47] Claudin-2 is upregulated in both IBD and CRC.[48,49] Interestingly, studies using murine model of claudin-2 overexpression (which is observed in IBD patients), have shown a maladaptive function for claudin-2 in mice when subjected to colitis-induced by an epithelial irritant (Dextran Sodium Sulfate; DSS) and infectious colitis.[47] However, when subjected to colitis induced by the adoptive transfer of activated T cells, the effects of claudin-2 expression contrast with the effects from DSS- or *C. rodentium*-induced colitis, suggesting a rather complex and context-dependent role of claudin-2 in mucosal inflammation.[50]

In contrast to claudin-2, claudin-3 is abundantly expressed in the gut epithelium and considered to be a barrier-sealing protein as its loss in mice manifests into a more permeable intestinal barrier, upregulates IL-6/Stat3 signaling, and promotes aggressive colon cancer.[51,52] Notably, *Clostridium perfringens*, one of the most common cause of foodborne illness, uses claudin-3 and 4 as receptors for deregulating gut barrier integrity.[53] Studies have also demonstrated a key role for claudin-7 in intestinal epithelial homeostasis, and post-embryonic lethality occurs with genetic deletion of claudin-7 expression primarily due to the loss of cell–cell and cell-matrix adhesions.[54,55] Likewise, claudin-15 deficiency not only dysregulates the intestinal paracellular Na^+ transport but also results in a "mega-intestine" phenotype characterized by increased intestine length and hyperproliferation in addition to glucose malabsorption.[56,57] Remarkably, when mice lacked expression of both claudin-2 and 15, they experienced severe defects in paracellular Na+ permeability, which disrupted nutrient absorption and resulted in death due to malnourishment.[58] Both the claudin-2 and −15 are paracellular pores for the passage of Na+, and results from this study also highlighted the critical role of gut barrier integral proteins in regulating Na^+/glucose transport and thus the luminal milieu.[59] Altogether, the afore mentioned studies highlight the complexity of the TJ integral and related proteins as well as their complex role in the maintenance of the intestinal barrier integrity and luminal environment, which may be critical in creating appropriate niches for specific members of the gut microbiota.

The gut microbiome and intestinal barrier function: a new frontier

Studies in developmental biology support a role for host–microbiota interactions in intestinal barrier function as early as birth.[60] Establishment of the commensal microbiota shortly after birth prompts the rapid development of a functional intestinal barrier and a subsequent decrease in intestinal permeability.[61] Furthermore, the expression of claudin proteins during functional maturation of the gut barrier is dynamic, with high expression of claudin-2 and low expression of the barrier-forming claudins, including claudin-3, 4, 7, and

15, at birth. As the gut barrier matures, expression of claudin-2 is downregulated, while expression of the barrier sealing proteins claudin-3, 7, 15 is upregulated.[62] Such a pattern suggests a dynamic relationship between claudin proteins and gut barrier functions.

Integration between the gut microbiota and barrier structure/function is also supported by reports using adult animal models. For instance, short-term antibiotic treatment markedly increased intestinal permeability in rats, which was accompanied by the downregulation of tight junction proteins including claudin-1, ZO-1, and occludin.[63] Furthermore, the antibiotic-induced increases in intestinal permeability that are accompanied by reduced claudin-3 expression can be corrected following the administration of probiotics.[64] Other signaling pathways are also activated following antibiotic administration that confer deleterious effects on TJ proteins and intestinal permeability, further highlighting a connection between the gut microbiome and barrier function. Notably, alterations in the gut microbiome following antibiotic treatment promote intestinal activation of the NLRP3 inflammasome.[65] Similarly, stress induced by environmental or psychological factors also induces gut barrier dysregulation and gut microbial dysbiosis.[66,67]

Taken together, these studies suggest a potential regulatory feedback mechanism between the intestinal barrier and the gut microbiota. A general postulation is that translocation of commensal microbes or their metabolites, due to a breach in the intestinal barrier, stimulates the mucosal immune system[68] which, in turn, contribute to the dysregulation of TJ expression. Other studies indicate that TJ expression may regulate the gut microbiota. For example, JAM-A KO mice harbor significantly greater levels of *Desulfovibrionaceae* and less *Akkermansia* in their gut compared to their wild-type counterparts, indicating a potential role for JAM-A in modulating the composition of the gut microbial community.[69,70] Notably, JAM-A KO mice also experience increased barrier permeability and elevated levels of bacterial translocation.[37,69] Similarly, gut epithelium-specific overexpression of claudin-1 or knockdown of claudin-3 resulted in dysregulated barrier function and changes in gut microbiota composition (Unpublished data). A recent report has demonstrated a similar effect of claudin-7 loss upon gut permeability and gut microbial dysbiosis.[71] Although claudin-2 expression is known to increase gut barrier permeability,[72] its effects on the gut microbiota remain to be examined.

As with the intestinal barrier and the microbiota, a similar regulatory feedback mechanism also likely exists specifically between the mucus layer and the gut microbiota. As discussed previously in this review, intestinal mucus trap microbes and water-insoluble antigens to limit their contact with the underlying epithelium and immune cells. Additionally, some beneficial, mucolytic microbes have even adapted to the mucus layer where they can heavily utilize glycosylated mucins as metabolic substrates.[73] This relationship, however, represents a double-edged sword as insufficient dietary fiber consumption by the host leads to degradation of the mucus layers as mucolytic species encroach upon the epithelium and increase host susceptibility to inflammation.[74] A similar relationship has also been highlighted in studies with *Muc2*-deficient mice, which spontaneously develop colitis soon after birth due to excessive microbial contact with the colonic epithelium.[13,75] However, considering the complex interactions between the gut microbiota and IEC, further detailed mechanistic investigations are required that explain and model the dynamic host-microbe interdependent relationship needed to balance microbial entry, recognition, and immune activation.

Neurohormones: potential regulators of gut microbiota-intestinal barrier dynamics

A specialized group of cells in the intestinal epithelium known as Enterochromaffin cells (EC) produce and secrete melatonin, serotonin, cholecystokinin, and somatostatin.[76] These neurotransmitters, in turn, play a crucial role in maintaining homeostasis in the human body,[77] and mounting evidence supports the existence of bidirectional communication between the gut and the central nervous system, referred to as the gut-brain-axis.[78]

A burgeoning literature suggests that serotonin and melatonin, in particular, play an important role in gut barrier function in addition to mediating

crosstalk with the gut microbiota.[79,80] Of note, serotonin has been shown to play a role in several gastrointestinal diseases, including IBS and IBD.[81,82] In this regard, expression of serotonin reuptake transporters (SERT) is suppressed in IBD patients, and re-expression of SERT in genetically deficient mice exacerbates colitis.[83] The endogenous production of serotonin appears to be dependent on gut microbiota as germ-free mice have lower basal plasma serotonin compared to the conventional mice.[84] Moreover, commensal intestinal bacteria such as *Escherichia coli, Enterococcus* species, *Streptococcus* species, and *Bifidobacterium infantis* have all been shown to modulate 5-hydroxytryptamine (5-HT) levels by increasing plasma levels of its precursor, tryptophan.[85] Proximity is likely an important factor in this relationship, as epithelial cells in the GI tract serve as the largest reservoir of serotonin – alternatively, 5-HT in the body.[86] Small amounts of 5-HT are transcytosed through the intestinal barrier to enter the systemic circulation and are absorbed by platelets for generalized neuronal functions.[87] In a case–control study, the oral administration of 5-HTP, an intermediary serotonin substrate, reduced intestinal permeability, upregulated ZO-1, and remodeled the TJ proteins in healthy individuals but not in IBS patients.[88] Together, these findings collectively implicate dysregulated serotonergic signaling in the pathophysiology of gastrointestinal disorders associated with increased gut permeability. However, details of the causal association with the commensal gut bacteria in regulating the serotonergic signaling in human health and disease remain to be understood.

The GI tract is also the primary reservoir for melatonin as the gut contains ~400 times more melatonin compared to the pineal gland.[89] Melatonin mediates endocrine, paracrine, and autocrine actions and regulates multiple aspects of GI physiology, including intestinal motility, ion transport mechanisms, and mucosal immune responses, possibly through TLR4-dependent signaling mechanisms.[80] A recent study demonstrated that exogenous administration of melatonin to DSS-treated mice significantly improved intestinal barrier function, antimicrobial peptide secretion and wound healing responses in wild-type but not in TLR4 deficient mice.[80] The gut microbiota may also mediate some of the anti-inflammatory effects of melatonin.[90] In this regard, melatonin can influence the structure of the gut microbiota, including richness and diversity,[91] and the abundance of specific species such as *Akkermansia, Bacteroides*, and *Faecalibacterium*.[92] Melatonin can also prevent obesity by modulating the composition of gut microbiota.[93] Together, these findings suggest that mechanistic investigations linking gut-derived neurohormones, the gut microbiota, and intestinal permeability are certainly warranted. Also, additional knowledge about the role of the gut-brain axis in regulating intestinal permeability is essential for improving our understanding of human disease processes and developing effective therapies.

Repairing the rampart: diet–microbiota interactions to the rescue

In recent years, the gut microbiota has emerged as an attractive therapeutic modality to target for multiple acute and chronic conditions. Because host diet is a recognized determinant of gut microbiota ecology and function,[94,95] many investigators have turned to examine the effects of dietary components on the microbiota in hopes of better understanding the systemic interactions connecting the microbiota to human health.[96] However, given the highly personalized nature of both the microbiome and nutrition, rational, microbiome-targeted dietary interventions with predictable effects on the microbiome remain elusive.[97]

Despite the complex nature of diet–microbiota interactions, an existing body of literature has extensively documented the effects of diet on the regulation of intestinal barrier function, including permeability of the GI tract.[98] Therefore, reevaluating the literature through the lens of the gut microbiome's contribution to those effects may provide novel insights into the reciprocal mechanisms governing the diet-barrier function-microbiota axis. Moreover, studies examining the effects of specific bacteria, namely probiotics, on intestinal permeability can also suggest mechanisms by which microbial organisms may beneficially regulate host barrier function to improve health through interactions with their host.

Probiotics: regulators of intestinal barrier function

Probiotics are defined by an expert consensus as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host".[99] Probiotic microbes are typically supplemented in the range of 10^8–10^{10} colony forming units (CFU) per gram. In general, these bacteria do not become permanent members of the host microbiota, but the transient increase (direct/indirect) in the abundance of a single species can have a significant effect on collective intestinal barrier function.[100] However, the precise mechanisms by which probiotics enhance intestinal barrier function are complex, and research supports species- and even strain-specific effects of probiotics on host health.

The capacity of probiotic organisms to participate in communal short chain fatty acid (SCFA) production is one mechanism by which probiotics are generally considered to promote health. Namely, *Bifidobacterium* and lactic acid bacteria (LAB), such as *Lactobacillus* and *Streptococcus* species, provide lactic acid and acetate substrates for butyrate production in a community metabolic reaction referred to as the "bif(id)-shunt".[101,102] Although these species only transiently occupy the GI tract, they maintain much of their metabolic activity during transit through the harsh conditions of the upper GI tract.[103] Consequently, their ability to promote SCFA synthesis and butyrogenic gut microbial communities can regulate intestinal barrier functions through mechanisms similar to those mentioned above.

SCFA production alone, however, is insufficient to explain the therapeutic benefits and strain-specific health benefits of probiotic supplementation – molecular organization of the microbial cell surface is also an important aspect of probiotic functions. This concept has been extensively studied for *Lactobacillus* species and may account for some strain-level differences observed in the probiotic literature.[104] For example, lipoteichoic acids, which are anionic, polymeric units linked to peptidoglycan, can direct the organization of intestinal TJ via binding to TLR2 on the apical IEC membrane. TLR2 stimulation in the Caco-2 cell line induced phosphorylation of PKC in a PI3K/Akt/mTORC1-dependent manner, subsequently promoting ZO-1 translocation to TJ.[105] A similar effect has also been observed following *Lactobacillus* treatment in human volunteers.[106] In support of such mechanism, one study reported that heat-killed *L. rhamnosus* was sufficient to prevent DSS-induced intestinal permeability *in vivo*.[107] *L. plantarum* WCFS1 also promoted organization of TJ in healthy humans and Caco-2 cells.[106] Thus, it appears likely that some combination of metabolism and strain-specific variations in cell wall organization may be necessary to explain the benefits of LAB probiotics on intestinal barrier function.

The probiotic, *Escherichia coli* Nissle 1917 (EcN), has a rich history of use in human gastrointestinal disease that spans a century.[108] Several studies support the notion that EcN regulates IEC-specific functions to control intestinal TJ functions. The first *in vivo* study to examine EcN influence on intestinal TJ reported that germ-free mice monocolonized with EcN had higher baseline mRNA and protein expression of ZO-1 and that intragastric supplementation of EcN to conventional mice prevented DSS-mediated increases in intestinal permeability.[109] Another study found that EcN increased the trans-epithelial resistance (TEER) of intact T84 colon cells and restored their barrier function following infection with a strain of enteropathogenic *E. coli* (EPEC).[110]

The specific components of EcN that propagate the signals regulating tight junction components are not yet clear. As with other probiotics, immunomodulatory ligands expressed on the outer cell membrane are likely partially responsible for the barrier function enhancing effects of EcN. For instance, flagellin expressed by EcN promotes the secretion of antimicrobial peptides by IEC *in vitro*.[111] However, the supernatant from a mutant *E. coli* Nissle strain lacking flagellin had no effect on TJ function in T84 cells.[112] Rather, the TIR domain-containing protein encoded by the gene *TcpC* in *E. coli* has been identified as at least partially responsible for TJ modulating effects of EcN.[112,113] Although the presence of *TcpC* is generally associated with bacterial pathogens, these studies suggest that the immunogenic effects of *TcpC* in *E. coli* may be contextual.[114] Furthermore, supernatants or isolated outer

membrane vesicles from EcN, of which TcpC may be a component, are sufficient to increase TEER and counteract the effects of EPEC on TJ.[112,113,115] In conclusion, these molecular investigations not only increase our understanding of how probiotics interact with IECs to promote barrier function but also provide valuable insights to guide the future design and selection of live biotherapeutics that benefit human health.

Fermentable fibers, the gut microbiota, and intestinal permeability

Fermentation of dietary biomolecules by commensal gut bacteria accumulates a wealth of metabolic by products that serve as signaling molecules to direct host-microbiota cross-talk as well as regulate gut microbial ecology and function.[116] Although the aforementioned neurohormones and their substrates are among these metabolites, SCFA derived from fermentation of complex carbohydrates (i.e., dietary fiber) are the most abundant and widely studied microbial metabolites. Among their many functions, the SCFA butyrate, propionate, and acetate are important regulators of intestinal barrier function through their direct activity on enterocyte biology as well as peripheral anti-inflammatory effects.

It has been widely reported that the biological activity of microbiota-derived SCFA on colonocytes is linked with activation of the 5' adenosine monophosphate activated kinase (AMPK). AMPK activation is well-recognized to promote intestinal barrier function, either by inducing the differentiation of intestinal epithelial cells or as mediators of cellular signaling in differentiated enterocytes.[117–119] Evidence suggests that the induction of AMPK by SCFA is essential to their barrier-enhancing functions. For example, butyrate has been shown to facilitate the association between transcription factors and the claudin-1 promoter to increase AMPK activity and reduce bacterial translocation. Supplementing butyrate to monolayers of Caco-2 cells also promotes re-localization of ZO-1 to the paracellular junction in a calcium- and AMPK-dependent manner.[120] Interestingly, acetate and propionate can also activate AMPK and decrease the paracellular permeability of Caco-2 monolayers in this model.[121] However, AMPK inhibitors and siRNA-mediated inhibition of AMPKα only partially abrogated the effects of SCFA on intestinal permeability, suggesting that other AMPK-independent mechanisms contribute to this mechanism.

Independent of AMPK, evidence also suggests that SCFA regulates IEC barrier functions through their respective apical-free fatty acid receptors (FFARs). Three de-orphaned GPCRs – GPR41, GPR43, and GPR109A – have been identified as SCFA receptors and are essential in regulating the biology of IECs.[122] A study reported that physiological concentrations of SCFA increased TEER and decreased paracellular permeability of Ussing chamber mounted rat cecal tissues within 10 min of application independently of SCFA transport and metabolism. This finding suggests that intestinal permeability is regulated by SCFA through interactions with membrane-bound, extracellular receptors rather than as a metabolic substrate.[123] Furthermore, butyrate has been reported to increase the expression of claudin-3 in Caco-2 cells in a GPR109a-dependent mechanism.[124] In line with this finding, others have confirmed that the presence of either GPR43 or GPR109a SCFA receptors on colonocytes is required for the anti-inflammatory benefits of a high-fiber diet in the context of a chemically induced colitis injury, where loss of barrier integrity is a major pathophysiological mechanism.[125] The SCFA-mediated activation of AMPK has not yet been investigated in the context of FFAR, thus it is possible that AMPK is activated downstream of FFAR induction. Given the reported global benefits of SCFA for intestinal barrier functions, including the regulation of intestinal permeability, thorough mechanistic investigations are essential for our understanding of the relationship between these gut microbiota-derived metabolites and human health.

Insoluble fibers can also regulate intestinal permeability

Although generally considered non-fermentable, it is worth noting that insoluble fiber can modulate gut microbiome composition and affect host physiology via both microbiome-dependent and -independent mechanisms.[126] Dietary insoluble fiber is derived primarily from the structural components of plant cell

walls as cellulose and complexed lignin polymers.[127] Gut health benefits of dietary cellulose were historically believed to be limited to increasing fecal bulk and accelerating GI transit.[128] Although cellulose's effects on GI transit are microbiome-independent, cellulose-mediated changes in intestinal motility were associated with alterations in the microbiome composition of humanized mice.[129] Moreover, microbiome-dependent effects of cellulose on intestinal health have now been reported in the literature, often conferring some health benefits in such experiments.[130–132] In one notable study of septicemic mice, feeding a high cellulose diet (20% w/w) increased expression of claudin-1 by two-fold and occludin by more than three-fold compared to feeding a low cellulose diet (5% w/w) prior to the onset of severe IEC apoptosis.[130] The authors further noted that mice consuming a high cellulose diet experienced an increase in the abundance of *Akkermansia muciniphilia* in their feces. An expansion of *A. muciniphilia* was also observed in C57BL6/J mice fed with 30% cellulose diet for 12 weeks. In this case, the high cellulose diet protected mice from DSS colitis when compared to low-cellulose (5% w/w) and normal chow (6% crude fiber) diets.[132] In both studies, treating animals with antibiotics abolished these effects, thereby supporting a microbiome-dependent health effect for cellulose consumption. Furthermore, the association among cellulose, *A. muciniphilia*, and TJ protein regulation is novel, and certainly challenges preconceived notions concerning the functional activities of dietary cellulose.

The claims of beneficial and microbiome-dependent effects of cellulose consumption may be considered controversial, as cellulose is widely considered "inert" as a fermentative substrate and is frequently used as a control in experimental nutrition research where dietary fiber is involved.[133] This controversy is compounded by reports from several groups in which mice consuming experimental diets devoid of fermentable fiber develop an abnormal gut physiology characterized by severely atrophied colons and ceca as well as an increased susceptibility to DSS colitis.[134–138] Moreover, mice fed high cellulose diets secrete fewer antimicrobial peptides, thereby promoting encroachment of bacteria toward epithelial cells.[135] Still others have reported that mice consuming a high cellulose (15% w/w) diet for only one-week experienced increased intestinal permeability compared to mice consuming a high soluble fiber diet (15% psyllium fiber, w/w) and concluded that this effect was microbiome-dependent.[139] These discordant results collectively suggest a failure to recognize the totality of the physiological effects of cellulose consumption and that future nutrition studies would benefit from considering the influence of insoluble fiber in their models.

Conclusions and future directions

Mounting evidence supports that regulation of GI homeostasis is complex and dynamic. In current review article, we have specifically discussed the regulation of intestinal barrier functions and the likely critical role of the gut microbiota in maintaining intestinal homeostasis (Figure 1). In addition, we have discussed the role of the diet in regulating these attributes in the context of human health and disease. In discussing these key relationships, we have also stressed upon the canonical and non-canonical functions of the barrier integral and associated proteins and possible impact of such functions upon gut barrier integrity and microbiota. However, during these deliberations, we have also noted the limitations of the current knowledge regarding gut barrier dysfunction and microbiota-related therapeutic interventions, due primarily to the plasticity of observed associated changes. For example, despite the well-recognized role of increased gut permeability in promoting inflammation, defined probes to accurately gauge the extent of gut permeability of pathological significance are lacking. The same is true for the gut microbiota since there are distinct microbiota colonization patterns specific to the various portions of GI tract that are not likely reflected in the stool samples frequently used to assess microbiota changes. Similarly, studies performed in mice or other mammals regarding the effects of diet upon intestinal homeostasis may not recapitulate outcomes in human studies due to differences in dietary habits and genotypes.

Thus, a closer (and deeper) look at the dynamics of gut microbiome changes in causal association with epithelial permeability is needed, which requires refined animal models and tools. However, animal models where host-microbe interdependence can be studied/modeled in a dynamic manner remains a major bottleneck in such an endeavor, though mice modified for specific barrier integral protein/s expression in a gut epithelium-specific manner hold great promise to provide novel insights into these causal relationships. Nonetheless, the genetic manipulation of animal models of barrier protein function carries its own caveats depending on the nature of gene manipulation (constitutive/inducible) and fails to offer an opportunity to examine any compensatory changes in other barrier proteins and/or epithelial or immune homeostasis.

As noted in this review, diet, including consumption of prebiotics and probiotics, has a tremendous impact upon both gut microbiome composition and barrier function, and thus offers an additional line of investigation into novel approaches to influencing interactions between gut microbes and the intestinal barrier. However, the utility of probiotics as a therapeutic modality also remains uncertain as these supplements are currently regulated by the FDA. Moreover, the question remains whether dietary control alone can serve as a therapy or play a supporting role in maintaining GI homeostasis. In our current times of fast-changing dietary habits and notable increases in the incidence of colon cancer and other intestinal diseases, particularly in young adults,[140] a deeper examination of the causal relationships between diet, the gut microbiome, and intestinal permeability is clearly warranted as a way to provide valuable knowledge for a healthier future.

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Biorender.com was used to create the Figure 1 illustration.

Disclosure statement

There are no potential conflicts of interest to disclose.

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