Review

Gut barrier disruption and chronic disease

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The intestinal barrier protects the host against gut microbes, food antigens, and
toxins present in the gastrointestinal tract. However, gut barrier integrity can be
affected by intrinsic and extrinsic factors, including genetic predisposition, the
Western diet, antibiotics, alcohol, circadian rhythm disruption, psychological
stress, and aging. Chronic disruption of the gut barrier can lead to translocation
of microbial components into the body, producing systemic, low-grade inflam-
mation. While the association between gut barrier integrity and inflammation in
intestinal diseases is well established, we review here recent studies indicating
that the gut barrier and microbiota dysbiosis may contribute to the development
of metabolic, autoimmune, and aging-related disorders. Emerging interventions
to improve gut barrier integrity and microbiota composition are also described.

Structure and function of the gut barrier

Maintenance of epithelial and endothelial barriers in the gut, skin, blood vessels, respiratory tract,
and the brain is critical for human health [1]. The intestine forms the largest and one of the most
important internal barriers in the body as it protects the host from noxious substances and mi-
crobes present in the gut lumen. The gut barrier consists of the mucus layer, commensal bacteria,
epithelial cells, and immune cells residing in the **lamina propria** (see Glossary) (Figure 1A). In the
intestinal epithelium, goblet cells secrete mucus glycoproteins that prevent direct contact be-
tween gut microbes and colonocytes [2], while the mucus in the small intestine is loose and allows
passage of bacteria [3]. In the small intestine, Paneth cells secrete antimicrobial proteins that can
specifically lyse bacterial cells [4]. In the lamina propria, B cells secrete IgA that can bind to bac-
teria and their toxins to prevent their translocation into the body [5].

Commensal microbes of the gut microbiota help to maintain gut homeostasis in various ways
(Figure 1A). For instance, they oppose colonization by pathogens [6] and promote differentiation
of regulatory T (Treg) cells, which induce tolerance to lumen antigens [7]. When sequestered into
the lumen, **microbe-associated molecular patterns (MAMPs)** such as flagellin, lipopolysac-
charide (LPS), and peptidoglycan strengthen the gut barrier by binding to Toll-like receptors
(TLRs) on the apical surface of intestinal cells to induce production of antimicrobial proteins [5].
Commensal bacteria can induce the production of mucus from goblet cells by activating interleukin
(IL)-22 secretion by innate lymphoid cells [8]. Commensals also convert dietary fiber into short-
chain fatty acids (SCFAs), which protect the gut barrier in various ways, including by providing
energy for colonocytes and stimulating the production of mucus, antimicrobial proteins, and
Treg cells [5]. Depletion of commensals and their replacement by pathogens, a condition termed
dysbiosis, may therefore affect the gut barrier and produce detrimental effects on the host
(Figure 1B–F).

Absorption of nutrients and water by the intestine can occur via the transcellular and paracellular
pathways (Figure 2). Intestinal cells are linked by a series of proteins forming junctional complexes
consisting of tight junctions, adherens junctions, and desmosomes, allowing absorption of water

Highlights

Maintenance of gut barrier integrity is in-
dispensable for health as the gut barrier
protects the host against gut microbes,
food antigens, and toxins.

Many factors such as enteric infection,
antibiotics, low-fiber diets, circadian
rhythm disruption, and psychological
stress can affect gut barrier integrity and
lead to systemic, low-grade inflammation
due to translocation of bacteria and their
components.

While the body can resist transient
gut barrier disruption, it may be over-
whelmed by mild insult due to genetic
predisposition, chronic stress, and
aging, which may contribute to the de-
velopment of autoimmune, metabolic,
and mental health disorders.

Consideration of the various intrinsic and
extrinsic factors that affect gut barrier in-
tegrity and microbiota composition is
needed to maintain or restore human
health.

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and small solutes (<8 Å) via the 'pore' pathway [9,10]. Transient and reversible rearrangement of the actin cytoskeleton and tight junctions allows passage of larger molecules (<100 Å) via the 'leak' pathway [9,10] (Figure 2). For instance, activation of glucose-Na⁺ co-transport following food intake increases the leak pathway [11], which enhances absorption of food nutrients but also small food antigens and MAMPs (Figure 2). Proinflammatory cytokines such as tumor-necrosis factor-alpha (TNF-α) [12] can also activate the leak pathway and cause diarrhea, which may help to expulse proinflammatory stimuli into the gut lumen. Intestinal erosion, ulceration, and epithelial cell death may allow larger particles, including MAMPs and bacteria, to unrestrictedly cross the intestinal epithelium and induce inflammation [9] (Figure 2).

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Effect of gut barrier dysfunction on intestinal diseases

Gut barrier dysfunction is involved in intestinal diseases such as enteric infections, intestinal bowel disease (IBD), and celiac disease [13]. For example, pathogenic bacteria and viruses such as *Salmonella* and rotaviruses can breach the intestinal epithelium and alter tight junctions, causing diarrhea via water and electrolyte loss into the gut lumen [14,15] (Figure 1B). Gastrointestinal infections can lead to bacterial translocation to the gut mucosa (Figure 1B), producing inflammation that further increases gut barrier dysfunction and may result in a vicious cycle [16].

IBD, which consists of Crohn's disease and ulcerative colitis, is characterized by excessive immune reaction towards the gut microbiota and mucosa of the small and large intestine, respectively. More than 200 single nucleotide polymorphisms (SNPs) in various genes coding for NOD-like receptors (NLRs), antimicrobial proteins, and cytokines have been implicated in IBD [17]; however, only a fraction of ulcerative colitis subjects have a family history of IBD [18], indicating the importance of environmental triggers. Mice that lack the major mucus glycoprotein, mucin-2, show gut barrier dysfunction and spontaneously develop colitis and colorectal cancer [19,20], illustrating the role of mucus in maintaining homeostasis [21]. Moreover, mice fed a high-glucose diet develop more severe dextran sodium sulfate (DSS)-induced colitis than controls due to increased mucolytic bacteria in the gut and reduced mucus barrier, leading to bacterial translocation to the lamina propria [22] (Figure 1B). In humans, weakening of the colonic mucus barrier is an early event in the development of ulcerative colitis [23] and bacterial DNA is increased in the blood of IBD subjects compared with healthy controls [24]. The development of IBD is therefore associated with genetic and environmental factors that lead to intestinal erosion and inflammation in susceptible individuals.

Celiac disease is a well-known condition involving gut barrier disruption. In this disease, gluten from wheat and other grains has been identified as the environmental trigger of autoimmune reactions in genetically susceptible individuals (Table 1). Gliadin proteins found in gluten induce the release of the protein **zonulin** from the gut epithelium [25] (Figure 1B). Zonulin is a mammalian ortholog of the zonula occludens toxin (Zot) from the cholera pathogen *Vibrio cholerae*. Similar to the cholera toxin, zonulin induces tight junction disassembly and increases gut permeability to peptides larger than three amino acids [25]. Celiac patients harbor SNPs in various genes, including human leukocyte antigens (HLAs) (e.g., HLA-DQ2 and HLA-DQ8) that render gliadin peptides capable of activating T cells and inducing autoimmune reactions [26]. In addition, increased gut permeability and antibodies against LPS and flagellin have been observed in people with non-celiac gluten sensitivity [27], which may involve SNPs in non-HLA genes [26]. Given the difficulty in identifying gluten sensitivity and the observation that gliadin can induce the release of zonulin even in healthy individuals [25], it is likely that gluten sensitivity is more prevalent than presently recognized. A combination of genetic and environmental factors thus affects gut barrier integrity and is involved in the development of intestinal diseases.

Effects of the diet on gut barrier integrity

Given that absorption of nutrients, including glucose, amino acids, and fatty acids, occurs in the small intestine, the bulk of the gut microbiota, which resides in the colon, must rely on indigestible dietary fiber as their main source of energy and nutrients. However, people who consume a Western diet usually eat less than 15 g of fiber per day, in sharp contrast with the recommended daily intake (25 g/day for women and 38 g/day for men) [28] or the diet of our ancestors (100 g/day) [29]. Following intake of a fiber-depleted, Western diet, many bacterial taxa that normally feed on fiber gradually disappear from the gut microbiota [30], while other commensals such as *Bacteroides thetaiotaomicron* shift their metabolism to degrade mucus glycans that normally protect the intestine [31]. A low-fiber diet reduces SCFA producers in the gut microbiota, which can affect gut barrier integrity by reducing production of mucus, antimicrobial proteins, and Treg cells [5], as well as affecting tight junction assembly [32] (Figure 1C). Accordingly, the Western diet reduces mucus thickness and increases gut permeability and proinflammatory markers in mice [33] (Table 1).

The Western diet also induces systemic inflammation associated with changes in bile acid synthesis and signaling [34]. Bile acids are emulsifiers that affect mucus properties [35] and increase gut permeability in intestinal cell monolayers [36] and mice [37]. Emulsifiers are also added to processed foods to improve lipid–water mixing and food texture. Chronic intake of relatively low amounts of emulsifiers (1% w/v) for 12 weeks is sufficient to induce gut permeability, low-grade inflammation, and metabolic syndrome in wild-type mice and produce robust colitis in inflammation-prone IL-10-deficient mice [38]. Emulsifiers may affect gut barrier integrity by inducing gut dysbiosis and affecting mucus thickness [38]. Other food additives that can disrupt the gut barrier and induce dysbiosis in animal models include fructose [39], salt [40], and artificial sweeteners [41] (Table 1).

The seminal work of Cani *et al.* was instrumental in elucidating a link between diet, gut barrier dysfunction, and metabolic diseases. This group showed that feeding a high-fat diet (HFD) to mice for 4 weeks increases serum LPS levels, and subcutaneous injection of LPS is sufficient to increase fasted glycemia, insulinemia, and body weight similar to feeding a HFD [42]. The HFD reduces tight junction expression and induces MAMP translocation into the lamina propria, which promotes inflammation via activation of TLRs on the basolateral surface of enterocytes or on immune cells [43] (Figure 1C). In humans, analysis of a 3-day food survey shows that people who consume a high-energy diet, but not a high-carbohydrate diet, have higher levels of plasma LPS [44], a condition called **endotoxemia**. Diabetic subjects show signs of translocated bacteria into the blood and treatment with probiotics can prevent this process [45]. Moreover, systemic influx of microbial products correlates with levels of **hemoglobin A1c** (HbA1c), a marker of poor glycemic control in humans [46]. Endotoxemia is also observed in subjects with non-alcoholic fatty liver disease [47], and individuals with high endotoxemia levels have a threefold higher risk of atherosclerosis [48].

These observations indicate that gut barrier dysfunction, dysbiosis, and inflammation induced by poor diet affect organs connected to the gut (e.g., pancreas, liver, and blood vessels), thus contributing to the development of various metabolic conditions, including type 2 diabetes, obesity, non-alcoholic fatty liver disease, and cardiovascular disease.

The autoimmune connection

Increased gut permeability, dysbiosis, and altered mucosal immunity have also been observed in autoimmune diseases (Figure 1D). Mice carrying a transgenic T cell receptor specific for a beta cell autoantigen spontaneously develop gut permeability and mucus layer dysfunction, leading

Glossary

Dysbiosis: imbalance in the composition of the gut microbiota characterized by the reduction of commensal microbes and increase of opportunistic or pathogenic microbes. This condition is usually associated with increased gut permeability and inflammation.

Endotoxemia: low-grade systemic inflammatory condition caused by translocation of lipopolysaccharide from intestinal Gram-negative bacteria into the circulation. Endotoxemia is likely involved in the pathogenesis of cardiovascular disease, obesity, and type 2 diabetes.

Hemoglobin A1c: a form of hemoglobin that is bound to sugar when the glycemia is excessively high for an extended period of time. This glycated protein is used as a marker for diabetes and correlates with diabetic complications such as cardiovascular disease, kidney disease, erectile dysfunction, and neuropathy.

Hormesis: biphasic dose response produced by stress such as exercise, intermittent fasting, phytochemicals, and heat on biological organisms. Hormetic responses are usually characterized by beneficial effects at low doses/intensity and detrimental or toxic effects at high doses/intensity.

Lamina propria: a thin layer of connective tissue found in the various mucosa of the human body, including in the gastrointestinal tract.

Microbe-associated molecular patterns (MAMPs): microbial molecules such as flagellin, lipopolysaccharide, and peptidoglycan that are produced by microbes and can be recognized by innate immune cells of the host. Within the gut lumen, MAMPs improve gut barrier function by promoting production of mucus, antimicrobial proteins, IgA, and regulatory T cells, but they can also induce inflammation if they translocate into the body through the intestinal epithelium.

Vagus nerve: tenth cranial nerve involved in the parasympathetic control of various organs, including the heart, lungs, muscles, sweat glands, and the digestive tract.

Zonulin: a mammalian ortholog of *Vibrio cholerae*'s Zot enterotoxin, zonulin is released from human intestinal cells in response to bacteria and gluten, leading to alterations of tight junctions and increased gut permeability. Research

to increased Th17 cells, reduced Treg cells, and development of type 1 diabetes [49]. Increased intestinal permeability also precedes type 1 diabetes onset in humans [50]. Systemic lupus erythematosus can also be triggered by TLR7-induced gut dysfunction in various mouse models [51]. For instance, continuous topical treatment with imiquimod, a TLR7 agonist, induces bacterial translocation and lupus-like symptoms in wild-type mice [52]. Bacterial translocation of *Enterococcus gallinarum* to lymph nodes and the liver occurs in lupus-prone mice carrying a TLR7 gene duplication and in human lupus subjects [53]. Moreover, the human gut commensal *Prevotella histicola* protects against neurodegeneration by reducing gut permeability and increasing levels of Treg cells and tolerogenic dendritic cells in a murine model of multiple sclerosis [54]. Bacterial DNA of intestinal origin is found in the circulation of subjects with psoriasis [55], suggesting the involvement of gut barrier dysfunction in this autoimmune condition as well. A time-course experiment showed that increased gut permeability preceded intestinal inflammation and the onset of arthritis in mice [56]. However, another study showed that co-transfer of splenocytes and gut microbiota from arthritic mice is required to induce gut permeability and arthritic symptoms in recipient mice [57], indicating that a combination of immune and microbiota-related factors may be needed to disrupt gut barrier integrity and induce autoimmune diseases.

The Western diet may contribute to the development of autoimmune diseases in part via its effects on the gut microbiota and SCFAs. Lupus subjects are more likely to consume a low-fiber diet [58], which may affect gut barrier integrity by reducing SCFAs, mucus, IgA, and Treg cell levels [3,5,59] (Figure 1D). Translocation of *Lactobacillus reuteri* was observed in lupus-prone mice and a subset of lupus subjects and a fiber-rich diet containing resistant starch reduced lupus mortality in mice by increasing SCFA levels [60]. The SCFAs butyrate and acetate improved gut barrier integrity, increased Treg cell levels, and reduced autoreactive T cells in a mouse model of type 1 diabetes [61], supporting the use of fiber-enriched diets against autoimmune diseases.

Lifestyle and the gut barrier

Antibiotics affect microbiota composition and gut barrier integrity and their overuse has been implicated in the development of various health issues (Box 1). Likewise, long-term intake of nonsteroidal anti-inflammatory drugs (NSAIDs) can induce gastroduodenal ulcers, inflammation, and bleeding by increasing gastric acid secretion, reducing mucus production, and inducing gut barrier leakage and endotoxemia [62] (Table 1). Another group of widely used drugs, proton pump inhibitors, enhance alcohol-induced fatty liver disease in mice and humans by reducing gastric acid, which increases growth of commensal bacteria in the small intestine and leads to translocation of microbial products and liver inflammation [63]. One of the most commonly used toxins that disrupt gut barrier integrity and the intestinal microbiota is alcohol. As such, chronic alcohol abuse is associated with increased gut barrier leaks, gut dysbiosis, and translocation of bacterial components into internal organs, which contribute to alcohol-induced health complications even before liver disease development [64].

Psychological stress also increases gut permeability in rodents and humans (Table 1). Water-avoidance stress increases gut permeability and affects the cohesive properties of mucin in mice [65]. Maternal separation induces the release of corticotropin-releasing factor by the hypothalamus and acetylcholine by cholinergic enteric neurons in rat pups, which results in increased gut permeability to large proteins [66]. In humans, a public speech test increased gut permeability in a subset of healthy subjects who had concomitant increased salivary cortisol levels [67]. Chronic stress can exacerbate symptoms in IBD patients by increasing gut permeability and inducing low-grade inflammation [68,69]. Conversely, **vagus nerve** stimulation reduces gut permeability and intestinal injury in mouse models of burn injury [70], indicating that stress management strategies may help to mitigate the effects of psychological stress on the gut barrier.

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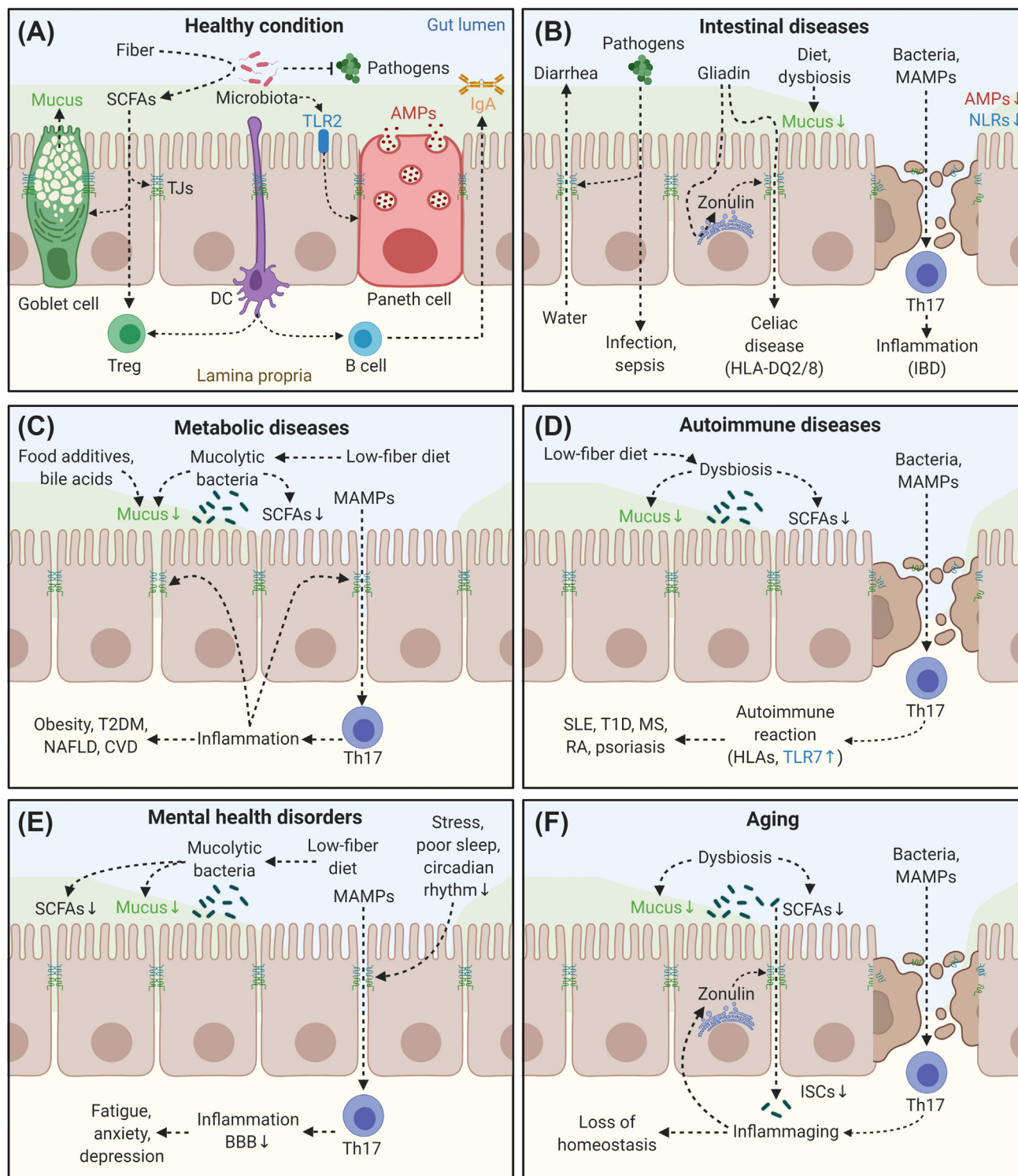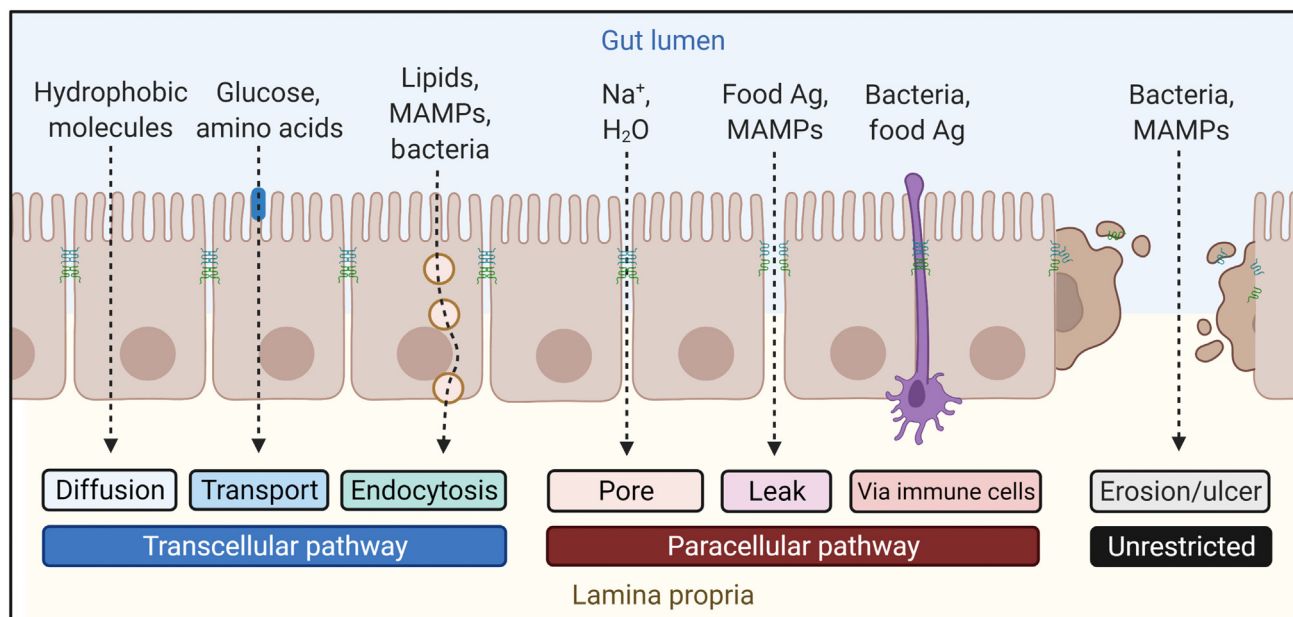
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Figure 2. Nutrient absorption and translocation of microbial components across intestinal cells. Hydrophobic molecules are absorbed by diffusion through the membrane bilayer. Specific transporters for glucose and amino acids facilitate transport through enterocytes. Lipid micelles, which may contain bacterial lipopolysaccharide and other microbe-associated molecular patterns (MAMPs), are absorbed by endocytosis. Water and small ions (<8 Å) such as sodium (Na$^+$) can also pass through the 'pore' pathway formed by claudin-2 proteins. Tight junction rearrangement in response to proinflammatory cytokines allows passage of food antigens (Ag) and MAMPs (<100 Å) via the 'leak' pathway. Dendritic cells send protrusions through the paracellular pathway to sample lumen antigens. Erosion, ulcers, and intestinal cell death can lead to unrestricted passage of whole bacteria and MAMPs into the lamina propria.

Sleep deprivation also induces gut permeability and increases proinflammatory cytokines in mice [71]. Night shift workers are more prone to develop various disorders, including gastric and duodenal ulcers [72,73], obesity, type 2 diabetes, and cardiovascular disease [74], which are associated with gut barrier dysfunction. In view of the pleiotropic effects of the circadian rhythm in regulating physiological functions, chronic disruption of the circadian rhythm by sleep deprivation or unrestricted, *ad libitum* feeding patterns has emerged as a critical factor in the development of metabolic disease [75,76]. Accordingly, circadian rhythm disruption through genetic or environmental means increases colonic permeability, endotoxemia, and hepatosteatosis in alcohol-treated mice [77] (Table 1).

Proinflammatory cytokines produced as a result of increased gut permeability and chronic inflammation may also affect the blood–brain barrier, leading to fatigue and possibly contributing to

Figure 1. Gut barrier and disease conditions. (A) The gut barrier consists of gut commensal microbes, mucus, the intestinal epithelium, and immune cells in the lamina propria. Dendritic cells (DC) continually sample the lumen and promote proliferation of regulatory T (Treg) cells in response to commensals, therefore inducing a default state of tolerance. DCs also stimulate B cells to secrete immunoglobulin (Ig)A, which prevents translocation of bacteria into the mucosa. Dietary fibers are converted by the gut microbiota into short-chain fatty acids (SCFAs), which induce mucus production by goblet cells and expression of tight junctions (TJs). Paneth cells secrete antimicrobial peptides (AMPs) in response to Toll-like receptor-2 (TLR2) signaling induced by the gut microbiota. (B) Intestinal diseases involve gut barrier disruption due to pathogens, genes, and poor diet. (C) Metabolic diseases, including obesity, type 2 diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD) have been linked with food additives, bile acid metabolism, low-fiber diets, and dysbiosis, which together may affect gut barrier integrity. (D) Autoimmune diseases are associated with genetic predisposition and environmental factors that affect gut barrier integrity. (E) Mental health issues may be linked with psychological stress, poor sleep, diet, and circadian rhythm disruption, which can affect the gut barrier, producing systemic inflammation that in turn affects the blood–brain barrier (BBB). (F) Aging eventually leads to gut dysbiosis, exhaustion of intestinal stem cells (ISCs), and inflammaging, which may induce a vicious cycle of inflammation and gut barrier dysfunctions. Abbreviations: IBD, inflammatory bowel disease; MAMPs, microbe-associated molecular patterns; MS, multiple sclerosis; NLRs, NOD-like receptors; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

Table 1. Stimuli that alter gut barrier integrity in model organisms or humans

Stimuli	Main finding	Refs
Acrolein (food toxin)	Endoplasmic reticulum stress↑, intestinal cell death↑, gut permeability↑, and endotoxemia↑ in mice	[158]
Aging	Serum zonulin↑, proinflammatory cytokines↑, and gut permeability↑ in aging individuals (>67 years old)	[98,159]
Alcohol	Endotoxemia↑ in alcoholic cirrhotic, non-alcoholic cirrhotic and healthy individuals after large intake	[160]
Antacid drugs	Gastric acid↓, commensal bacteria↑ in the small intestine, BT, liver inflammation, and alcohol-induced fatty liver disease in mice	[62]
Antibiotics	Gut permeability↑, ZO-1↓ and occludin↓, gut dysbiosis, and inflammasome activation in mice treated with a broad-spectrum antibiotic cocktail	[161]
Bile acids	TJ rearrangement in Caco-2 cells; 10-week feeding dose-dependently disrupted gut barrier in mice	[36,37]
Burn injury	Reduced TJ protein expression and increased gut permeability in mice after burn injury	[162]
Chemotherapy	Cyclophosphamide induced BT into lymph nodes, in turn inducing proinflammatory T helper 17 immune cells and anticancer effects in mice	[163]
Circadian rhythm disruption	Alcohol-induced colonic permeability and endotoxemia in transgenic clock$^{\Delta19/\Delta19}$ mice; increased gut permeability and dysbiosis in mice maintained in constant 24-hour light	[77,164]
Corticosteroids	Daily subcutaneous injection for 10 days produced a threefold increase of colon permeability to 400-Da PEG, but not to larger molecules, in rats	[165]
Dextran sodium sulfate	Reduced body weight, colon length, and survival in mice	[166]
Emulsifiers (food additives)	Gut permeability↑, inflammation, obesity↑, and metabolic syndrome↑ in wild-type mice and colitis in colitis-prone IL-10$^{-/-}$ and TLR-5$^{-/-}$ mice	[38]
Exercise (strenuous)	Mild endotoxemia was observed after a 2–4 hour marathon; strenuous exercise (≥2 hours) at 60% VO$_2$ max increased gut permeability and endotoxemia in healthy subjects and trained athletes, irrespective of fitness status; modest endotoxemia and pronounced proinflammatory response was observed after a 230-km ultra-marathon	[89,167,168]
Fasting/starvation	Fasting for 16 hours increased endotoxemia-induced intestinal cell apoptosis in mice; fasting for 3 days increased intestinal cell apoptosis and gut permeability in rats; fasting for 48 hours impaired Paneth cell function, reduced antimicrobial proteins, and induced BT in mice	[153,169,170]
Fructose	*Ad libitum* high-fructose feeding induced diabetes and hepatosteatosis in monkeys, while calorically controlled high-fructose feeding induced endotoxemia, microbial translocation, and liver injury; TJ proteins↓, endotoxemia, inflammation, and hepatosteatosis in rats; TJ proteins↓ and liver inflammation in biopsies of obese humans	[39,171]
Fructan	Induced more gastrointestinal symptoms than gluten in individuals with non-celiac gluten sensitivity	[172]
Gliadin (wheat protein)	Permeability↑ in human biopsy explants from all individuals following treatment with gliadin, but more so in explants from subjects with active celiac disease and non-celiac gluten sensitivity	[173]
Heat	Splanchnic blood flow↓ and portal endotoxemia↑ in rats exposed to 41.5°C	[174]
High-fat diet	Dysbiosis, mucus thickness↓, and inflammation in mice fed a HFD for 12 weeks; endotoxemia↑ in healthy subjects fed a HFD for 1 month; endotoxemia↑ in healthy subjects fed a HFD for 5 days	[33,175,176]
High-salt diet	Chronic salt feeding (2% NaCl) for 8 weeks induced BT and kidney injury in mice	[40]
High-sugar diet	Gut mucolytic bacteria↑, BT, SCFAs↓, inflammation, and severe DSS-induced colitis in mice	[23,177]

Table 1. (continued)

Stimuli	Main finding	Refs
Hyperglycemia	Gut permeability↑, systemic TLR ligands↑, and susceptibility to infection↑ in streptozotocin-treated mice	[46]
Hypoxia	Long-term gut tissue hypoxia reduced gut TJs in mice and increased blood bacterial DNA in some patients (31%)	[145]
Lectins	Endotoxemia↑ and BT in rats fed a diet of 26% crude red kidney beans for 24 hours	[178]
Leptin deficiency	Gut permeability↑, systemic TLR ligands↑, and susceptibility to infection↑ in db/db obese mice	[46]
Low-fiber diet	Mucus thickness↓, inflammation↑, and colitis↑ in gnotobiotic mice harboring a human gut microbiota and inoculated with Citrobacter rodentium	[143]
Nightshade alkaloids	Solanine and chaconine disrupted gut barrier integrity and aggravated IBD in colitis-prone IL-10$^{-/-}$ mice	[179]
NSAIDs	Intestinal permeability↑ and inflammation in subjects on long-term NSAID treatment	[180]
Parenteral nutrition	Gut permeability↑ and BT to lymph nodes in 70–90% of rats fed parenterally for 7 or 14 days; no obvious mucosal changes in human intestinal biopsies after 1 month of total parenteral feeding	[152,155,181]
Pesticide	Chlorpyrifos induced BT to the spleen in weaning and adult rats	[182]
Phytochemicals	Plant extracts of hops and marigold increased permeability of human intestinal Caco-2 cell monolayers	[183]
Proinflammatory cytokines	IL-1β induced gut permeability and dissemination of IgA in cardiovascular tissues in a mouse model of Kawasaki disease; TNF-α induced occludin endocytosis, gut barrier loss, and diarrhea in mice	[184,185]
Psychological stress	A public speech test increased gut permeability via activation of mast cells in some healthy volunteers; maternal separation induced gut permeability and BT to the liver and spleen in rat pups; water avoidance stress increased gut permeability and reduced mucin layer's cohesive properties in rats	[66–67,186]
Radiation	Severe gastrointestinal damage, BT, sepsis, and death in γ-irradiated mice	[187,188]
Rapamycin	Gut permeability↑, inflammation↑, and mortality↑ in a mouse model of ischemia-reperfusion injury	[189]
Sleep deprivation	Plasma melatonin↓, gut permeability↑, dysbiosis, oxidative stress↑, and proinflammatory cytokines↑ in mice	[71]
Smoking	Chronic smoking induced BT, gut permeability, TJ alteration, and inflammation in mice	[190,191]
Stroke	Gut permeability↑ and BT to multiple organs in mice and humans following stroke	[192]
Sweeteners	Permeability↑ of human intestinal Caco-2 cell monolayers by reducing claudin-3	[41]
Trauma/surgery	Gut permeability↑ and TNF-α↑ in mice following traumatic brain injury; BT in 15% of surgical patients	[193,194]
Vitamin C	Increased gut permeability to lactulose more than aspirin in healthy female volunteers	[195]

Abbreviations: BT, bacterial translocation; HFD, high-fat diet; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PEG, polyethylene glycol; TJ, tight junction; TLR, Toll-like receptor; TNF-α, tumor-necrosis factor-alpha; VO$_2$ max, maximum volume of oxygen; ZO, zonula occludens.

behavioral disorders and depression [78,79] (Figure 1E). Increased anti-LPS antibodies have been observed in subjects with major depressive disorder [80,81]. Endotoxemia and proinflammatory cytokines induce sickness behavior, which includes fatigue, anxiety, and depressive

Box 1. From killing the bad to fostering the good

While antibiotics remain important tools for treating infections, evidence suggests that their overuse in the last 50 years has produced many detrimental effects on the human gut microbiota [129]. Many bacterial species that are depleted by antibiotics return after treatment, but some species are lost indefinitely [130]. Recovery of the gut microbiota following antibiotic treatment is slow and inefficient in mice consuming a fiber-depleted diet [131], demonstrating that the gut microbiota requires dietary fiber to thrive. Antibiotic treatment affects gut microbiota diversity, which can reduce resistance to colonization by pathogens [6]. For instance, antibiotics such as clindamycin, fluoroquinolones, and cephalosporins increase the risk of infection by the opportunistic pathogen *Clostridium difficile* [132].

Depletion of commensals can also have long-lasting systemic effects. For instance, antibiotics used in the first year of childhood increase the risk of developing asthma and other allergies such as hay fever and eczema in children [133]. Early antibiotic use is also associated with increased body weight and is possibly a culprit in emergence of the obesity epidemic [134]. Similarly, zealous use of alcohol-containing mouth washes depletes mouth bacteria that produce nitric oxide, which increases the risk of type 2 diabetes [135] and hypertension [136], possibly due to reduced nitric oxide bioavailability.

Moreover, gut barrier integrity and the microbiota are intimately linked. Transgenic mice that express intestinal-specific, constitutively active myosin light chain kinase (MLCK), an enzyme that induces gut permeability by altering the cytoskeleton and tight junctions, show low-grade gut inflammation and dysbiosis [137]. Conversely, gut microbiota composition changes produced by housing two mouse colonies in different rooms of the same specific pathogen-free facility can also impair the colonic mucus layer and gut barrier integrity [138]. These observations suggest that the gut barrier and microbiota are involved in a crosstalk that is pivotal for maintaining health.

A large epidemiological study that examined nearly 70 000 diabetic subjects in Northern Denmark showed that hyperglycemia is strongly associated with community and hospital-acquired infections [139]. The severity of coronavirus disease 2019 (COVID-19) symptoms has also been associated with increased gut permeability, [140] suggesting that gut barrier integrity may represent a marker for the progression of infectious diseases. The factors that affect the gut barrier–microbiota relationship, including underlying conditions such as diabetes and aging, may be involved in the development of infectious diseases. Therefore, treating a metabolic condition or an infection without consideration of gut barrier integrity and dysbiosis is unlikely to provide a stable long-lasting cure.

symptoms [79]. Gut barrier dysfunction and dysbiosis have been linked to other mental health issues such as chronic fatigue syndrome [82], schizophrenia [83], suicide [84], and autism [85], although the mechanisms remain to be examined in more detail. While mental health disorders are multifactorial in nature, gut barrier defects may represent a contributing factor in some individuals.

Exercise can also affect gut barrier integrity (Table 1). Strenuous exercise for more than 2 hours at 60% VO_2 max appears to be the threshold above which increased gut permeability and endotoxemia are observed in healthy subjects and trained athletes, irrespective of fitness status [86]. These effects may be attributed to stress hormones and increased heat, which induces a redistribution of blood flow to the periphery to dissipate heat, thereby reducing blood flow and oxygen levels in the gastrointestinal tract [87]. However, swimming at moderate intensity improved gut barrier integrity in rodents [88], implying the occurrence of biphasic **hormesis** responses (Box 2).

Do poor diet and lifestyle habits that increase gut permeability, such as a low-fiber diet and psychological stress, necessarily lead to autoimmune, metabolic, and cognitive disorders? Obviously not (Box 2). However, it is likely that chronic ruptures of the gut barrier, as may occur in individuals with a modern lifestyle, may overwhelm the body's defenses and contribute to inflammation and disease development, especially in aging individuals.

When the fence grows old

Major changes occur in the gut during aging, including increased intestinal cell apoptosis, reduced mucus thickness and antimicrobial peptides, intestinal stem cell exhaustion, and dysbiosis [89–92] (Figure 1F). The term 'inflammaging' has been used to describe the association between

> **Box 2. Leaky gut as the cause of all diseases? Not so fast…**
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> Gut barrier defects have been associated with a surprisingly large number of diseases, from cardiovascular disease [141] and cancer [142], to autism [85] and even COVID-19 [140]. But can gut barrier disruption be blamed for such a broad spectrum of diseases?
>
> Feeding mice with a low-fiber diet transiently increases mucus production to offset barrier dysfunction, whereas prolonged feeding induces a breach in intestinal integrity [143]. Mice treated with microbial toxin from *Vibrio cholerae* present a transient gut barrier breach that enhances their resistance to subsequent colitis [144]. Similarly, brief stress, such as hypoxia applied for a short period, results in fortified tight junctions and improved gut barrier integrity, whereas prolonged hypoxia damages barrier function [145]. Clearly, transient and low-intensity stress can be beneficial, while chronic and acute stress is detrimental, a biphasic dose response called hormesis. Hormetic responses are observed for various physiological functions in response to stress, ranging from exercise and intermittent fasting to consumption of drugs and phytochemicals [146–150].
>
> Studies also indicate that the human gastrointestinal tract is more robust than the murine one. Feeding rodents with a total liquid diet containing no fiber, enterally or parenterally, for 7 or 14 days, induces bacterial translocation to internal organs [151,152]. Similarly, fasting for 3 days increases the gut permeability and endotoxemia in rodents [153], possibly due to reduced nutrient supply to intestinal cells and reduced mucus production. In humans, total parenteral nutrition also induces gut barrier dysfunction in critically ill patients [154] and bacterial translocation occurs in abdominal surgery, trauma, ischemia-reperfusion injury, and pancreatitis [155], but parenteral nutrition for 1 month apparently does not lead to bacterial translocation or dramatic mucosal changes in immunocompetent individuals [155]. Findings from rodent studies therefore need to be confirmed in humans.
>
> Bacterial translocation does occur in humans following surgery, burn injury, or stroke (Table 1), which can lead to sepsis [155], but MAMP translocation does not necessarily induce symptoms of sepsis or fever in humans [145], possibly due to normal immune functions. *In vitro* models indicate that ulceration or erosion of epithelial cell monolayers is resealed within a minute of injury [156]. In the human body, the intestinal epithelium is renewed every 3–5 days due to stem cell proliferation, which helps to remove infected or damaged cells [157]. Disease may therefore develop only when the body's defenses are overwhelmed, which may occur in genetically susceptible and aging individuals, or in individuals exposed to a high and prolonged stress burden, a possibility that requires further investigation.

aging and chronic, low-grade inflammation [93,94]. For instance, serum levels of zonulin and HMGB1 (a nuclear protein whose extracellular form is known to induce inflammation) increase in healthy, old individuals compared with young subjects [95]. Germ-free mice fail to show an aging-dependent increase in inflammatory mediators and an aging-dependent increase in gut permeability and proinflammatory cytokines can be transferred to germ-free mice that are co-housed with aged, but not young, mice [96]. These data suggest that gut dysbiosis observed during aging promotes gut permeability and inflammation. While proinflammatory cytokines initially act to contain microbial infection and promote tissue regeneration following injury or infection [97], these molecules may accumulate in aging individuals, producing a vicious cycle of gut barrier loss and chronic inflammation [98].

Research even suggests that increased gut permeability may be a critical event leading to death from 'natural cause'. In *Drosophila*, in which gut permeability can be observed as accumulation of a blue dye throughout the body following feeding (thus creating blue flies called 'Smurfs'), gut permeability has been found to be more accurate than chronological age for predicting the time of death [99]. Aging-induced gut permeability is also observed in nematodes and zebrafish and it increases quasi linearly with age, occurring in all individuals prior to death, regardless of chronological age [100]. Notably, increased gut permeability is observed in critically ill patients prior to multiple organ failure [101]. In addition to the gut, increased epithelial and endothelial permeability in the kidneys, lungs, and the liver is observed in critically ill patients [102], indicating that loss of integrity in various barriers may contribute to the demise of the human body.

Interventions to maintain gut barrier integrity

Many interventions can improve gut barrier integrity in human and animal studies (Table 2). Arguably, one of the main strategies to improve health is the reintroduction of dietary fiber in

Table 2. Interventions that maintain or restore gut barrier integrity in model organisms or humans

Intervention	Main finding	Refs
Alkaline phosphatase	Oral treatment reduced alcohol-induced endotoxemia, gut barrier dysfunction, and hepatosteatosis in mice	[124]
Amuc 1100	This *A. muciniphila* protein reduced fat mass, endotoxemia, and insulin resistance in HFD-fed mice	[120]
Berberine	Reduced TNF-α-induced disruption of TJs and gut barrier in rat colon	[196]
Butyrate	Bacterial translocation↓ across human intestinal cell monolayers *in vitro*; gut permeability↓ and onset of arthritis↓ in mice	[56,197]
Caloric restriction	4 weeks of 800 kcal/day reduced gut permeability, body weight, and insulin resistance in obese women	[125]
CB1R agonists	Gut permeability↓ and onset of arthritis↓ in mice; permeability↓ and ZO-1↑ in *C. difficile*-treated Caco-2 cells	[56,198]
Curcumin	LPS-induced MLCK levels↓ in human intestinal cell monolayers *in vitro*; gut permeability↓, endotoxemia↓, weight gain↓, and liver steatosis↓ in ApoE$^{-/-}$ mice	[106,199]
Dietary fiber	Zonulin↓, serum hepatic enzymes↓, insulin resistance↓, and fatty liver index score in NAFLD subjects; mucus secretion↑ in gut of rats	[104,200]
Divertin	Reversed gut barrier loss in human jejunal mucosae *ex vivo* and IBD development in mice	[185]
Exercise (moderate)	Swimming increased TJ gene expression in the small intestine of rats, but reduced expression in the colon	[88]
Fasting	Early-life IF using the 2:5 diet for 1 month improved late-life gut integrity and longevity in flies; IF improved gut barrier integrity, endotoxemia, and diabetes-induced cognitive impairment in mice; fasting reduced gut permeability in arthritis subjects	[201–203]
Fasting-mimicking diet	Intestinal stem cells↑, gut dysbiosis↓, inflammation↓, and pathological scores↓ in the DSS-colitis model in mice	[127]
Fecal microbiota transplantation	Small intestinal permeability↓ in NAFLD subjects with initially high permeability	[204]
Fermented food	BT↓, gut permeability↓, dysbiosis↓, and proinflammatory cytokines↓ in DSS-induced colitis in mice treated with a mixture of fermented barley and soybean	[205]
Fish oil	Gut permeability↓, antimicrobial defense↑, mucus components↑, and insulin resistance↓ in HFD-fed mice	[206]
Gelatin tannate	Increased mucus and reduced disease severity and blood LPS in the mouse model of DSS-induced colitis	[207]
Ganoderma lucidum polysaccharides	Reduced gut permeability, dysbiosis, endotoxemia, obesity, and insulin resistance in HFD-fed mice	[208]
GLP-2	Reduced gut permeability to 4-kDa FITC in enteritis-suffering mice induced by irinotecan	[209]
Glutamine	Reduced gut permeability, endotoxemia, and inflammation in abdominal postoperative patients; reduced gut permeability in malnourished children	[210,211]
Hirsutella sinensis polysaccharides	Reduced gut permeability, dysbiosis, endotoxemia, inflammation, and type 2 diabetes in HFD-fed mice	[118]
Hydrogen (H$_2$)	Reduced gut permeability, BT, inflammation, and dysbiosis in a murine model of sepsis	[212]
Infrared light	Abdominal irradiation reduced inflammation, amyloidosis, dysbiosis, and cognitive dysfunctions in a murine model of Alzheimer's disease	[213]

(continued on next page)

Table 2. (continued)

Intervention	Main finding	Refs
Larazotide (zonulin inhibitor; AT1001)	Reduced gut permeability in DSS-treated mice; reduced morbidity and mortality in transgenic Hp2 mice; reduced gut permeability and onset of arthritis in mice	[56,214]
Lubiprostone	Reduced gut permeability, inflammation, and atherosclerotic lesions in ApoE$^{-/-}$ mice red a Western diet; reduced diclofenac-induced gut permeability in healthy volunteers	[215,216]
Mesalamine	Gut permeability↓, TJs↑, and inflammation↓ in mice exposed to burn injury; wound healing in colon cells	[217,218]
ML-9 (MLCK inhibitor)	Reduced TJ alterations, gut permeability, and mucosa injury in mice following burn injury	[162]
Nicotinamide riboside	Rejuvenated intestinal stem cells and improved repair of gut damage	[219]
Nicotine	Gut permeability↓, occludin↑, ZO-1↑, and gut injury↓ induced by burn injury in mice	[220]
Quercetin	Transepithelial electrical resistance↑ and claudin-4↑ in human intestinal Caco-2 cell monolayers	[221]
Probiotics	Reduced gut permeability, endotoxemia, obesity, inflammation, and insulin resistance in HFD-fed mice; reduced symptoms in patients with IBS, C. difficile infection, or antibiotic-associated diarrhea; failure to improve outcome against anxiety or in children with gastroenteritis	[112,115–118,120]
Rebamipide	Reduced diclofenac-induced gut permeability in mice	[222]
Resveratrol	Restored TJ protein expression and reduced LPS-binding protein and inflammation in DSS-treated colitic mice	[107]
Spermidine	Gut barrier function↑, dysbiosis↓, endotoxemia↓, body weight↓, and insulin resistance↓ in HFD-fed mice	[223]
Time-restricted feeding	Intestinal TJ↑, inflammation↓, and protection against ischemia-reperfusion-induced injury in mice	[128]
Tofacitinib	Reduced IFN-γ-induced permeability in human intestinal cell lines and primary colonoids	[224]
TNF-α antibody	Gut permeability↓ assessed by lactulose/mannitol ratio in subjects with Crohn's disease 7 days after treatment	[122]
Urolithin A	Intestinal TJ↑ and Nrf2↑ in intestinal cells; gut permeability↓, systemic inflammation↓, and colitis↓ in mice	[108]
Vagus nerve stimulation	Reduced gut permeability to 4-kDa FITC-dextran and TNF-α levels, prevented changes in occludin expression and localization, and improved gut histology in a mouse model of burn injury	[70,225]
Vasoactive intestinal peptide	Reduced Citrobacter rodentium-induced gut permeability and colitis in mice	[226]
Vitamin D	Increased susceptibility to DSS-induced colitis in vitamin D receptor-deficient mice; vitamin D supplementation maintained gut barrier integrity in a double-blind RCT in Crohn's disease subjects, compared with controls; abrogated bacterial translocation in DSS-induced colitis in mice	[237–229]
Yogurt	Gut permeability↓ assessed by lactulose/mannitol ratio in a rat model of methotrexate-induced mucositis	[230]
Zinc	Gut permeability↓ to macromolecules and bacterial translocation↓ in α-hemolysin-producing Escherichia coli-treated mice	[231]

Abbreviations: ApoE, apolipoprotein E; BT, bacterial translocation; CB1R, cannabinoid receptor type 1; DSS, dextran sodium sulfate; FITC, fluorescein isothiocyanate; GLP-2, glucagon-like peptide-2; HFD, high-fat diet; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IF, intermittent fasting; IFN-γ, interferon-gamma; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MLCK, myosin light chain kinase; NAFLD, non-alcoholic fatty liver disease; RCT, randomized controlled trial; TJ, tight junction; TLR, Toll-like receptor; TNF-α, tumor-necrosis factor-alpha; ZO, zonula occludens.

the Western diet [103]. For example, adding 10 g of fiber per day for 6 months reduced serum zonulin, insulin resistance, and serum liver enzymes and improved fatty liver score in non-alcoholic fatty liver disease subjects [104]. Given that human subjects show notoriously poor compliance with dietary modifications, dietary fiber supplements may be a viable option for these patients.

Many phytochemicals such as berberine, curcumin, quercetin, and resveratrol improve gut barrier integrity and reduce inflammation in animal models (Table 2). While these phytochemicals show poor bioavailability, we suggested earlier that they may produce beneficial effects by serving as prebiotics and biological stress inducers [105]. Phytochemicals may thus reduce inflammation by fortifying the gut barrier and preventing the translocation of microbial components, as shown in recent studies for curcumin [106], resveratrol [107], and urolithin A [108] in mice and cultured cells. Conversely, phytochemicals from hops, chili pepper, and marigold may instead increase gut permeability [109] and a diet deficient in specific phytochemicals and lectins may be highly beneficial in individuals who show signs of inflammation [110].

In addition to maintaining gut barrier integrity by inducing the production of mucus, antimicrobial proteins, IgA, and Treg cells (Figure 1), commensals can reinforce the gut epithelium by promoting tightening of intestinal cellular junctions [111]. First-generation probiotics such as *Lactobacillus* and *Bifidobacterium* stimulate resistance against gastrointestinal diseases, enteric infection, antibiotic-induced diarrhea, depression, and anxiety [112–114]; however, negative results were also obtained, for instance, against anxiety [115] or gastroenteritis [116,117], possibly due to variations in diet, lifestyle, and gut microbiota composition.

Second-generation probiotics such as *Akkermansia muciniphila*, *Roseburia* spp., and *Parabacteroides* spp. are currently being studied to improve gut homeostasis. Our group observed that *Parabacteroides goldsteinii* reduced gut permeability, serum endotoxemia, body weight gain, insulin resistance, and inflammation in HFD-fed mice [118]. In humans, supplementation with heat-killed *A. muciniphila* for 3 months reduced serum endotoxemia, slightly decreased body weight and fat mass, and improved insulin sensitivity in overweight and obese volunteers [119]. A membrane protein (i.e., Amuc 1100) from *A. muciniphila* may be responsible for these benefits as it reduced signs of obesity and diabetes and improved gut barrier integrity in mice, possibly by inducing TLR2 signaling [120].

Corticosteroids, anakinra (IL-1 receptor antagonist), and anti-TNF-α antibodies can reduce inflammation and improve gut barrier integrity in IBD subjects [121,122]. Glutamine reduced intestinal permeability and improved inflammatory bowel syndrome severity scores in a randomized placebo-controlled clinical trial of patients following enteric infection [123]. In a mouse model of arthritis, treatment with butyrate, cannabinoid type 1 receptor agonists, or larazotide (a zonulin antagonist) reduced gut permeability and arthritis symptoms [56]. Notably, larazotide is currently in Phase III clinical trials for the treatment of celiac disease. In addition, oral supplementation with alkaline phosphatase, which can dephosphorylate and inactivate LPS, can reduce endotoxemia, gut barrier dysfunction and liver damage induced by alcohol in mice [124].

Caloric restriction, the fasting-mimicking diet, and time-restricted feeding can also produce benefits for the gut (Table 2). A 4-week caloric restriction diet (800 kcal/day) reduces gut permeability, body weight, insulin resistance, and inflammation markers in obese women [125]. The fasting-mimicking diet, which involves consuming a low-protein, low-calorie diet (800 kcal/day) for 4 or 5 consecutive days per month, reduces markers of aging, diabetes, cancer, and cardiovascular disease in humans [126]. The fasting-mimicking diet increased intestinal stem cells and reversed

dysbiosis, inflammation, and pathological scores in the mouse model of DSS-induced colitis [127]. Time-restricted feeding in which food is consumed within 4–8 hours (during daytime for humans or nightime for rodents) also reduces gut barrier disruption and ischemia-reperfusion injury in mice [128].

An interesting strategy to improve gut homeostasis and reduce inflammation consists of combining nonpersonalized interventions centered around limiting the inappropriate use of antibiotics coupled with personalized interventions involving consumption of plant-based, high-fiber foods, engineered fiber-enriched foods, prebiotics supplementation, and reintroduction of volatile and/or associated negatively with industrialized societies of humans (VANISH) taxa in the gut microbiota [103].

Concluding remarks and future perspectives

Multiple factors involving poor diet and lifestyle habits affect gut barrier function and the composition of the gut microbiota. These factors play a role in the development of intestinal diseases as well as metabolic, autoimmune, and mental disorders involving inflammation. Many promising therapies have been tested in animal models and require confirmation in clinical trials (see Outstanding questions). However, treatments such as probiotics or pharmaceutical drugs aimed at restoring gut barrier integrity are likely to fail when taken in isolation. Instead, we believe that lifestyle changes involving consideration of diet composition, pharmaceutical drug and alcohol use, exercise, sunlight exposure and vitamin D levels, circadian rhythm regulation, and stress management are more likely to show positive results. Recent advances related to gut barrier integrity and gut microbiota composition therefore offer the opportunity to reassess the importance of the diet and lifestyle in the prevention and treatment of chronic diseases associated with gut barrier disruption, inflammation, and aging.

Declaration of interests

Y-F.K. is President of Chang Gung Biotechnology. J.D.Y. is Chairman of the Board of Chang Gung Biotechnology. J.M., Y-F.K., T-L.H., J.D.Y., and D.M.O. are named on patents held by Chang Gung University and/or Chang Gung Biotechnology related to the preparation and use of prebiotics, probiotics, and bioactive compounds.

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Outstanding questions

What is the role of gut barrier disruption in diseases such as autism, cancer, schizophrenia, multiple sclerosis, and COVID-19?

Can dietary fiber supplementation and fiber-enriched food help to prevent or treat metabolic, autoimmune, and cognitive disorders?

Can lifestyle interventions involving changes in diet and exercise, alcohol and antibiotic use, sunlight exposure, and stress management improve conditions associated with increased gut permeability?

Can transient low-intensity stress such as intermittent fasting, moderate exercise, and specific phytochemicals be used to improve gut barrier integrity via hormesis?

What is the role of gut barrier disruption in inflammaging in humans?

Can aging be delayed by treatments aimed at maintaining or restoring gut barrier integrity, such as fiber, probiotics, phytochemicals, vitamin D, and targeted drugs?

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