PERSPECTIVE

Perspective: Prospects for Nutraceutical Support of Intestinal Barrier Function

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ABSTRACT

Impairment of intestinal barrier function is linked to certain pathologies and to aging, and can be a cause of bacterial infections, systemic and hepatic inflammation, food allergies, and autoimmune disorders. The formation and maintenance of intestinal tight junctions is supported by glucagon-like peptide-2 (GLP-2), which via insulin-like growth factor I activity boosts phosphoinositide 3-kinase/Akt/mammalian target of rapamycin complex 1 (PI3K/Akt/mTORC1) signaling in enterocytes. 5′-AMP-activated protein kinase (AMPK) activity as well as estrogen receptor-β (ERβ) activity are also protective in this regard. Conversely, activation of mitogen-activated protein kinases (MAPKs) and cellular Src (c-Src) under inflammatory conditions can induce dissociation of tight junctions. Hence, nutraceuticals that promote GLP-2 secretion from L cells—effective pre/probiotics, glycine, and glutamine—as well as diets rich in soluble fiber or resistant starch, can support intestinal barrier function. AMPK activators—notably berberine and the butyric acid produced by health-promoting microflora—are also beneficial in this regard, as are soy isoflavones, which function as selective agonists for ERβ. The adverse impact of MAPK and c-Src overactivation on the intestinal barrier can be combatted with various antioxidant measures, including phycocyanobilin, phase 2–inducer nutraceuticals, and *N*-acetylcysteine. These considerations suggest that rationally designed functional foods or complex supplementation programs could have clinical potential for supporting and restoring healthful intestinal barrier function. *Adv Nutr* 2021;12:316–324.

Keywords: nutraceuticals, intestinal permeability, tight junction, intestinal barrier, glucagon-like peptide 2, AMPK, phycocyanobilin, *N*-acetylcysteine, berberine, butyric acid

Introduction

The enterocyte tight junction

The intestinal epithelial monolayer represents the body's largest interface with the external environment. It serves dual opposing functions. It selectively absorbs needed nutrients while preventing absorption of detrimental luminal components, including antigenic peptides, proinflammatory factors, oxidants, toxins, bacteria, yeasts, parasites, microbial components or their secreted mobilome, and various allergens and carcinogens (1). Adjacent intestinal enterocytes form tight junctions that are an integral part of the physical intestinal barrier, regulating the paracellular traffic. The tight junctions represent evolutionarily well-conserved sealing complexes between adjacent enterocytes. Also called occluding junctions or zonulae occludentes, they are composed of a branching network of sealing strands, acting independently from each other. Each one of them is composed of a row of transmembrane proteins embedded in both adjacent enterocytes' plasma membranes, with extracellular extensions joining one another. There are $\geq$40 different proteins in the tight junction complex, each containing both cytoplasmic domains and transmembranous elongations. The 3 major ones are occludin, claudins, and junction adhesion molecule proteins. The parallel strands are attached to zona occludens-1 (ZO-1), located in the enterocyte's cytoplasm, which anchors the strands to the actin component of the cytoskeleton. Thus, tight junctions are fully integrated with the cytoskeletons of adjacent enterocytic cells.

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Abbreviations used: AMPK, 5′-AMP-activated protein kinase; ASK, apoptosis signal-regulating kinase; CDX, caudal type homeobox; c-Src, cellular Src; ERβ, estrogen receptor-β; ERK, extracellular signal-related kinase; GLP-2, glucagon-like-peptide-2; IGF-I, insulin-like growth factor I; JNK, c-Jun N-terminal kinase; MLC-2, myosin light chain 2; MLCK, myosin light chain kinase; NAC, *N*-acetylcysteine; p38, p38 MAP kinase; PCB, phycocyanobilin; PI3K/Akt/mTORC1, phosphoinositide 3-kinase/Akt/mammalian target of rapamyin complex 1; ZO-1, zona occludens-1.

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Not surprisingly, the Hippocratic quote "all disease begins in the gut" is proving to be true. Two millennia later, it appears that dysfunction of the tight junctions is associated with numerous pathological conditions. Gastrointestinal infections, allergic, autoimmune, cancerous, and metabolic diseases have been linked to increased intestinal permeability (1–5). Even the elderly's senescent gut is leaky (6). The term "leaky gut" refers to the failure of tight junctions to execute their multiple homeostatic functions. Loss or impairment of intestinal barrier function owing to a failure to form or maintain tight junctions can lead to infections, an increase in systemic and hepatic inflammation reflecting LPS absorption, and induction of food allergies or autoimmune disorders. Hence, it is pertinent to examine what safe nutraceutical measures might be useful for maintaining an effective intestinal barrier.

Regulation of intestinal tight junctions

Formation of tight junctions requires synthesis and translocation to the enterocyte apical membrane of a range of proteins, including claudins, occludin, junction adhesion molecules, and ZO-1, which integrate to form junctional complexes that, as noted, form tight links to neighboring enterocytes and are linked via actin to the cell's actomyosin cytoskeleton. Signaling mechanisms that can promote tight junction formation and maintenance have been characterized, though the precise details of this induction require much further clarification. Specifically, as discussed below, the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin complex 1 (PI3K/Akt/mTORC1) pathway, 5′-AMP-activated protein kinase (AMPK), and estrogen receptor-β (ERβ) function to promote tight junction formation. In contrast, inflammatory circumstances that activate the mitogen-activated protein kinases (MAPKs)—c-Jun N-terminal kinase (JNK), p38 MAP kinase (p38), and extracellular signal-related kinases 1 and 2 (ERK1/2)—and cellular Src (c-Src) tend to promote the disaggregation of tight junctions. Hence, nutraceuticals that promote the activity of PI3K, AMPK, or ERβ might be expected to aid intestinal barrier function whereas, when enterocyte MAPKs are activated in pathological conditions, nutraceuticals that inhibit MAPK activation might likewise have a favorable impact in this regard.

Trophic Impact of Glucagon-Like-Peptide 2 on Enterocytes is Mediated by Insulin-Like Growth Factor I and PI3K/Akt/mTORC1 Signaling

A key mediator of protective PI3K/Akt/mTORC1 activation in enterocytes is the hormone glucagon-like-peptide 2 (GLP-2), produced in response to various signals by special neuroendocrine L cells in the intestinal mucosa (7–9). GLP-2 does not act directly on enterocytes, but rather acts on intestinal subepithelial fibroblasts, which respond by secreting insulin-like growth factor I (IGF-I) (10). The latter acts on enterocytes to stimulate the PI3K/Akt/mTORC1 pathway, thereby promoting enterocyte proliferation, inhibiting enterocyte apoptosis, and supporting the formation and maintenance of tight junctions (7, 11–14). GLP-2 fails to exert these effects on enterocytes that lack IGF-I receptors, so IGF-I is an essential mediator of the trophic impact of GLP-2 on intestinal epithelium (12). The PI3K/Akt/mTORC1signaling pathway triggered by IGF-I activity on enterocytes can induce expression at the mRNA and protein level of a range of proteins required for tight junction formation, including occludin, claudins, and ZO-1 (15–20). Inhibitors of any of these 3 kinases block IGF-I–mediated induction of these proteins.

Pre/Probiotics, Glycine, and Glutamine Can Promote GLP-2 Secretion

Agents that stimulate L-cell secretion of GLP-2 appear to be identical to those that stimulate secretion of the better-studied GLP-1, because these 2 hormones are stored in the same secretory granules (21). The best-known stimulants of L-cell secretion are SCFAs, primarily butyrate and propionate, produced by healthful intestinal flora from inefficiently absorbed carbohydrate or soluble fiber that reaches the proximal intestine or colon. These SCFAs activate a Gq-coupled receptor expressed by L cells, free fatty acid receptor 2 (FFAR2), to provoke a release of endoplasmic reticulum calcium to the cytoplasm, increasing cytoplasmic free calcium; this in turn induces secretory granules to merge with plasma membranes, provoking release of GLP-1, -2, and other hormones that promote satiety, slow gastric emptying, and exert protective trophic effects on pancreatic β cells (22, 23). Probiotics are nutraceutical bacterial cultures capable of promoting a healthful intestinal microflora proficient at generating SCFAs or lactic acid; the latter is used by some bacteria as substrate for production of SCFAs (24–28). Prebiotics are poorly digested carbohydrates, such as inulin, that can reach the proximal intestine or colon, where they can serve as substrate for SCFA or lactic acid generation. Diets rich in soluble fiber or resistant starch can function as prebiotics.

The amino acids glutamine and glycine also can function as GLP-2 secretagogues. Glycine activates a chloride channel in L cells that is strychnine-inhibitable (29). Although this receptor has a hyperpolarizing impact in many tissues, L cells concentrate chloride against a gradient; hence, glycine channel activation in L cells cause chloride to stream out of these cells, causing a depolarization that induces calcium uptake through voltage-sensitive calcium channels. This calcium influx likewise induces secretory granules to fuse with the plasma membrane, resulting in secretion of GLP-1 and -2. Because the EC50 for activation of glycine receptors is similar to plasma glycine concentrations, it follows that a moderate elevation of plasma glycine achieved through glycine supplementation could be expected to boost GLP-2 secretion and thereby promote effective intestinal barrier function (30, 31). Surprisingly, however, glycine's potential to promote intestinal health appears so far to have received little if any study. When improvement of intestinal barrier function is desired to counter systemic or hepatic inflammation, it is pertinent to note that supplemental

glycine can act via its receptor to exert anti-inflammatory effects on a range of cell types, and that it also serves as a substrate for synthesis of the protective cellular antioxidant glutathione (31, 32).

In contrast, glutamine, which is a key substrate for enterocyte energy metabolism in addition to acting as a secretagogue for GLP-2, is well known to aid intestinal health (33, 34). Indeed, it is commonly employed as an adjuvant to cancer chemotherapy or radiotherapy to minimize their toxic impact on the intestinal tract (35). The mechanism whereby glutamine evokes secretory granule release in L cells involves both an influx of calcium and a boost in cAMP concentrations (35, 36). Uptake of glutamine by L cells is required for this response, which is not mediated by Gq and is still inadequately characterized.

Berberine and SCFA-Induced AMPK Activity Promotes Tight Junction Formation

The favorable impact of AMPK activation on intestinal barrier function is well established, and is mediated at least in part by increased expression of caudal type homeobox 2 (Cdx2), a master transcription factor driving differentiation of intestinal enterocytes (37–40). This increased expression reflects increased transcription of the *CDX2* gene, though how AMPK promotes this is still unclear. An additional effect of AMPK favorable to tight junction maintenance is its ability to confer an inhibitory phosphorylation (Ser815) on myosin light chain kinase (MLCK) (41). This prevents the latter from phosphorylating myosin light chain 2 (MLC-2). Tight junctions are linked to actomyosin rings that form part of the cellular cytoskeleton; activating phosphorylation of MLC-2 causes a contraction of these rings, which can cause dissociation of tight junctions (42). Hence, AMPK activity helps to maintain cellular actomyosin in a relatively relaxed condition, favorable to the maintenance of tight junctions. Modulation of the contractile state of actomyosin rings is a key mechanism whereby various measures promote the maintenance or the dissociation of tight junctions (42).

The diabetic drug metformin is believed to exert its favorable impact on glycemic control via activation of AMPK (43–45). The nutraceutical berberine, a compound found in various Chinese medicinal herbs, can likewise activate AMPK and is widely employed for diabetes management in China (46–48). Not surprisingly, both metformin and berberine are reported to have favorable effects on the intestinal barrier and tight junction maintenance (49–54).

The SCFA butyrate likewise can activate AMPK in enterocytes (55). This effect is mediated by store-operated calcium entry (how butyrate provokes this remains unclear); this increase in cytosolic calcium activates calmodulin-activated kinase kinase β, which then confers an activating phosphorylation on AMPK (55). Hence, pre/probiotics and fiber-rich diets can also help to maintain the intestinal barrier via butyrate-mediated activation of AMPK in enterocytes.

Soy Isoflavones Aid Intestinal Barrier Function Via ERβ

Colonic epithelium expresses the β but not the α isoform of ER. This is suspected to mediate the favorable impact of postmenopausal hormone replacement on colorectal cancer risk (56, 57). ERβ activity also promotes an effective intestinal barrier and aids tight junction formation (58). Intestinal ERβ expression tends to be decreased in patients with inflammatory bowel disease, and in rodent models of this disorder. Exposure of enterocyte cell cultures to estrogen or to specific agonists for ERβ has been reported to boost epithelial barrier function in vitro—an effect that is blocked by coincubation with an estrogen receptor antagonist (59–61). Conversely, ovariectomy adversely affects intestinal barrier function (62). How ERβ achieves this protective effect remains unclear, but increased expression of occludin at the mRNA and protein level plays a part in this effect (59, 61).

The favorable impact of ERβ activity on intestinal permeability is not solely of interest to women, insofar as soy isoflavones, in free unconjugated plasma concentrations achievable with feasible intakes of dietary soy products or soy isoflavone supplements, can stimulate ERβ activity while minimally impacting ERα (63). Genistein acts directly as an ERβ agonist, whereas daidzein can be converted by the gut bacteria of some individuals to S-equol, a compound that likewise acts as a selective ERβ agonist at physiological concentrations (64–66). Consistent with these findings, soy isoflavone administration has been found to promote a healthy intestinal barrier in rodent studies (67, 68).

Antioxidants Can Aid Tight Junction Maintenance by Downregulating MAPK Activity

In many cell culture or rodent models of intestinal barrier breakdown, activation of MAPKs—JNK2, p38, and/or ERK1/2—has been shown to play a mediating role; the tyrosine kinase c-Src also disrupts tight junctions (69–79). p38 and ERK1/2 do so, in part, by increasing expression of MLCK; p38 accomplishes this by conferring an activating phosphorylation on the transcription factor activating transcription factor 2 (ATF2), whereas ERK1/2 does so by phosphorylating and activating the transcription factor ETS-like 1 (Elk-1) (80, 81). In addition, these kinases suppress the activity of myosin light chain phosphatase, further upregulating activating phosphorylation of MLC-2 (82).

The impact of JNK2 could largely reflect its ability to enable autoactivation of c-Src by conferring a threonine phosphorylation on it (69). c-Src activity is capable of breaking down tight junctions through tyrosine phosphorylation of occludin and ZO-1; these phosphorylations prevent the association of occludin and ZO-1, such that tight junctions cannot form or be maintained (83).

Oxidant stress impedes tight junction formation, and this could in large part reflect upregulated activity of MAPKs and

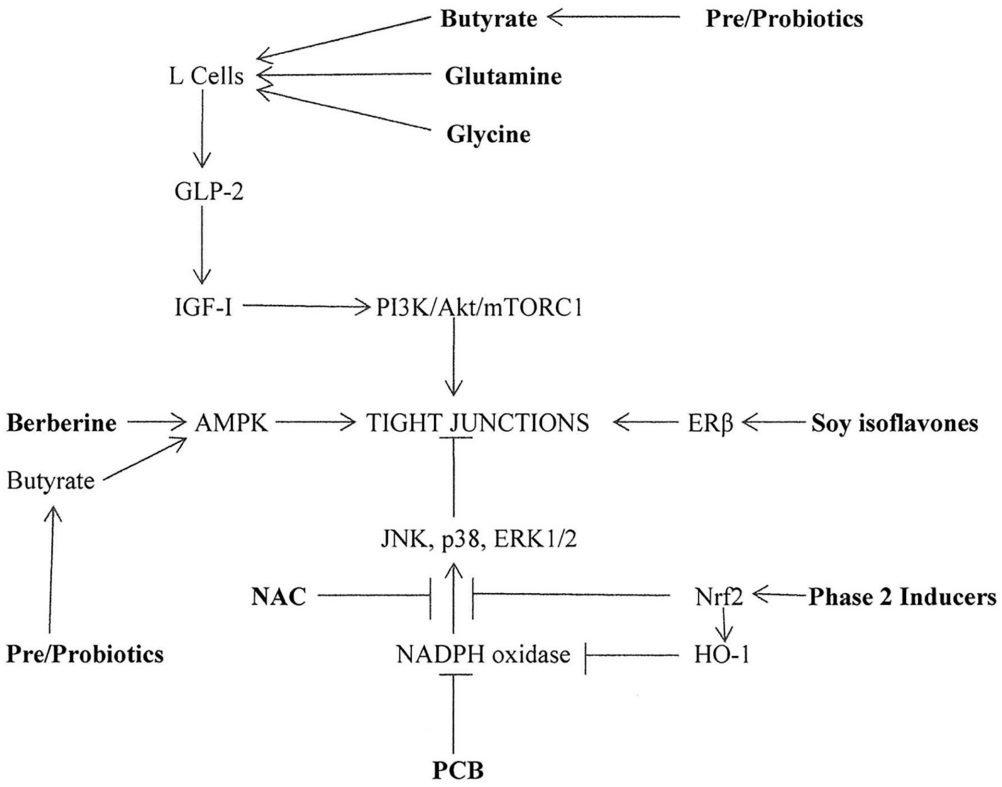

FIGURE 1 Nutraceutical strategies for promoting tight junction formation in enterocytes. Nutraceuticals are highlighted in bold. AMPK, 5′-AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; ERβ, estrogen receptor-β; GLP-2, glucagon-like-peptide-2; HO-1, heme oxygenase-1; IGF-I, insulin-like growth factor I; JNK, c-Jun N-terminal kinase; NAC, *N*-acetylcysteine; Nrf2, nuclear factor erythroid 2-related factor 2; p38, p38 MAP kinase; PCB, phycocyanobilin; PI3/Akt/mTORC1, phosphoinositde 3-kinase/Akt/mammalian target of rapamycin complex 1.

c-Src (84–89). Hydrogen peroxide reversibly inhibits dual-specificity phosphatases that deactivate the MAPKs (90–93). It can also promote activation of JNK and p38 MAPKs by oxidizing thioredoxin and thereby dis-inhibiting the kinase apoptosis signal-regulating kinase 1 (ASK1), which functions as a MAPKKK upstream from both JNK and p38 (94–97). Hydrogen peroxide can also assist the formation of signaling complexes upstream from JNK/p38 activation in certain proinflammatory signaling pathways (98, 99). And hydrogen peroxide also promotes c-Src activation, in part via JNK2 activation as described above (100–103). Hence, nutraceuticals that can suppress oxidant production, promote catabolism of hydrogen peroxide, or reverse the sulfhydryl-oxidizing effects of hydrogen peroxide on signaling proteins, have potential for supporting intestinal barrier function in the context of inflammation.

The oxidant stress that can impair tight junction formation and maintenance in enterocytes often stems from NAD(P)H oxidase complexes (89, 104–106). The unconjugated bilirubin generated by heme oxygenase–mediated catabolism of heme functions as a direct inhibitor of such complexes (107–111). Unconjugated bilirubin has been found to improve intestinal barrier function in a rat model of ulcerative colitis, and to alleviate the loss of barrier functions associated with bile duct ligation (112, 113). The biliverdin metabolite phycocyanobilin (PCB), which within cells is reduced by biliverdin reductase activity to the bilirubin homolog phycocyanorubin, can mimic the inhibitory impact of bilirubin on NAD(P)H oxidase activity (114–116). PCB functions as a light-harvesting chromophore in cyanobacteria (such as the food and nutraceutical spirulina) and certain blue-green algae; its ability to inhibit NAD(P)H oxidase activity could rationalize many of the antioxidant/anti-inflammatory effects of spirulina ingestion (or of phycocyanin, the spirulina protein to which PCB is covalently bound) in rodent studies (114, 117–119). Hence, spirulina or PCB-enriched spirulina extracts could have clinical potential for supporting intestinal barrier function in certain inflammatory circumstances in which NAD(P)H oxidase is activated in enterocytes. Spirulina feeding has been reported to help preserve the intestinal barrier in rats fed a high-fat diet (120).

Clinically useful phase 2–inducing nutraceuticals, such as lipoic or ferulic acids, can promote induction of heme oxygenase-1, and hence inhibit NAD(P)H oxidase activity via intracellular bilirubin generation (121–125). Moreover, they can also induce peroxidases, which catabolize hydrogen peroxide, induce thioredoxin and thioredoxin reductase,

which function to suppress ASK1 activation, and also help to reverse the hydrogen peroxide–induced oxidation of protein sulfhydryl groups via induction of γ-glutamylcysteine synthase, rate-limiting for glutathione synthesis (126–128). Concurrent supplementation with *N*-acetylcysteine (NAC) can aid the latter mechanism, because cysteine is a rate-limiting substrate for glutathione synthesis (129). Consistent with these considerations, lipoic and ferulic acids as well as NAC have shown favorable effects on intestinal barrier function in experimental studies (130–136). With respect to ferulic acid, it has a poorly understood anti-inflammatory effect that might enable it to suppress JNK/p38 MAPK activity in some circumstances (137–139). Hence, it is proposed that PCB (or spirulina), phase 2 inducers, and NAC can collaborate in suppressing the adverse impact of oxidant stress on tight junction formation and intestinal permeability.

A Nutraceutical Program for Promoting Intestinal Barrier Function

Figure 1 depicts suggested mechanisms whereby the nutraceuticals glutamine, glycine, berberine, soy isoflavones, PCB, phase 2 inducers (e.g., lipoic or ferulic acids), NAC, and pre- and probiotics could be expected to aid tight junction formation and maintenance in enterocytes, thereby supporting intestinal barrier function. Functional foods or complex supplementation programs incorporating several of these agents can be envisioned as aids to intestinal health.

Conclusions

A failure of intestinal barrier function reflecting inefficient formation or maintenance of the tight junctions linking enterocytes can lead to unregulated absorption of bacteria, yeast, parasites, bacterial toxins, and intact proteins or peptides derived from food or microbes. Such a failure can lead to infections and systemic and hepatic inflammation, and is suspected to trigger allergic and autoimmune disorders. Hence, promoting effective intestinal barrier function is an important goal for preventive medicine. An analysis of the enterocyte signaling mechanisms that either promote or oppose effective tight junction function—notably the PI3K/Akt/mTORC1 axis, AMPK, ERβ, the MAPKs, and c-Src—enables us to pinpoint certain nutraceutical and dietary measures that could be expected to aid intestinal barrier function. In particular, effective pre- and probiotics, the amino acids glycine, glutamine, and cysteine (provided as NAC), the herbal compound berberine, soy isoflavones, the spirulina antioxidant PCB, and phase 2–inducing nutrients or phytochemicals such as lipoic acid or ferulic acid, appear to have practical potential in this regard.

It should also be noted that those measures that protect the intestinal barrier by boosting L-cell secretion of GLP-2 could also be expected to boost production of GLP-1, and thereby aid effective β-cell function while acting in multiple other ways to promote leanness and metabolic, vascular, and neurological health (140–144).

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