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REVIEW

Host-Gut Microbiota Crosstalk in Intestinal Adaptation

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SUMMARY

Intestinal adaptation is a multifactorial compensatory process that occurs in the remaining bowel of intestinal failure patients after small-bowel loss or damage. This review provides an overview of the current knowledge on host-microbiota interactions and their potential ability to modulate the intestinal adaptive response.

Short-bowel syndrome represents the most common cause of intestinal failure and occurs when the remaining intestine cannot support fluid and nutrient needs to sustain adequate physiology and development without the use of supplemental parenteral nutrition. After intestinal loss or damage, the remnant bowel undergoes multifactorial compensatory processes, termed *adaptation*, which are largely driven by intraluminal nutrient exposure. Previous studies have provided insight into the biological processes and mediators after resection, however, there still remains a gap in the knowledge of more comprehensive mechanisms that drive the adaptive responses in these patients. Recent data support the microbiota as a key mediator of gut homeostasis and a potential driver of metabolism and immunomodulation after intestinal loss. In this review, we summarize the emerging ideas related to host-microbiota interactions in the intestinal adaptation processes. *(Cell Mol Gastroenterol Hepatol 2018;6:149–162; https://doi.org/10.1016/j.jcmgh.2018.01.024)*

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Intestinal failure (IF) describes a state of reduced absorptive function in which the intestine cannot support fluid, electrolyte, or micronutrient needs that are required to sustain adequate physiology and growth without the use of intravenous supplemental parenteral nutrition (PN) and/or fluids.[1,2] Because of continued reliance on PN, IF has a high incidence of morbidity and mortality, and is associated with complications including gastric hypersecretion, dysbiosis, D-lactic acidosis, catheter-related bloodstream infections, and intestinal failure–associated liver disease.[1,3] Although there are multiple etiologies resulting in IF, short-bowel syndrome (SBS) is the most common cause in both pediatric (50%) and adult (75%) populations.[4] SBS is the result of extensive surgical resection resulting from disease entities such as necrotizing enterocolitis (NEC), gastroschisis, Hirschsprung's disease, volvulus, intestinal atresia, Crohn's disease, pseudo-obstruction, or microvillus inclusion.[1,2]

The multidisciplinary management of SBS has been well reviewed and focuses on gaining independence from PN.[1] However, one major gap in clinical management is the strategies used to avoid attenuated functional ability of the remaining bowel with management decisions that we can control: diet, probiotics, antisecretion medications, and/or oral antibiotics. One example of this concept is the use of broad-spectrum antibiotics for the management of sepsis and the associated decrease in functional absorptive capacity of the bowel owing to presumable changes of the enteric flora. How do other long-term therapies that alter the microbiota affect the functional nutritional profile of patients? To address this, the first goal is to understand the mechanisms that alter the normal existing flora and contribute to the development of dysbiosis in patients with IF. The effect of the microbiota and the metabolism of luminal nutrients on the adaptive response are areas of active research and are the focus of this review.

Intestinal Adaptation Features

Intestinal adaptation is a spontaneous physiological compensatory process that occurs after intestinal resection to restore the digestive and absorptive capacity of the intestine. Traditionally, animal models relied on morphometric changes of the remnant bowel to measure the adaptive response. Because access to human adaptive bowel sample is not always feasible, secondary measurements such as plasma citrulline levels or absorption of inert sugars have been developed to evaluate intestinal adaptation.

Different surgical animal models have been designed to better understand the premise of SBS and intestinal adaptation to find new therapies. Three common types of resection performed in SBS patients have been studied in animals: small-bowel resection (jejunoileal anastomosis),

Abbreviations used in this paper: **CONV, conventional; ENS, enteric nervous system; GF, germ-free; GI, gastrointestinal; GLP-2, glucagon-like peptide 2; IBD, inflammatory bowel disease; ICR, ileocecal resection; IF, intestinal failure; IL, interleukin; NEC, necrotizing enterocolitis; PN, parenteral nutrition; SBR, small bowel resection; SCFA, short-chain fatty acid; SFB, segmented filamentous bacteria; SBS, short-bowel syndrome; TGR5, Takeda-G-protein-receptor 5.**

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ileocecal resection (jejunocolic anastomosis), and extensive small-bowel and colon resection that results in a high-output jejunostomy.[4,5] In human beings, small-bowel resection (SBR) is associated with rapid adaptation and has the best clinical outcome. These factors have led to the SBR model being the most represented in SBS animal models.[6–10] However, jejunocolic anastomosis and jejunostomy are the most common surgeries resulting in clinical IF, usually as a consequence of NEC disease–related or distal small bowel lesions. The ileocecal resection (ICR) model represents a model of jejunocolic anastomosis that has been investigated in rodents as well as in pigs.[11,12] The jejunostomy is the least common surgical model in animal studies, however, these patients are the most challenging to manage clinically because of the massive loss of tissue and its associated functions.[13,14] The discrepancy between animal models of SBS and what is encountered clinically should be recognized when discussing long-term intestinal adaptation in SBS and IF patients.

In experimental models, the remnant bowel undergoes macroscopic and microscopic structural changes within 48 hours after resection.[11] Macroscopically, the small bowel dilates and elongates. Microscopically, the adaptive responsive is characterized by stem cell expansion and an increased crypt cell proliferation resulting in taller villi and deeper crypts.[6,11] An increase in enterocyte apoptosis also is observed after resection, and is suggested to be a response to counterbalance enhanced proliferation and maintain homeostasis.[6] Taken together, the bowel is adapting by increasing its available surface area to accommodate for the surgical loss thereof. After intestinal resection, an early expansion of secretory cell lineages, including Goblet and Paneth cells, occurs while the number of absorptive enterocytes increases at a later time point.[15] Early hemodynamic alterations also may contribute to local angiogenesis as well as increased tissue oxygen utilization.[16,17] Collectively, these changes support mucosal growth, lead to an increase in transporter cells, and promote a slower bowel transit time; ultimately enhancing the absorptive capacity of the remaining bowel.[18,19]

Because of the invasiveness of required procedures, limited data sets exist in human patients; however, similar morphologic changes have been observed.[20] McDuffie et al[21] showed that increased villus height and crypt depth correlated with the length of the small bowel resected in pediatric NEC patients. Studies also have described enterocyte hyperplasia as well as changes in villus and crypt size after small-bowel resection or jejunoileal bypass.[22,23] In contrast, some reports did not find significant morphometric changes after bowel resection in SBS patients, suggesting that the propensity for adaptation may not be universal in humans.[24,25]

SBS animal models have been helpful in understanding some of the underlying processes occurring during intestinal adaptation and therefore in finding novel therapies that enhance adaptation. For example, glucagon-like peptide 2 (GLP-2) was found to be a potent epithelial trophic factor in surgical animal models, and this eventually led to the release of teduglutide (analog of GLP-2) for SBS patients.[26–29] Teduglutide has been shown to increase structural adaptation with increased villus height and crypt depth as well as to improve intestinal absorptive capacity with a reduction in PN use in patients with end jejunostomy (Table 1).[28,30–36]

Multiple factors can enhance intestinal adaptation of the small bowel including anatomic features, intraluminal nutrients, gastrointestinal (GI) secretions, and systemic factors.[20,37–41] The roles of growth factors, hormones, and, to a lesser extent, cytokines have been previously well reviewed and are summarized in Table 1.[42,43]

Impact of Intestinal Resection on the Gut Microbiota

The gut microbiota includes thousands of bacterial species heterogeneously distributed with lengthwise and cross-sectional variation along the GI tract. Host-microbiota cross-talk is essential for maintaining host homeostasis and health. However, in the context of disease, these interactions can become disrupted and result in a state of dysbiosis.

The impact of surgery on the host-microbiota balance acts at multiple levels. Factors such as the physiological stress of surgery, fasting, and antibiotic treatment all participate in the disruption of microbiota.[77] The surgical procedure itself also induces changes in the microbiome, likely resulting from exposing the bowel lumen to oxygen and temporarily interrupting local blood flow. Depending on the length and location of the bowel resected, the loss of intestine also may induce long-term changes such as a lower fecal pH, faster transit time, and/or altered pancreaticobiliary secretions. These changes modify the gut environment and can trigger the prevalence of certain gram-positive bacterial communities such as the facultative anaerobe *Lactobacillus*.[78]

Along the GI tract, the microbiota is composed mainly of *Firmicutes* and *Bacteroidetes* phyla. Experimental models have shown that intestinal resection reduces the diversity of the microbiota present in the remnant bowel and the colon.[79,80] After surgery, rodent and porcine models show a drastic decrease of *Bacteroidetes* phylum with an associated predominance of gram-positive *Firmicutes* bacteria in both the small bowel and colon. By using pyrosequencing and quantitative polymerase chain reaction, Devine et al[79] showed an established dominance of *Firmicutes*, mainly *Clostridia*, in the murine ICR model, whereas *Lactobacillus* dominated the *Firmicutes* phylum in the SBR model.[80] In contrast, another model of SBR failed to show any significant difference in the colonic bacterial diversity but rather identified an adverse local effect in the luminal content of the remnant ileum after resection.[81]

Metagenomics studies in SBS patients are rare and mainly based on noninvasive fecal sample analysis, which may not reflect the actual small-bowel physiology. Joly et al[23] were the pioneers in the study of both fecal and mucosa-associated microbiota in patients with SBS. Among 11 patients with a jejunocolonic anastomosis, both fecal and colonic biopsy samples were found to have a high prevalence of *Lactobacillus* with an associated depletion of *Clostridia* and *Bacteroidetes*. By using temperature gradient gel

Table 1. Intestinal Adaptation Factors and Hormones

	Human studies		Animal studies	
Limitations	Structural adaptation	Functional adaptation	Structural adaptation	Functional adaptation
GH[a]	No change[44]	Absorptive capacity improved (weaned off PN)[45–48] Multiple studies used glutamine + GH[44,48] Effects disappeared after GH was stopped[44,47,48]	Increased structural adaptation[49] Synergistic effect with glutamine[49]	Increased absorptive capacity[44]
EGF	No studies	Absorptive capacity improved[50] Increased tolerance to EN[50] No changes in intestinal permeability[50]	Increased structural adaptation[51–53] Timing of administration is crucial[52] Enterocyte EGF receptor is not needed for normal intestinal adaptation after resection[54,55] Synergistic effect with GLP-2[56]	Jejunal permeability decreased with combined EGF and GLP-2[56] No change in fat absorption or weight gain[56]
GLP-2 Teduglutide[b] (long-acting analog GLP-2)	Structural adaptation of small intestine[30–32] Decreased effect if patient had intact colon[31]	Absorptive capacity improved (weaned off PN)[28,31–33] GLP-2 levels correlate with residual small bowel length and nutrient absorption[34] Synergistic effect with GLP-1[33]	Increased structural adaptation[13,57–61] Timing of administration is crucial[62] Synergistic effect with enteral nutrition and EGF[56,58,63] Effects are region-specific (jejunum > ileum)[58,61]	Decreased intestinal permeability[57,61] Increased absorptive capacity[13] No difference in total fat absorption, messenger RNA expression of nutrient transporters[58] Effects are region-specific (jejunum > ileum)[58,61]
IGF-1	Decreased plasma levels in SBS patients[64] No other studies		Increased structural adaptation[65–67] May stimulate muscular lengthening[66] Enterocyte receptor is not needed for adaptation[55]	Increased absorptive capacity (weaned off PN)[12] Increased digestive enzymes[68]
IGF-2	No studies		May signal mesenchyme to induce villus growth[69] IGF-2 is not needed for adaptation[55]	No studies
TGF-α	No studies		Increased structural adaptation[70–72] Increases enterocyte proliferation[72] TGF-α not needed for adaptation[70]	No studies
Leptin	No change in plasma levels in SBS patients[64] No other studies		Increased structural adaptation[73,74] Increased enterocyte turnover[74]	Enhanced carbohydrate absorption[75] Altered absorptive enzymes in leptin-deficient obese mice after resection[76]
No standard definitions for structural or functional intestinal adaptation				
Intestinal adaptation does not necessarily equal a meaningful clinical outcome				

Table 1. Continued

Limitations	Human studies		Animal studies	
	Structural adaptation	Functional adaptation	Structural adaptation	Functional adaptation
Animal resection models differ from typical anatomy found in patients clinically				
Paucity of human clinical studies				
Human studies			Animal studies	
Low number of patients (small studies)			Variable resection models	
Hard to get tissue owing to invasive procedures			Short follow-up period	
Varying amounts of intestinal failure and PN dependence			Healthy animals	
Variable anatomy after resection				
Long and differing time intervals between last resection and enrolling in study				
Intestinal failure etiology and subsequent adaptive response in adults does not equal etiology and response in neonates				

EGF, epidermal growth factor; en, enteral nutrition; FDA, Food and Drug Administration; GH, growth hormone; IGF, insulin growth factor; TGF-α, transforming growth factor-α.
[a]Somatropin (Zorbtive, EMD Serono, Inc, Rockland, MA) and glutamine (NutreStore, Anderson Packaging, Inc, Rockford, IL) were approved by the FDA in 2003 and 2004 for clinical use in patients with SBS.
[b]Teduglutide (Hospira, Inc, McPherson, KS) was approved by the FDA in 2012 for clinical use in patients with SBS.[29]

electrophoresis and quantitative polymerase chain reaction, the investigators established a high predominance of *L mucosae* in both luminal content and mucosal biopsy of SBS patients compared with controls. Engstrand et al[82] showed similar microbiota alterations from fecal samples of children with SBS compared with their healthy siblings. Children with SBS on PN had reduced microbial diversity owing to the prevalence of *Enterobacteriaceae* compared with both PN-weaned SBS children and their healthy sibling. Another recent study also showed an increase in the relative facultative anaerobic *Proteobacteria* in children with IF who had prolonged PN and intestinal failure–associated liver disease.[83] These results point out the impact of prolonged PN on intestinal dysbiosis in pediatric SBS patients.

Dysbiosis also corresponds with a decrease in metabolic diversity, which may promote pathogenic infections or induce adverse metabolic effects for the host.[80] For instance, because of their ability to produce lactate and deconjugate bile acids, the abnormal dominance of *Lactobacillus* species observed in SBS patients can reduce vitamin absorption or cause D-lactic acidosis.[84,85] A recent report using a systems biology approach also showed that dysbiosis was correlated with an altered metabolome in a pig model of SBS-associated liver disease.[86] Alteration of the intestinal microbiota also can lead to insufficient breakdown of dietary components such as lipids and complex polysaccharides. This can result in a decrease in the production of short-chain fatty acids (SCFAs), malabsorption, reduced energy availability, and dysmotility.[87,88]

To date, it remains difficult to identify if dysbiosis is causative or a consequence of intestinal loss. It is important to consider that surgical intervention may not be the only factor altering the microbiota. Dysbiosis may also be due to an accumulative effect of a pre-existing disease state, as suggested in patients with inflammatory bowel disease (IBD), obesity, or cancer.[89,90] For instance, 1 recent report that examined the ileal mucosal microbiota of patients with Crohn's disease at the time of ICR found that dysbiosis was already present. They noted a high prevalence of facultative anaerobic and aerobic bacteria including *Streptococcus* and *Sphingomonas*.[91] Six months after surgery, ileocolonic biopsy specimens from these patients showed an increase in anaerobic bacteria such as *Clostridia* compared with their initial biopsy specimens. The investigators also identified 2 operational taxonomic units related to butyrate-producing bacteria that were predictive of Crohn's remission along with 2 other operational taxonomic units, *Eubacterium rangiferina* and *Proteus mirabilis*, which were predictors of Crohn's recurrence after ICR.[91]

Our current methodologies for studying the microbiome in both animal and human models are not without limitations. For instance, surgeries in animal studies are performed mainly on healthy animals, negating the effects of pre-existing conditions that are commonly found in patients. Most human data compare patient microbiota with healthy controls, although characterizing the microbiota of each patient before and after surgery would be more informative to identify predictive bacterial species and their associated surgical outcomes. In addition, the

majority of studies in the literature mainly focus on microbiome changes in luminal or fecal samples, but little is known about the changes occurring to adherent bacteria after intestinal resection. However, mucosal-associated bacteria appear important because Shogan et al[92] showed that the microbiota profile at the anastomosis is affected differently than the luminal contents after colectomy in rats. The investigators found an increase of *Enterococcus* and *Escherichia/Shigella* bacteria at the mucosal level, which may affect anastomotic healing.[92]

Impact of Gut Microbiota on Intestinal Adaptation Processes

By using different approaches, animal experiments support a role of microbiota in promoting intestinal adaptation. Several studies have reported that germ-free (GF) animals have a different baseline intestinal structure owing to the absence of microbial exposure. GF animals show smaller crypts, a lower proliferative index, but taller villi compared with conventional (CONV) animals.[93–95] Introducing microbes into GF mice stimulates an increase in proliferative index and crypt depth.[93] In a murine model of IBD, Speck et al[93] showed that microbiota-induced inflammation was associated with significantly deeper crypts, taller villi, and an increased enterocyte proliferation index in CONV interleukin (IL)10 null mice compared with GF IL10 null mice after ICR. Ileocecal resection of GF mice also supports the importance of microbiota in inducing crypt fission, an indirect marker of intestinal stem cell expansion, as well as in regulating genes that are related to bile acid metabolism.[93,96] Probiotics or mono-inoculation of bacteria such as *Lactobacillus* species or *Escherichia coli* has shown the specific role of each commensal colonizing organism on the regulation of enterocyte turnover rate.[94,97,98] However, SBR on GF rats failed to show a link between luminal bacteria and the induction of enterocyte life cycle; potentially indicating a regional effect of bowel loss in the regulation of microbiota-induced effects.[95] Antibiotic treatment also commonly is used in animal models to deplete intestinal microbiota. However, the conclusions on intestinal adaptation still are controversial because the effects from antibiotic-induced depletion models do not always mimic GF models.[95]

Although studies in human beings that focus on dysbiosis in SBS patients are emerging, detailed data on the role of microbiota on intestinal adaptation and metabolism require further investigation. The clinical use of probiotics to help promote intestinal adaptation in patients with SBS is emerging, but evidence of their benefit remains limited.[99] A reduction of pathogenic overgrowth and improved growth and nutrition status in SBS patients have been shown with probiotic and synbiotic treatment.[100] However, other case reports and clinical studies found no consistent positive or adverse effects of probiotics such as *Lactobacillus rhamnos* GG.[101] Further clinical studies that include the variability of probiotic treatment (ie, strain and live vs inactive) are needed to determine the safety and efficacy of probiotics in SBS patients.

A recent report showed that microbiota is a complex "reservoir of metabolic signals involved in postresection adaptation" in adult patients with jejunocolic anastomosis.[102] In this study, Gillard et al[102] categorized SBS patients into lactate accumulator or non–lactate accumulator groups according to the lactate content observed in feces. Accumulation of lactate was associated with an altered prevalence of lactate-producing bacteria including *Lactobacillus*, along with a reduced community of lactate-consuming bacteria such as *Clostridium leptum*.[23] This study showed that gut remodeling after surgery alters microbiota metabolism. In turn, this dysbiosis can induce metabolic changes contributing to clinical outcomes such as D-lactic acidosis (or D-encephalopathy; 1 patient of 9) in lactate accumulator patients.[102] The investigators also showed that the transfer of fecal material from the patient with D-lactic acidosis into GF rats did not induce a D-encephalopathy. However, the partial conservation of SBS microbiota induced higher levels of gut hormones including GLP-1 and ghrelin, also known to be induced in SBS patients.[102]

Microbiota and Host Immune System Cross-Talk During Intestinal Adaptation

The intestine represents the largest lymphoid organ of the body where gut-associated lymphoid tissues, including Peyer's patches and lymphoid follicles, interact with different cell types under a specialized regionalization.[103] The intestine is a primary site of interaction between the host immune system and microorganisms. The importance of intestinal commensal bacteria on immune system development and maturation has been reviewed previously.[104,105] Early studies on GF animals have identified developmental defects of their intestinal immune system as well as impaired activation. In addition to decreased IgA secretion, GF animals show a reduced number of intraepithelial lymphocytes.[106,107] Microbial colonization of GF animals results in an increase of immunoglobulin levels as well as re-organization of gut-associated lymphoid tissues and cell populations, indicating an intimate connection between gut homeostasis and intestinal bacteria.[108] Studies of intestinal resection of GF and CONV mice showed that bacteria-induced inflammation augments adaptation of the small intestine. A recent study using a model of SBS zebrafish also showed an up-regulation of genes involved in innate and adaptive immunity after resection.[109] These studies suggest that the synergistic effects between the immune system and microbiota can contribute to enhance intestinal adaptation.[93] In addition, rodent studies have shown that massive SBR results in a reduction of the lymphocyte subpopulation including CD4+ and CD8+ T cells, as well as B cells in blood, mesenteric lymph nodes, and spleen.[110,111] The decrease in systemic immunity also was associated with increased levels of the proinflammatory cytokine IL6 in the plasma at day 5 after surgery.[110]

The paucity of published data on the immune system status in SBS-associated microbial dysbiosis context represents a significant gap in the management of clinical outcomes. In adult SBS patients, an impairment of T-cell

proliferation correlated with the duration of home PN has been observed.[112] A recent report evaluating the immunologic status of 10 adult SBS patients on PN compared with 9 controls showed a higher frequency of regulatory T cell population as well as CD4+ and CD8+ T cells producing interferon-γ in the peripheral blood.[113] SBS patients also showed higher levels of IL6 in their plasma. However, the analysis was conducted on patients in different phases of disease because the time from bowel resection varied widely, and still receiving PN likely contributed to these impaired immunity observations. Additional studies are required to better understand the interactions between microbiota and the immune system after resection and their roles in intestinal adaptation.

Impact of Microbiota on Shaping the Enteric Nervous System During Intestinal Adaptation

Motility disorders within the context of SBS and IF often are related to poor gastric emptying and a shortened intestinal transit time secondary to loss of intestinal length and impaired peristalsis.[114] The enteric nervous system (ENS) is a complex autonomous network of neurons and glial cells organized as plexuses (myenteric and submucosal) distributed along the GI tract. It regulates the intestinal secretory and motor functions of the gut. Studies using mice deficient for Ret, a transmembrane tyrosine kinase receptor that is essential for ENS development, showed reduced intestinal contractility and altered enteric neurotransmitter release.[115] Intestinal resection in Ret+/- mice have shown enhanced intestinal adaptation features and suggests that a neuronal mechanism may dampen intestinal adaptation.[116] However, only limited data have been published confirming the precise impact of intestinal resection on the ENS and its associated functions. A recent report showed that rats who underwent SBR showed an increased proportion of myenteric nitrergic neurons that correlated with a thicker muscularis propria and higher crypt cell proliferation in both the jejunum and colon.[117] This study suggested that modulation of the neuronal population potentially could be a compensatory mechanism that reduces motility and improves nutrient/fluid absorption.[117]

The role of the microbiota on ENS organization and its functions has been highlighted by the reduced number of enteric neurons and associated gut dysmotility in GF mice.[118] Knocking out Toll-like receptor 4, a microbial ligand receptor on intestinal epithelial cells, induced intestinal dysmotility and a reduced number of nitrergic inhibitory neurons comparable with the physiology seen in GF or antibiotic-treated mice.[118] Experimental studies have indicated that microbiota-driven interactions between the innate immune system and the ENS control gut motility and GI tract functions.[119,120] Although diseases such as IBS with dysmotility symptoms are linked to impaired luminal microbial metabolites and mucosal immune cells, the tripartite interactions after intestinal resection have not been elucidated in SBS patients.

Modulation of Host Intestinal Adaptation by Microbiota and Microbial-Derived Metabolites

Microbiota plays a key role in the modulation of host nutrient/energy salvage, the development of the GI epithelium, the development and activation of the mucosal and systemic immune system, as well as the modulation of ENS. Commensal bacteria have the ability to sense and modulate their local and systemic environment through direct and indirect pathways (Figure 1). For example, gram-positive segmented filamentous bacteria (SFB) are known to adhere closely to the intestinal epithelium and can coordinate postnatal maturation of gut immune functions.[121] By using GF mice, studies have shown that the colonization of SFB induced the production of antimicrobial peptides and serum amyloid A in the terminal ileum, where serum amyloid A then acted on dendritic cells to restore T-helper 17 cell differentiation.[121,122] Another commensal bacteria, *Akkermansia muciniphila*, has been shown to be involved in wound healing by stimulating enterocyte proliferation and migration.[123] Although the mechanisms are not completely defined, several studies have highlighted epithelial Toll-like receptor and bacterial glycans as key mediators.[124–126] Therefore, identifying the mucosa-attached bacteria may help to understand some of the host-microbiota interactions that likely are involved in the intestinal adaptation process.

It is estimated that more than 50% of fecal and urinary metabolites are derived from the gut microbiome.[127] Among the microbial metabolites participating in the intestinal adaptation, SCFAs remain the most studied and have been shown to modulate energy salvage, intestinal barrier functions, and the immune response. In the colon, multiple commensal bacteria are able to produce SCFAs including acetate, propionate, and butyrate by anaerobic fermentation of nondigestible dietary fibers and resistant carbohydrates. In a SBS animal model, the supplementation with SCFA or dietary pectin fiber improved adaptation of both small intestine and colon after resection.[128,129] Intravenous or intracecal supplementation with SCFAs also has been shown to recover total parenteral nutrition-induced mucosal atrophy and enhance structural markers of intestinal adaptation.[130,131] Specifically, butyrate appears to be the main SCFA responsible for the increased structural and functional changes seen in early intestinal adaptation processes, likely by modulating gene expression and transport activities.[132,133] Although the effect of dietary fibers or SCFAs on intestinal adaptation appears promising in animal studies, it has not been clearly defined in human beings.[134,135]

In animal IBD models, SCFAs also have been suggested to display a variety of anti-inflammatory properties.[136,137] Butyrate serves as a specific endogenous agonist for GPR109A, expressed in colonic epithelium and immune cells. Activation of GPR109A as well as inhibition of histone deacetylase by butyrate leads to a decrease of proinflammatory cytokine expression in colonic macrophages and dendritic cells.[138,139]

A link between microbiota and gut motility has emerged because GF mice show impaired ENS organization along

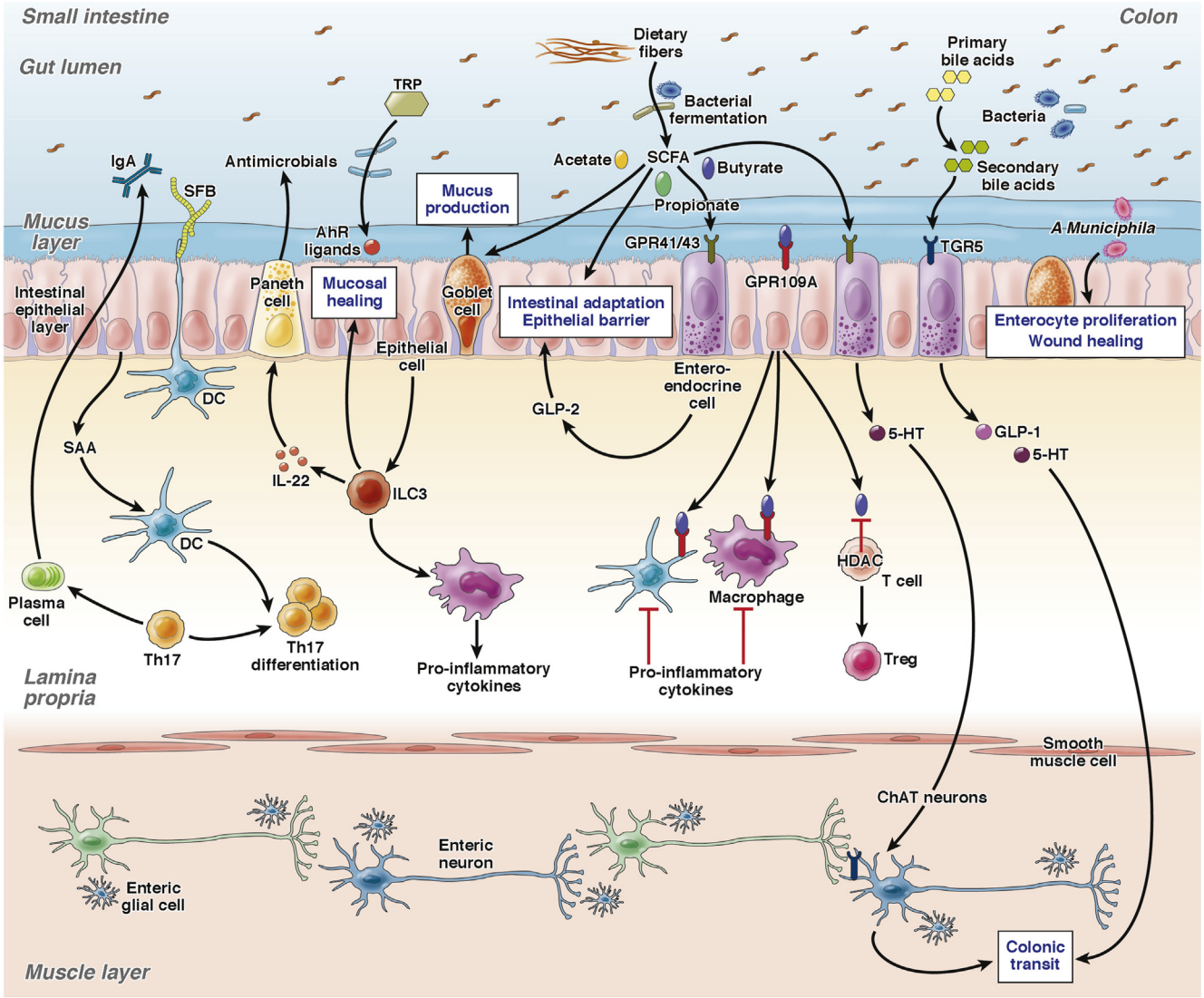

Figure 1. Microbiota and microbiota-derived metabolites effects on intestinal layers. Bacteria have the ability to modulate local and systemic environments through direct or indirect pathways. For example, in the small intestine (ileum), commensal SFB bacteria can adhere directly to the epithelial cell and trigger the immune responses. In the colon, *A municiphila* can reach the epithelial cells by degrading the mucus layers, and promote enterocyte proliferation and wound healing. Indirectly, microbial AhR ligands are able to induce mucosal healing and antimicrobial production through ILC3-mediated IL22 secretion. The microbial-derived SCFA can promote intestinal adaptation, modulate immune responses, and alter gut motility through the activation of G-protein–coupled receptors (eg, GPR41, GPR43, and the butyrate-specific GPR109A) or HDAC inhibition. Activation of GPR41/43 or TGR5 receptor induce the release of 5-HT and GLP-1 from enteroendocrine cells and alters colonic transit. Bile acids also can modulate gut motility by activating the TGR5 receptor on enteric neurons. AhR, aryl hydrocarbon receptor; ChAT, choline acetyltransferase; DC, dendritic cell; 5-HT, serotonin; GLP-1, glucagon-like peptide 1; HDAC, histone deacytalse; ILC3, innate lymphoid cell 3; SAA, serum amyloid A; Th, T-helper cell; Treg, regulatory T cell; TRP, tryptophan.

with defects in gut motility.[118] Recently, the transplantation of dysbiotic fecal microbiota from patients with constipation into an antibiotic-depleted mouse model was found to induce slower peristalsis and abnormal defecation in the mice.[140] This alteration of the GI transit time was associated with an increase in serotonin-receptor expression.[140] Among the different microbial products, SCFAs have been specifically shown to modulate gut motility through the production of serotonin by epithelial enterochromaffin cells.[141,142] The supplementation with dietary starch has shown that SCFAs augments the proportion of cholinergic neurons in the colon, likely through histone deacetylase inhibition, which results in increased colonic transit time.[143] Although the differential effects of SCFAs on intestinal adaptation have been described, their impacts on immune responses and gut motility in SBS patients remain poorly understood.

Other microbial-derived metabolites have been described for their roles in the regulation of intestinal homeostasis and immunomodulation including the de novo–produced adenosine triphosphate and vitamins.[144,145] Specific commensal bacteria such as *Lactobacillus* are able

to metabolize tryptophan, a dietary amino acid, into an indole-3-aldehyde, which then binds to the aryl hydrocarbon receptor. Activation of aryl hydrocarbon receptor induces the secretion of IL22 by innate lymphoid cells, which affects both mucosal healing and antimicrobial peptide repertoire.[146]

Microbial molecules also can be produced from host-derived metabolites. Gut commensal bacteria, including *Clostridia* species, have the capacity to convert primary bile acids into secondary bile acids. These secondary bile acids then can bind to the G-protein–coupled receptor Takeda-G-protein-receptor 5 (TGR5) and regulate epithelial cell integrity and immune responses.[147] The role of TGR5-mediated bile acid alterations on colonic motility has been shown using TGR5-deficient mice, which showed delayed GI transit time and constipation.[148] Although some IF patients experience bile acid malabsorption, intestinal failure-associated liver disease, and/or alteration of transit time after resection, changes in the bile acid–gut microbiota cross-talk during intestinal adaptation have not been fully explored. However, the gut–liver axis could represent a potential target for therapeutic interventions.

New technology and approaches are emerging to better understand the alteration of microbiota and the subsequent changes in microbial metabolism in a health/disease context. High-throughput 16S ribosomal RNA sequencing has allowed profiling of complex microbial communities for a wide spectrum of intestinal diseases. The recent shotgun DNA approach represents a promising method in determining microbial composition and metabolism by allowing for the possibility to discover new pathways and targets. Metabolomic approaches using mass spectrometry and nuclear magnetic resonance spectrometry are useful technologies to unravel specific microbial metabolites or novel clinical biomarkers. There is a need to understand not only the alterations in microbiota composition but also the functional impairments of the microbiome. Therefore, experimental and clinical research integrating both metagenomic and metabolomics will be essential to better understand the complex metabolic interactions in SBS patients after intestinal resection and potentially identify novel biomarkers or therapies.

Conclusions

Intestinal adaptation involves a combination of morphologic and microbiological processes that compensate for the loss of absorptive tissue. The morphologic and functional changes occurring at the epithelial layer after resection as well as the mediators involved have been well described. However, the underlying mechanisms involved in intestinal adaptation are still not clearly defined. The emergence of high-throughput technology has allowed identification of microbial imbalance after intestinal resection in SBS patients, suggesting a key role of this forgotten organ in intestinal adaptation. Intestinal resection affects the microbial ecosystem, which in turn modulates GI homeostasis and function. Further studies investigating the importance of molecular interactions between microbiota, the intestinal barrier, the immune system, and the ENS are needed to identify pathways or biomarkers that enhance the adaptive response of IF patients. Integrative studies using systems biology approaches will provide the opportunities to better understand the morphologic and functional changes occurring after intestinal resection and potentially lead to the development of personalized nutritional and pharmacologic therapies.

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The authors disclose no conflicts.

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