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REVIEW

Host-Gut Microbiota Cross-Talk 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;■:■–■; 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), ileocecal resection (jejunocolic anastomosis), and extensive

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, _____.

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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 human beings.[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* were dominated the *Firmicutes* phylum in the SBR model.[80] Q10 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