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REVIEW

The Pathogenesis of Resection-Associated Intestinal Adaptation

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SUMMARY

Intestinal adaptation is an important compensatory response to the loss of intestinal length. The process is complex, but a more thorough understanding will pave the way for innovative therapies intended to amplify this important response.

After massive small-bowel resection, the remnant bowel compensates by a process termed *adaptation*. Adaptation is characterized by villus elongation and crypt deepening, which increases the capacity for absorption and digestion per unit length. The mechanisms/mediators of this important response are multiple. The purpose of this review is to highlight the major basic contributions in elucidating a more comprehensive understanding of this process. *(Cell Mol Gastroenterol Hepatol 2016;2:429–438; http://dx.doi.org/10.1016/j.jcmgh.2016.05.001)*

Keywords: Adaptation; Epithelium; Angiogenesis; Absorption; Villus; Apoptosis; Proliferation; Growth Factors.

Intestinal adaptation is an important response to massive small-bowel resection (SBR) and represents a mitogenic signal to the intestine culminating in a compensatory expansion in mucosal digestive and absorptive surface area per unit length. Clinically, adaptation is heralded by the gradual tolerance of enteral nutrition that could not be tolerated at earlier time points. A complete adaptation response allows for tolerance of all nutrition to be absorbed from the gut, without the need for supplemental parenteral feeding. The expression of several immediate–early genes within the remnant bowel has been recorded to be increased within hours of intestinal resection.[1,2] Similarly, in a murine model of SBR, alterations in wet weight as well as DNA and protein content in the remnant bowel are increased as soon as 24 hours, but before the initiation of enteral feeding.[3]

Adaptation is characterized structurally by taller villi and deeper crypts, as well as enhanced rates of enterocyte proliferation and apoptosis. Although these features are a renowned characteristic of adaptation in animal models of massive SBR, similar structural alterations have not been described consistently in human beings. In one study, the intestine was evaluated in a uniform population of infants with neonatal necrotizing enterocolitis who required bowel resection.[4] Comparing villus height and crypt depth at the normal margin of tissue at the time of resection with the time of ostomy takedown showed significant increases in both parameters. In another report, a 70%–75% increase in villus height was documented in the small intestines of 13 patients at 2 years after jejuno-ileal bypass.[5] In addition, significant increases in crypt depth and cell number/crypt in the colons of 12 patients with jejunocolonic anastomosis compared with healthy controls was identified at a mean of 9.8 years after resection.[6] Unfortunately, the histologic status of the small intestine was not evaluated in that study. In contrast, other studies have failed to show changes in rates of enterocyte proliferation, crypt depth, or villus height in the small intestine of patients with short-gut syndrome compared with controls.[7–9] All of the earlier-mentioned human studies comprised small numbers of patients, variable lengths of resected intestine, assorted amounts of enteral feeding, and analysis at single time points after SBR. Despite these limitations, animal models for studying resection-induced adaptation continue to provide important mechanistic insights.

Mechanisms of Adaptation

The mechanisms and mediators of intestinal adaptation are multifactorial and include intraluminal nutrients, gastrointestinal secretions, as well as hormones[10,11] (Figure 1). In general, most research has focused on various growth factors and how they affect rates of enterocyte proliferation as the primary driver of resection-induced mucosal growth. It should be considered, however, that enhanced rates of enterocyte proliferation actually may occur secondary to growth of subepithelial structures.

Intraluminal Nutrients

Enteral nutrients appear to stimulate intestinal adaptation via several mechanisms including direct contact with epithelial cells as well as stimulated secretion of trophic gastrointestinal hormones and pancreaticobiliary secretions.[12] The contributions of luminal nutrients to the adaptive response of the intestine is underscored by the

Abbreviations used in this paper: **EGF, epidermal growth factor; GH, growth hormone; GLP-2, glucagon-like peptide-2; IGF-1, insulin-like growth factor-1; LA, lactate-accumulator; PN, parenteral nutrition; Rb, retinoblastoma protein; SBBO, small-bowel bacterial overgrowth; SBR, small-bowel resection.**

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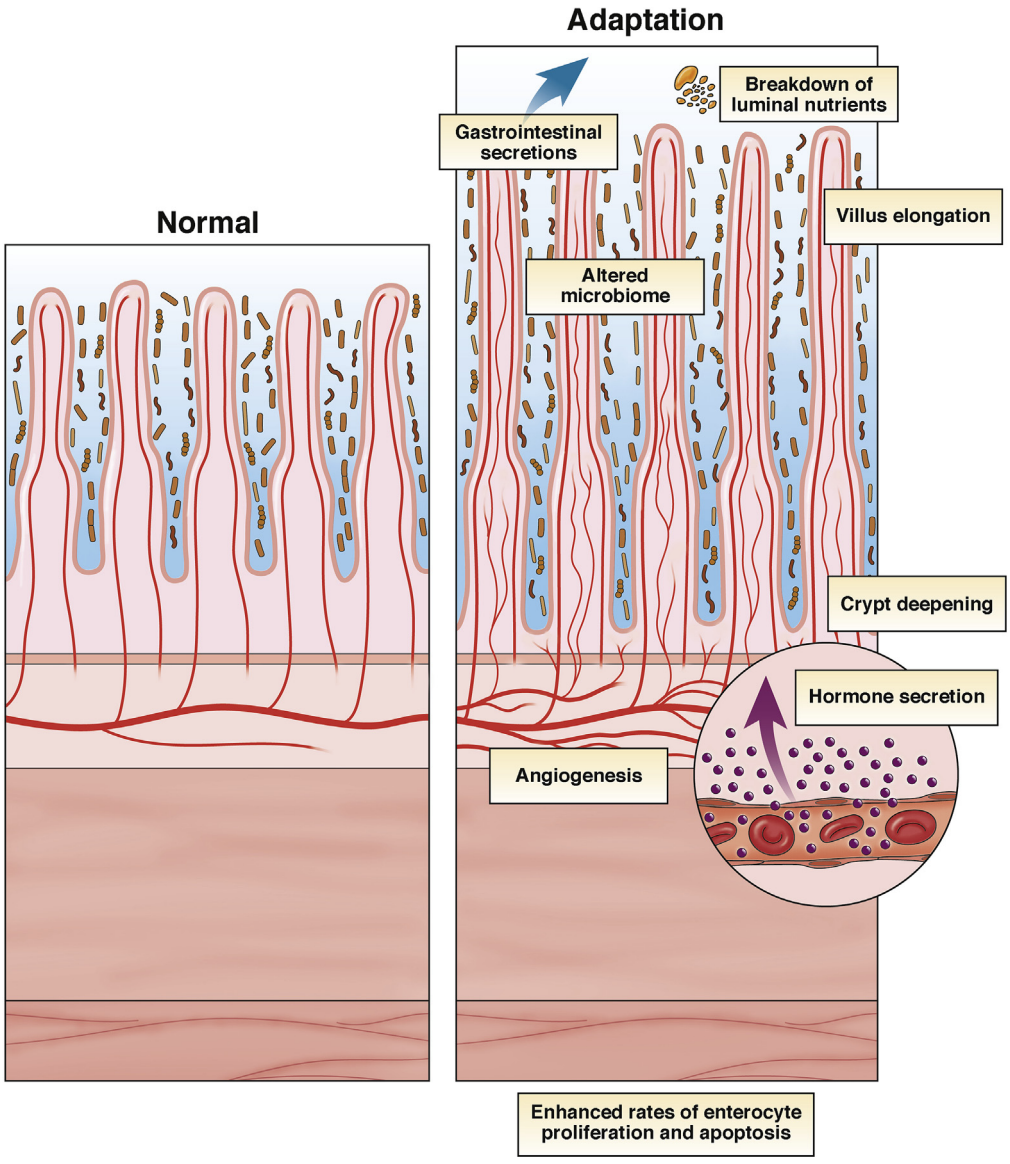

Figure 1. Factors that play a role in resection-induced intestinal adaptation.

observations that gut mucosal atrophy is associated with starvation and is reversed by refeeding. Furthermore, surgical transposition of a segment of the ileum into the more proximal intestinal stream results in structural and functional "jejunalization" of the transposed ileum.[13,14] Not only is the presence of luminal nutrition important for adaptation, but so is the nutritional composition. Luminal administration of non-nutrient substrates has little effect on adaptation. More complex nutrients requiring more metabolic energy to absorb and digest have been suggested to induce the greatest adaptation response, presumably by virtue of an increased functional workload of the enterocyte. Enteral fats appear to be the most trophic of the macronutrients in inducing adaptation.[15] More specifically, longer-chain and more polyunsaturated fats as present in fish oil may provide an even greater adaptive stimulus.[16–18]

Gastrointestinal Secretions

Multiple experimental observations have contributed to the notion that endogenous gastrointestinal secretions are important for adaptation. Experimental models in which the ampulla of Vater is transposed surgically to areas more distal in the gastrointestinal tract induces villus hyperplasia beyond the transposed segment.[19,20] Bile alone has been shown to stimulate intestinal RNA and DNA content when delivered directly to the mid–small bowel, but the effect seems to be more profound when combined with pancreatic secretions.[20] In other studies, pancreatic secretions seem to be more trophic to the intestinal mucosa when compared with bile.[20] Further evidence that pancreaticobiliary secretions are important for postresection adaptation is the observation that somatostatin, an agent that dramatically diminishes the output of endogenous gastrointestinal