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Mechanisms of Intestinal Adaptation

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Abstract

Following loss of functional small bowel surface area due to surgical resection for therapy of Crohn's disease, ischemia, trauma or other disorders, the remnant gut undergoes a morphometric and functional compensatory adaptive response which has been best characterized in preclinical models. Increased crypt cell proliferation results in increased villus height, crypt depth and villus hyperplasia, accompanied by increased nutrient, fluid and electrolyte absorption. Clinical observations suggest that functional adaptation occurs in humans. In the immediate postoperative period, patients with substantial small bowel resection have massive fluid and electrolyte loss with reduced nutrient absorption. For many patients, the adaptive response permits partial or complete weaning from parenteral nutrition (PN), within two years following resection. However, others have life-long PN dependence. An understanding of the molecular mechanisms that regulate the gut adaptive response is critical for developing novel therapies for short bowel syndrome. Herein we present a summary of key studies that seek to elucidate the mechanisms that regulate post-resection adaptation, focusing on stem and crypt cell proliferation, epithelial differentiation, apoptosis, enterocyte function and the role of growth factors and the enteric nervous system.

Keywords

short bowel syndrome; intestinal adaptation; regeneration; crypt cell proliferation; epithelial cell differentiation

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Introduction

Following loss of functional small bowel surface area due to surgical resection for therapy of Crohn's disease, ischemia, trauma or other disorders, the remnant gut undergoes a morphometric and functional compensatory adaptive response. In experimental rodent surgical models of short bowel syndrome in which 50-75% of the small bowel is resected, morphometric adaptation is characterized by increased crypt cell proliferation resulting in increased villus height, crypt depth and villus hyperplasia (Fig. 1; [1, 2]). Morphometric adaptation is also accompanied by a functional adaptive response, with increased nutrient, fluid and electrolyte absorption.

Studies of the gut adaptive response have focused on understanding the molecular mechanisms that regulate post-resection changes in stem and crypt cell proliferation, enterocyte migration, apoptosis and enterocyte function (Fig. 2). Although the morphometric changes following resection in humans have not been well-described due to the inaccessibility of tissue for biopsy, clinical observations indicate that functional adaptation occurs in humans [1, 3, 4]. In the immediate postoperative period, patients with substantial small bowel resection have massive fluid and electrolyte loss with reduced nutrient absorption. However, in the majority of patients with at least 100 cm of small bowel or 50 cm of small bowel with residual colon, the adaptive response permits partial or complete weaning from parenteral nutrition (PN) within two years following resection. However, patients with residual small bowel length <100 cm or <50 cm with residual colon generally exhibit life-long PN dependence [4, 5].

An understanding of the molecular mechanisms that regulate the adaptive response is essential for developing novel therapies. For example, preclinical studies identified glucagon-like peptide 2 as a potent epithelial trophic factor released from enteroendocrine cells, for which mRNA and protein expression are upregulated following resection [6]. These studies led to successful clinical trials and the release of teduglutide, a glucagon-like peptide 2 analog, which is the first new therapeutic agent for SBS since growth hormone was approved by the FDA) and which is specific for short bowel syndrome [7-10].

A. Investigational models of the adaptive response

The rodent intestinal resection model is the best studied. Rat models were the first to be developed; rats can tolerate 75% bowel resection and have a robust, long lasting adaptive response [1]. Development of the resection model in the mouse [11, 12] has permitted the use of a wide variety of genetically modified mice (transgenic, global and selective intestinal knock out) to precisely dissect the contribution of growth factor regulated pathways to the adaptive response. Mouse models include a 50% mid-resection [11] and an ileocecal resection (ICR) procedure [13]. More recently, porcine/piglet models have been developed which may more closely mimic the human response ([14]). Finally new short bowel syndrome models in simpler organisms such as zebrafish [15] may facilitate more rapid identification of novel mediators of adaptation.

B. Morphometric response

i. Early stem cell responses—In mice and rats, resection of 50-75% respectively of the small bowel, or resection of the ileum and cecum in mice results in a well-characterized adaptive response in the residual epithelium. The stem cell response following ileocecal resection is temporally regulated, with a rapid expansion of putative stem cells that peaks at 48-72 h post resection, persists up to 5-7 days postoperatively and then returns to baseline after six weeks ([13]. These CD45- “side population” cells were not further characterized for expression of stem cell marker proteins such as Lgr5, Sox9, Bmi1, mTert, Hopx, Lrig1 and Olfm4 which mark stem cells in the +1 vs. +4 positions in the crypt (Figs. 2 and 3 [16]); thus the precise identity of the expanded stem cell population remains unknown.

The early adaptive crypt proliferative cell response is regulated by IFRD1 (Tis7) a transcriptional co-regulator that interacts with the mSin3B complex and histone deacetylases to alter transcription of target genes [17]. Tis7/IFRD1 plays a role in injury-repair in multiple tissues ([18]). Globally deleted *Tis7*^{-/-} mice had reduced crypt cell proliferation at 72 hours post 50% mid small bowel resection [19]. Potential IFRD1 targets include *cyclin D1* and hedgehog signaling pathway genes including *Gli1*, *Hhip* and *Gli2*; expression of these genes was inhibited in *Tis7*^{-/-} compared to normal mice post resection [19]. Tis7/IFRD1 also affects functional and metabolic adaptation (see “Functional adaptive response, below).

Intestinal dilation of the adaptive residual gut is a well-recognized consequence of massive resection in humans as well as in mice following resection [13]. In mice this process appears to be driven by increased crypt fission which was significantly increased compared to sham operated mice. Increased mucosal surface area at later times post resection was primarily due a persistent increase in the numbers of crypts per unit area [13].

ii. Temporal regulation of increases in crypt depth and villus height—In the ICR model increased crypt depth and villus height was sustained up to 6 weeks but returned to normal by 14-16 weeks [13]. Similarly in a 50% mid small bowel resection model in mice, increases in crypt depth and villus height occur early post resection [11] and persist up to 6 weeks postop. Similar temporal dynamics have been observed in piglet models of short bowel syndrome . Similar information about the temporal regulation of the morphometric adaptive response is unavailable for humans.

iii. Epithelial cell response—An early increase in a subset of gut epithelial secretory cells, including goblet [20] and Paneth cells [21] occurs coincident with expansion of the putative stem cell population. Goblet cell numbers on the villus and Paneth cell numbers in the crypt were noted to increase as early as 12 hours after resection; this expanded population persists up to 28 days postop. In contrast, the number of absorptive enterocytes per villus begins to increase later, at 36 h post resection, yet the percentage of enterocytes per villus does not increase at any time post-resection [21]. Given the functional importance of the absorptive enterocyte, strategies to increase the percentage of absorptive enterocytes per villus, and thereby increase critical nutrient absorptive enzyme and transporter levels per villus may provide a therapeutic strategy to enhance the “innate” adaptive process. Studies

of the early adaptive response in humans in the first month post-resection are critical for determining the clinical relevance of these observations.

iv. Apoptosis—Regulation of the balance between crypt cell proliferation and programmed cell death is required for maintenance of the normal crypt-villus axis. Damaged stem cells are eliminated by apoptosis and are a major mechanism by which the crypt maintains normal stem cell numbers. Studies in mice ([12, 22, 23] and rats [24] have shown that crypt apoptosis increases early post resection; this increase persists at least up to one week postop. The expression of pro-apoptotic genes also increases early after resection [12]. Treatment of rats with an ACE inhibitor reduced resection-induced apoptosis and resulted in increased villus heights although no change in crypt depth or crypt cell proliferation [24]. Vitamin A deficiency inhibited adaptation, resulting in reduced crypt cell proliferation and increased apoptosis [25], and chronic retinoic acid administration enhanced the morphometric adaptive response by inhibiting apoptosis and increasing crypt cell proliferation and enterocyte migration [26]. Bax is one of several highly expressed pro-apoptotic proteins that play an important role in regulating intestinal crypt apoptosis. *Bax*^{-/-} mice demonstrated an inhibition of resection-induced increases in apoptosis and also an increase in villus height post resection compared to *Bax*^{+/+} wild type mice [12]. The increase in villus height reflected both an increase in cell number (hyperplasia) as well as cell size (hypertrophy). *Bax*^{-/-} mice also had reduced expression of Fas, caspase 8, FADD, FAF, TRAIL and TRADD mRNA, suggesting a link between Bax and death domain receptor mediated apoptotic pathways belonging to the TNFR-FAS extrinsic signaling pathways. However, in these studies inhibition of apoptosis was associated with an inhibition of the normal increase in crypt cell proliferation that occurs following resection. Thus therapies designed to alter apoptosis will likely have limited utility due to compensatory (inhibitory) effects on crypt proliferative morphometric responses..

v. Molecular mechanisms regulating stem cell expansion and increased crypt cell proliferation—The maintenance of crypt stem cell populations and regulation of epithelial cell differentiation are in largely dependent on Wnt, Notch and Bmp signaling pathways. Hedgehog signaling also plays a role in regulating crypt cell proliferation.

v.1. Wnt signaling: Wnt signaling is highly active in the normal crypt, to maintain rapidly proliferating Lgr5+ stem cells and to promote Paneth cell identity. In the absence of Wnt signals, cytoplasmic β -catenin is targeted for degradation by a destruction complex that includes Apc and Axins. Upon binding of Wnt proteins or the Wnt agonist R-spondin to receptors including frizzled family members, Lrp5/6 and Lgr4/5, the destruction complex is inhibited and β -catenin accumulates in the cytoplasm, enters the nucleus and initiates a transcriptional cascade. Wnt signaling activity progressively declines as cells exit the crypt and enter the villus, permitting epithelial differentiation. Wnt signaling target genes include *Lgr4/5*, *c Myc*, *cyclin-D1*, *Sox9* and *Frizzled-5*. Wnt ligands are produced in stromal and Paneth cells.

The role of Wnt signaling in adaptation has been explored using the *Apc*^{min/+} mouse model of familial adenomatous polyposis coli [27]. Mutations in the *Apc* gene result in familial adenomatous polyposis coli, a genetic colon cancer family syndrome. These mice have

basally activated Wnt signaling and develop intestinal adenomas which are similar to human adenomatous polyps but are located predominantly in the small bowel. Massive bowel resection in these mice resulted in increased villus heights and increased crypt cell proliferation compared to wild type (WT) mice at early times (72 h) post resection [27]. Also, both normal and *Apc^{min/+}* intestine exhibited increased β -catenin and cyclin D1 expression post resection compared to sham operated mice; β -catenin and cyclin D1 expression was further upregulated in *Apc^{min/+}* gut compared to normal WT intestine.

The temporal regulation of Wnt signaling activity post resection is complex. Global gene expression analyses of rat intestine following 75% resection revealed a return to baseline for a subset of Wnt target genes [28] yet other studies have shown that expression of Wnt ligands (Wnts 5a, 5b and 7b) increased compared to sham resected gut at two weeks post resection, associated with a sustained increase in crypt cell proliferation [26].

Conclusions are limited regarding the requirement for active Wnt signaling in the adaptive response because experiments in which Wnt signaling is selectively inhibited (for example, using gut specific, inducible Cre-lox technology) have not yet been performed. However Wnt signaling is likely to play a crucial role in the gut adaptive response given its importance in stem cell maintenance and proliferation.

v.2. Notch signaling: Notch signaling has complex affects in the intestinal crypt. Notch acts in concert with the Wnt signaling pathway to regulate crypt cell proliferation, but also affects cell fate determination [29]. Active Notch signaling induces an absorptive rather than a secretory epithelial cell fate. Chen et al. [30] showed a marked increase in expression of several components of this pathway following resection in a rat model, with robust enhanced crypt expression of NICD1, Jaggel1 and Hes1 mRNA and protein. However the specific role for Notch remains unclear as studies using Notch inhibitors or mouse models in which Notch is activated or suppressed have not yet been performed.

v.3. Hedgehog and Bone morphogenetic protein signaling: Hedgehog (Hh) signaling is active in stomach, small bowel and colon but appears to have region-specific functions. Unlike in other tissues in which activated Hh signaling is associated with carcinogenesis, in the small bowel and colon Hh signaling suppresses crypt cell proliferation [31, 32]. Of the three Hh proteins expressed in the GI tract, Indian Hh is most abundant in the small bowel [22] and is produced by enterocytes, which signal through the mesenchyme to the crypt. Conditional activation of Hh signaling in adult intestine leads to reduced Wnt signaling and inhibited crypt cell proliferation; loss of Hh signaling activates Wnt and increases epithelial proliferation [33-35]. Following 50% small intestinal resection in mice, there is a rapid and sustained inhibition of expression of Hh signaling pathway components, up to two weeks post resection, suggesting that reduction in Hh signaling is required for the gut adaptive response to occur [22]. Further reduction in Hh signaling by administration of an anti-Hh antibody resulted in increased enterocyte migration and apoptosis following resection but did not augment the morphometric response.

v.4 Bone morphogenetic protein (Bmps): Bmps are produced in both epithelial and mesenchymal cells in the gut and signal via receptors that are expressed on the villus and

crypt epithelium (BmpRI and BmpRII). Bmps and their inhibitors have direct effects on stem cell signaling and are produced by stromal cells that surround the crypts ([36, 37]. Bmp signaling suppresses stem and crypt cell proliferation in the adult gut. Transgenic intestinal overexpression of Bmp inhibitors such as noggin or deletion of the Bmpr1a receptor results in polyposis in adult mice [38]. Also, noggin is a key component of specialized media that supports survival and growth of intestinal stem cell cultures *in vitro* [39], suggesting that Bmp inhibition is required for stem cell maintenance and epithelial proliferation. Bmps are transcriptional targets of Hh and Wnt signaling (e.g. Bmp4). Studies that have examined Bmp expression in the adaptive gut have reported conflicting data. Following resection in mice, Bmp expression is inhibited (including Bmp1, 2 and 4) compared to unresected gut at two weeks postop [22]. In contrast, in rats increased BMP expression was observed at two weeks post resection [40]. Neither study directly examined Bmp signaling by using Bmp inhibitors or transgenic expression models; thus the precise role of Bmps in the gut adaptive response remains to be clarified.

C. Growth factors and gut adaptation

i. Glucagon-like peptide 2—Glucagon-like peptide 2 (GLP-2) is a 33 amino acid peptide that is derived from post-translational processing of proglucagon in L-cells of the ileum and colon. GLP2 receptors are present on gut enteroendocrine cells. GLP2 receptors are also found in the hypothalamus, brain stem and lung [41]. Others have shown that GLP2 receptors are expressed on enteric neurons, leading to the postulation that GLP2 acts indirectly on the crypt via enteric neuronal signaling [42], as tetrodotoxin blocks GLP2 induced c Fos activation in crypt cells. Following mid jejunioileal resection, rats exhibit increased plasma GLP-2 levels and increased proglucagon mRNA levels, which correlated with resection induced hyperplasia [6, 43]. Exogenously administered GLP-2 has a marked trophic effect on the intestinal mucosa, with increased crypt cell proliferation resulting in increased villus height and enhanced mucosal surface area [44]. GLP2 has trophic effects in normal gut as well as in adaptive gut post-resection, and is the basis for teduglutide, a GLP-2 analogue that is the first new therapy for short bowel patients since growth hormone was approved by the FDA [45, 46]. It is postulated that the absence of circulating GLP2 in patients with ileal and colonic resections contributes to the poorer outcome and greater difficulty in weaning patients with jejunostomies from TPN.

The critical role for GLP2 in nutrient-regulated crypt cell proliferative responses is well illustrated by studies in *GLP2R*^{-/-} mice, which exhibit a complete loss of the robust crypt cell proliferative response that occurs in refeeding following fasting [47]. Also, immunoneutralization of GLP2 prevents adaptive-induced intestinal hyperplasia in diabetic rats [48]. However, the specific role for GLP2 in post-resection adaptation has not yet been elucidated, as experiments in which GLP2 antagonists are administered post resection, or in which resections are performed in *GLP2R*^{-/-} mice, have not yet been published.

ii. Epidermal Growth Factor (EGF)—Significant concentrations of EGF are produced in saliva and human breast milk. EGF has marked trophic effects on the intestinal mucosa and thus may be an excellent target for a therapeutic agent, although unlike GLP2, EGF receptors are present throughout the body. Administration of EGF luminally enhanced the

structural adaptive response when administered during the first week postop [49]. EGF also increased glucose uptake post resection in a rabbit model, in the absence of morphogenic effects [50], and increased maltase peptidase and glutamine uptake capacity [51]. A critical role for EGF in the post-resective adaptive response was shown in studies using EGF knock out mice with the waved 2 mutation. The adaptive response is completely blocked in these mice [52]. However, the mechanism by which EGF results in an increased adaptive response remains unclear, as subsequent analyses have shown that the gut-epithelial specific knockout of the EGF receptor does not block the adaptive response [53].

iii. Insulin-like growth factors 1 and 2—Multiple studies in mice and pigs have shown that IGF-1 has trophic effects on the intestinal mucosa, and enhances the gut proliferative adaptive response post resection [54, 55]. IGF1 has been postulated to mediate the effects of GLP2 on the crypt [56]. In mice in which the retinoblastoma protein (Rb) was deleted, a marked increase in villus height was observed and IGF2 expression was increased in enterocytes. The villus height increase was blocked in Rb null mice crossed into an IGF2 deficient background and thus was thought to be mediating the effects of Rb deletion [57]. However, examination of mice with intestine specific deletion of IGF1R and global knockout of IGF2 revealed an intact adaptive response at 1 week post 50% small bowel resection [58]; thus neither the epithelial IGF1 receptor nor IGF2 appear to be critical for gut adaptation. In addition, mice with intestine-specific EGFR/IGF1R double knockout also exhibit a normal postoperative adaptive morphometric response [59], suggesting that stromal/mesenchymal receptors for EGF and IGF1 indirectly mediate the crypt proliferative and morphometric response.

iv. Growth hormone—(see Chapter Tappenden)

D. Enteric nervous system regulation

The enteric nervous system (ENS) has been implicated in controlling crypt cell proliferative responses, potentially via GLP2. As mentioned above, the GLP2 receptor is expressed in enteric neurons and myofibroblasts as well as enteroendocrine cells. Destruction of enteric nerves blocks GLP2 induced c-Fos activation in crypt cells [42]. The role of the enteric nervous system in regulating the gut adaptive response has been examined using *Ret*^{+/-} mice, which are heterozygous for the *Ret* gene [60]. Ret is the receptor for glial cell line-derived neurotrophic factors (GDNFs) which are required for normal enteric ganglion formation in stomach, small bowel, and colon [61, 62]. *Ret*^{+/-} mice have reduced intestinal contractility and reduced release of selected neurotransmitters such as VIP and substance P [63] but do not exhibit a basal change in crypt-villus morphology compared to wild type mice. However, following resection compared to normal wild type mice the intestine of *Ret*^{+/-} mice unexpectedly exhibited increased villus heights, crypt depths and increased crypt cell proliferation, that was associated with increased small bowel expression of GLP2 and amphiregulin, an EGFR ligand [60]. Further confirmation for an inhibitory role for the ENS in post-resection adaptation came from studies in rats treated with benzalkonium chloride, a toxin that destroys the ENS. Denervated bowel also exhibited an enhanced adaptive response after small bowel resection [64]. These results suggest that the ENS plays

an inhibitory role in regulating crypt cell proliferation that is unmasked following resection. Future studies are required to elucidate the specific ENS mediators of this response.

E. Microbiome

Studies on the microbiome in short bowel syndrome are few but there is great interest in its role in the gut adaptive process. The possibility that a “favorable” microbiome might be developed as a therapeutic tool is supported by the observation that short bowel syndrome patients with residual colon in continuity are more likely to wean from parenteral nutrition compared to patients with ileostomies [3-5, 65]. Also short chain fatty acids generated by colonic bacteria promote intestinal epithelial growth [65]. Earlier studies of the microbiome in humans with short bowel syndrome used culture based methods to demonstrate a prevalence of lactobacilli [66]. An analysis of colonic mucosal-associated microbiota and fecal microbiota from 11 patients with “stable” short bowel syndrome who were studied more than two years out from initial resection showed markedly diminished anaerobes and an abundance of lactobacilli [67]. Two recent studies in children with intestinal failure showed reduced diversity of bacterial species and overabundance of lactobacilli, proteobacteria [68] and enterobacteriaceae [69]. This topic has been reviewed recently [70]. The role of the microbiome is also being explored experimentally in mouse [71] and piglet [72] models of short bowel syndrome.

F. Functional adaptive response

The functional adaptive response includes increases in fluid, electrolyte and nutrient absorption. Studies of adaptive changes in gut epithelial function are reported in many of the original publications using rat models of short bowel syndrome. These classic publications have shown that for some absorptive functions, functional adaptation occurs purely as a result of villus epithelial hyperplasia (e.g. in a rat model measuring glucose transport; [73], but for others, an increase in gut function on a per cell basis was observed. For example, studies have shown increased expression of apical membrane Na/H exchangers NHE2 and 3 [74], SGLT1, the apical sodium dependent glucose transporter [75], and increased alpha-glucosidase activities after jejunal resection [76]. Increased mRNA expression of absorptive genes such as *L-FABP*, *Apo AIV*, *sucrase isomaltase* and *glut 2* [26, 77, 78] have also been demonstrated. The molecular regulation of these functional adaptive responses remains largely unknown. *Tis7/IFRD1*, a transcriptional co-regulator with global effects on gene transcription, has been shown to regulate target genes that affect triglyceride absorption. *Tis7/IFRD1* expression is markedly increased in the adaptive gut early post resection [79]. Transgenic mice in which *tis7* is over-expressed in enterocytes have increased adiposity and an enhanced rate of triglyceride absorption [19, 80]; conversely, mice in which *tis7/IFRD1* is deleted are protected from weight gain when fed a high fat diet [19]. These mice have a markedly reduced proliferative response post resection (see Section B.i) and when fed a high fat diet have reduced survival post resection, associated with increased anastomotic inflammation [81]).

Conclusions

Short bowel syndrome is a major cause of morbidity and mortality and obligates extensive health care costs, because patients depend on parenteral nutrition to meet their nutritional

requirements. Understanding the mechanisms that regulate the intestinal adaptive response post-resection is critical for the development of novel therapies to enhance this response, to facilitate a return to enteral nutrition. The morphometric crypt proliferative response is characterized by early stem cell expansion and likely involves Wnt, Bmp, Notch and Hh signaling, and is regulated by genes such as *IFRD1*. It is enhanced by growth factors such as glucagon-like peptide and epidermal growth factor. Although functional adaptation occurs in the remnant small bowel epithelium, little is known about the underlying regulatory mechanisms. The role of crypt proliferative signaling pathways and the enteric nervous system, intestinal smooth muscle and microbiome in human gut adaptation in short bowel syndrome is the subject of active investigation.

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Research Agenda

- Future research will focus on efforts to identify new therapeutic targets (microbiome, novel growth factors) to enhance growth and proliferation of the residual bowel mucosa and increase functional adaptation.
- Methods need to be developed for safe and effective expansion and transplantation of adult isogenic stem cells to regenerate the small bowel [82, 83].
- Further research is necessary to determine the functional capacity of transplanted stem cells/enteroids and their ability to mimic native gut physiology [84].
- **Practice Points:** N/A.

Figure 1.

The intestinal morphometric response post-resection. Rats were subjected to 70% intestinal resection and the residual adaptive ileum was removed at 2 weeks postop. Hematoxylin and eosin staining was performed. A. Preoperative ileum. B. Adaptive ileum at 2 weeks postop. The structural adaptive response is characterized by an increase in intestinal villus height and crypt depth, with an expansion in the goblet cell population.

Figure 2.

Mechanisms of intestinal adaptation in short bowel syndrome (SBS). The adaptive response following massive small bowel resection is characterized by stem cell expansion and increased crypt cell proliferation, resulting in deepened crypts and increased villus height. Nutrient, fluid and electrolyte absorption per unit surface area is increased post-resection. Studies have focused on mechanisms that regulate expansion of stem cells, increase in transit amplifying (TA) cells, stromal (myofibroblast and other)-stem cell interactions, apoptosis, epithelial migration and enhanced enterocyte function.

Figure 3.

Stem cell hierarchies in the intestinal epithelium during homeostasis and regeneration. PC, Paneth cell, EEC, enteroendocrine cell, GC, goblet cell, TC, tuft cell. From Tetteh PW et al Trends in Cell Biology 25 (2) 2015 100-108.