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Abbreviations

SBS	Short bowel syndrome
Caspase	CysteinyI-aspartate-acid-proteinase
TPN	Total parenteral nutrition
LCFA	Long-chain fatty acids
OKG	Ornithine α -ketoglutarate
GH	Growth hormone
GLP	Glucagon-like peptide
EGF	Epidermal growth factor
TGF β	Transforming growth factor β
IGF	Insulin-like growth factor
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
PDGF	Platelet-derived growth factor

Definition of Short Bowel Syndrome

Short bowel syndrome (SBS) is defined as an intestinal failure following the loss of intestinal length or competence below the minimal amount necessary for the absorption of nutrients and a normal nutritional status [1–3]. The short gut

syndrome is a particularly important complication that occurs in newborns and infants suffering from necrotizing enterocolitis, intestinal atresia, and volvulus requiring massive intestinal resection. SBS typically follows resection of 50 % or more of the small intestine and is associated with diarrhea, steatorrhea, dehydration, electrolyte disturbances, malabsorption, and progressive malnutrition [2, 3]. SBS has significant morbidity and is potentially lethal especially when intestinal loss is extensive. An appropriate management of SBS requires reference centers using therapeutic strategies based on a multidisciplinary approach including pediatric gastroenterologists and pediatric surgeons, as well as specialized nurses, dieticians, social workers, and psychologists. This integrated approach should be adapted to each type and stage of intestinal failure including the home parenteral nutrition and transplantation program [4].

A number of mechanisms contribute to malabsorption after massive resection, including acid hypersecretion, hypergastrinemia, rapid intestinal transit (especially likely when the distal ileum is resected or parts of the colon containing peptide YY – the so-called breaking hormone – are lost), impaired residual bowel, loss of surface area, bacterial overgrowth in dilated segments of small bowel, and bile acid depletion. Diarrhea in patient with short bowel syndrome is due to a combination of increased secretions, increased motility, and osmotic stimulation

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of water secretion because of malabsorption of luminal contents. Hypertonic concentration of partially digested nutrients in the jejunum results in massive fluid losses that would normally be reabsorbed in the ileum and colon. If the ileum is resected, one of the primary reabsorptive sites for these secretions is lost, and the remaining colon is incapable of reabsorbing most of the fluid. Consequently, patient with distal bowel resection develops usually massive fluid losses in response to large bolus feeding or feedings containing high concentrations of rapidly digested carbohydrates [5]. The degree of malabsorption increases with the length of resection, and the variety of nutrients malabsorbed increases [6, 7]. Balance studies of energy absorption showed that the absorption of fat and carbohydrate was equally reduced to between 50 and 75% of intake [7]. However, nitrogen absorption was reduced to a lesser extent than that of carbohydrate and fat, namely, to 81% of intake. Although the ability to absorb many nutrients is decreased following resection, lipid absorption is generally considered the most vulnerable [8–12]. Therefore, patients with short bowel syndrome have been considered to benefit from a low-fat diet early in the course of therapy [13, 14]. Absorption of calcium, magnesium, zinc, and phosphorus is reduced in SBS patient, but does not correlate with the remaining length of bowel [15–17]. Colonic bacteria deconjugate the bile salts entering the colon to free bile acids that stimulate secretion, leading to the development of watery diarrhea. Therefore, the severity of diarrhea following ileal resection depends in part on the length of contiguous colon removed [18]. The gastrointestinal tract is also the site of synthesis of a number of important gastrointestinal hormones and growth factors. Many of these play an important role in regulating gastric emptying and small intestinal transit. Resection of the ileum results in delayed gastric emptying that is a major factor in adaptive increased transit time [19]. On the other hand, resection of the ileum may impair the “colon brake” phenomenon through to be controlled by neurotensin and peptide YY [20]. Other compounds, including prostaglandins, cholecystokinin, and secretin,

were not found to adequately maintain the mucosa in the setting of TPN [21]. Gastric acid hypersecretion is a common finding after massive small bowel resection and is proportional to the length of intestine resected. Gastric hypersecretion has been attributed to hypergastrinemia following the loss of gastric peptide production from the resected small intestine [22]. The increased gastric secretions and acidity inactivate pancreatic enzymes, reducing the efficiency of protein and lipid digestion [23]. The excess gastric acid and low intraduodenal pH may damage the bowel mucosa, inactivate digestive enzymes, and stimulate peristalsis [24]. Decreased secretion of cholecystokinin and secretin further reduces gallbladder contraction and pancreatic secretion. These factors along with secretion of a high salt load by the stomach may compound the diarrhea associated with short bowel syndrome [25].

Intestinal Adaptation: Definition

Intestinal adaptation means progressive recovery from intestinal failure throughout which the small bowel increases its absorptive surface area and its functional capacity in an attempt to meet the body's metabolic and growth needs [26]. Although intestinal transplantation has emerged as a feasible alternative in the treatment of children with SBS during the last two decades, intestinal adaptation remains the only chance for survival in a subset of these patients. Intestinal adaptation begins within 24–48 h of resection and includes morphologic (structural adaptation) and functional changes (functional adaptation) of the residual bowel. Structural adaptation includes increasing bowel diameter and length, lengthening the villi, deepening the crypts, and increasing the rate of enterocyte proliferation, finally resulting in increased absorptive surface area and in increased numbers of enterocytes. Functional adaptation entails modifications of the brush border membrane permeability and upregulation of carrier-mediated transport, ultimately resulting in increased nutrient absorption by isolated enterocytes.

In the early twentieth century, it was first observed that the residual intestine can undergo structural changes that result in increased surface area and enhanced nutrient absorptive capacity. In 1957 Piling and Cresson [27] described the first successful extensive resection in two infants, who survived with only 26 and 28 cm of remaining small bowel. Subsequently, many series of patients have documented survival in infants with even shorter small bowel remnants. A review of 50 infants with significant small bowel resection showed a good probability of survival with 15 cm or more of residual gut when ileocecal valve is preserved; a loss of ileocecal valve, however, requires at least 40 cm of residual small bowel for a reasonable chance to survive [28]. Several studies have shown that the functional integrity of the remaining intestine is of far more importance than the outward appearance of the bowel [29]. The nutritional benefits of an increased intestinal absorption in short bowel patients are usually reflected in changes of body weight and composition. The increases in the body weight and lean body and bone mass and the reduction in the fat mass seen as a result of the conservative treatment may be taken as clinical indications of a beneficial effect, which most probably is mediated through the effect on intestinal absorption. In addition, the increase in urine creatinine and the absence of clinical signs of edema supported that the increase in lean body mass, measured by dual-energy x-ray absorptiometry, actually reflects an increase in muscle mass. The increases in serum albumin and sodium are also encouraging [30]. Figure 2.1 illustrates a theoretic graphic presentation of gut function in relation to time after bowel resection.

A “spontaneous adaptation” or recovery of intestinal function is generally described, reaching a plateau at a certain time (usually after 18 months). When trying to improve intestinal adaptation, therapies could either reach a higher plateau phase (given as graph “enhanced adaptation”) or reduce the time period until the plateau was reached (given as graph “accelerated adaptation”). Enhanced accelerated adaptation refers to situation when adaptation reaches higher plateau and in shorter time. Accelerating the process may

be relevant in patients who are difficult to maintain on parenteral nutrition. However, the maximal increase in the functional absorptive capacity obtained by enhanced adaptation, represented by the level of the plateau, is the aim when trying to wean stable patients from parenteral support.

Intestinal Adaptation: Animal Models

Most studies investigating the process of adaptation have utilized animal models (rat, mouse, and dog) with a jejunoileal anastomosis. Therefore, the relevance of the physiological and structural changes that occur is of unclear clinical relevance to humans who uncommonly have this bowel anatomy remaining. Hyperplasia of the mucosal epithelium, not hypertrophy, is the primary event occurring in intestinal adaptation [30]. In rodent systems, animals subjected to extensive (70%) intestinal resection undergo a pattern of well-described morphological and functional changes. The remaining intestine changes macroscopically with dilatation, thickening, and an increasing length. There is an increase in villus height and diameter and an elongation of the crypts. Increased villus height and crypt depth is the result of increased proliferation and accelerated migration along the villus and is a marker for the increased absorptive surface area. Increased mucosal proliferation in a functioning intestine, as demonstrated by the increased cell proliferation index following bowel resection, suggests an activated enterocyte turnover and may be considered as a main mechanism of mucosal hyperplasia in residual bowel. An increase in epithelial cellular proliferation, coupled with an increase in apoptosis, produces increases in intestinal RNA, DNA, and protein content [31]. The dynamic process of enterocyte turnover is a function of the rates of crypt cell proliferation, migration along crypt-villus axis, and death via apoptosis. This process may be affected by nutritional status, the route of feeding, and the adequacy of specific nutrients in the diet. Apoptosis or programmed cell death is an active, genetically controlled process of cell

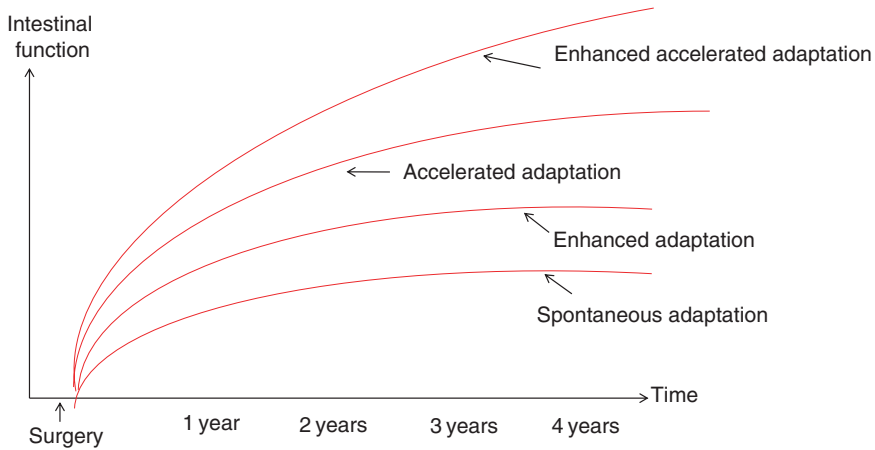


Fig. 2.1 Development of intestinal adaptation as a function of postoperative time

suicide. It is a physiologic process whereby the body disposes of unwanted cells by self-destruction and is our greatest defense against damaged cells [32]. In contrast to necrosis, which is more of an accidental death process, apoptosis comprises highly regulated and reproducible events that eventually lead to cell death. Several regulatory genes affecting apoptosis have been identified and divided into proapoptotic genes (*bax*, *bik*, *bak*, *bcl-xs*, *bad*, *p53*, *c-jun*, *hrk*) and anti-apoptotic genes (*bcl-2*, *bcl-x_L*, *rb*, *mcl-1*, *a1*, *brag-1*, *bfl-1*) [33]. Many reports on apoptosis focused on the role of the executioners, cysteinyl-aspartate-acid-proteinases, termed “caspases” which are triggered in response to proapoptotic signals. Caspases cleave numerous substrates at the carboxyl side of an aspartate residue upon induction of apoptosis. A key caspase involved in the apoptotic pathway is caspase-3 (also known as Yama, CPP32, and apopain). Inhibition of caspase-3 has been linked to prevention of apoptotic death in vitro, although certain stimuli can induce apoptosis by a caspase-3-independent pathway [34]. Bcl-2 and related proteins play an important role in the regulation of apoptotic cell death in mammalian systems [35]. At least two family members, Bcl-xs and Bax, act in opposition to Bcl-2. Recent evidence has demonstrated that apoptosis increases in SBS [36]. Enhanced enterocyte apoptosis following bowel resection is considered as being a mechanism

that counterbalances the increased enterocyte proliferation in order to reach a new homeostatic status during intestinal adaptation, promoting the disposal of genetically aberrant stem cells and preventing tumorigenesis. In a recent experiment, Jarboe et al. [37] examined the role of *bax* in exaggerated post-resection apoptosis induced by epidermal growth factor receptor inhibition in mice and demonstrated that *bax* is required for the induction of such cell death. Moreover, defective epidermal growth factor receptor signaling augmented resection-induced enterocyte apoptosis via a mechanism that also requires *bax* expression. Functionally there is an increase in absorption per unit length of carbohydrates, proteins, water, and electrolytes [38, 39].

Regulating Intestinal Adaptation

In response to a variety of stimuli, including luminal nutrients, hormones, growth factors, and pancreaticobiliary secretions, the small and large intestine increase their absorptive surface area and functional capacity to meet the body’s metabolic and growth needs. Considerable research over many years has focused on the identification of those trophic factors that may promote bowel absorption after massive intestinal resection and provide a successful outcome in patients with SBS. These factors include

nutrients and other luminal constituents, gastrointestinal secretions, hormones, and peptide growth factors [25–27].

Adaptation and Nutrients

The initial management of patients with SBS typically involves TPN. TPN is usually initiated as soon as clinical stability allows and provides adequate total caloric intake and the necessary amounts of nutrients and micronutrients. Importantly, it also “buys time” for gradual tolerance of enteral feedings and successful adaptation of the intestine. However, it is well documented that exposure to intraluminal nutrients is required for stimulation of intestinal adaptation in general and mucosal hyperplasia in particular [40]. Early gradual introduction of enteral feedings also plays an important role in successful postoperative management. It is well documented that exposure to intraluminal nutrients is required for stimulation of intestinal adaptation in general and mucosal hyperplasia in particular [41]. Therefore, many experts in the management of SBS recommend attempting enteral feeding as early as possible. The mechanism whereby food induces this adaptation is unknown. It is likely that enteral nutrition works through a number of mechanisms, including stimulation of mucosal hyperplasia by direct contact with the epithelial cells, stimulation of trophic gastrointestinal hormone secretion, and stimulation of the production of trophic pancreaticobiliary secretions [27, 28]. Although enteral feeding is one of the major trophic factors in the stimulation of intestinal adaptation, not all nutrients have equal stimulating trophic effects. Growing evidence suggests that glutamine, pectin, short-chain fatty acids, and long-chain fatty acids are considered the most effective among the factors promoting post-resection intestinal adaptation [41]. Although lipid absorption is generally considered the most vulnerable in SBS patient, growing evidence suggests that long-chain fatty acids appear to be more effective stimulators of intestinal adaptation than either medium-chain fats or carbohydrates [42].

Early exposure to a high-fat diet augmented and accelerated intestinal regrowth after massive small bowel resection in a rat model [43]. In addition, dietary lipids increased the absorptive capacity of the intestinal remnant, improved food and fat absorption, and restored plasma and tissue lipid content in this model [44]. In contrast, a low-fat diet significantly affected adaptive responses by an inhibition of enterocyte proliferation and did so independently of enterocyte apoptosis [45]. Depletion of dietary fat inhibited also cellular and molecular mechanisms of LCFA absorption by isolated enterocytes in the same model. This was evident from a decrease in LCFA plasma-membrane transport protein fatty-acid translocase (FAT) (the rat homologue of human CD36) and a decrease in isolated enterocyte [3H]-oleate uptake as measured by established cellular LCFA transport assay [46].

Extensive studies in various experimental models of SBS have established that many amino acids (e.g., glutamine) strongly stimulate the intestinal adaptive response. Glutamine, rather than glucose, is the major fuel for mitochondrial respiration in enterocytes. Glutamine is used for protein synthesis either directly or as a result of catabolic pathways. Within 24 h of 80% small bowel resection in the rodent, glutamine and total amino acid uptake per gram of tissue is increased [47]. However, with the decrease mass of tissue, overall glutamine consumption in the long term is less than controls, and muscle stores of glutamine remain unchanged [48, 49]. The addition of glutamine or arginine to enteral feeds after extensive resection does not seem to produce a consistent effect between studies; indeed, there is little evidence that either amino acid increases adaptation, with some groups reporting lower protein and DNA levels than controls [50]. Supplementation of enteral feeds with ornithine α -ketoglutarate (OKG), the soluble ornithine salt, does seem to have a positive effect on intestinal adaptation and mucosal polyamine synthesis [51]. However, another nonessential amino acid arginine impairs post-resection intestinal regrowth in rats through a decrease in enterocyte proliferation and increase in cell death via apoptosis [52].

Vitamin A is essential for normal growth and for differentiation of epithelial tissues. Extensive studies in various experimental models have established that vitamin A may regulate intestinal epithelial cell proliferation and regeneration. Swartz-Basile et al. [53] examined the mechanisms by which the status of vitamin A affects adaptation by analyzing proliferation, apoptosis, and enterocyte migration in the early postoperative period after bowel resection in rat. Both crypt cell proliferation and enterocyte migration rates were significantly decreased in the vitamin A-deficient rats subjected to submassive small bowel resection. In contrast, apoptosis was significantly greater in the remnant ileum of resected vitamin A-deficient rats compared to control animals. The authors concluded that vitamin A deficiency inhibits intestinal adaptation following partial small bowel resection by reducing crypt cell proliferation, by enhancing early crypt cell apoptosis, and by markedly reducing enterocyte migration rates.

Intestinal Adaptation and Hormones

It is widely accepted that the adaptive response is controlled in part by the release of one or more of the gut signaling hormones. These include enteroglucagon, neurotensin, peptide YY, growth hormone, and insulin-like growth factor [20]. Additionally, enteral feeding stimulates the release of enterotrophic hormones (gastrin, cholecystokinin, neurotensin) which have an important role in the process of gut adaptation. There is growing evidence in animal models of SBS that some hormonal manipulation can improve intestinal adaptation.

Growth hormone (GH) is a single-chain protein produced in the anterior pituitary gland. Because GH has been shown to induce growth and proliferation in many different tissues and cell lines and the receptor for growth hormone has been found throughout the intestine, its role in the setting of SBS has been studied extensively. Many studies in various experimental models of SBS have established that exogenous administration of growth hormone enhances

mucosal hyperplasia and increases water, electrolytes, and nutrient absorption [54, 55]. In a rabbit model of SBS, Avissar et al. [56] recently demonstrated that treatment with growth hormone for 2 weeks restored a Na(+)-dependent broad-spectrum neutral amino acid transporter (ATB(0)/ASCT2) protein in the jejunum and ileum, which is responsible for downregulated glutamine transport in rabbit residual bowel following 70% small bowel resection. Many studies in various experimental models of SBS have established that exogenous administration of growth hormone enhances mucosal hyperplasia and increases water, electrolytes, and nutrient absorption [54, 55]. Treated animals have shown mucosal hyperplasia and increased absorptive capacity above and beyond the normal adaptive response after small bowel resection. Other studies have demonstrated increased villus height and crypt depth, positive nitrogen balance, and bowel growth when rats were given GH combined with glutamine and/or a diet high in protein [57, 58]. These studies do not discredit GH as a driver of adaptation but underscore the interplay between the many factors involved in adaptation in SBS. Another very promising observation is that GH may augment the length of the remnant intestine after bowel resection. This finding is particularly important when you consider that remnant intestinal length is the greatest predictor for long-term parenteral nutrition requirement.

Since Wilmore et al.'s [59] demonstration that a combination of growth hormone, glutamine, and a specialized diet enhances intestinal compensation and optimizes nutrient absorption in patients with intestinal failure, many similar studies were conducted and yielded inconsistent results. For example, Matarese et al. performed a systematic search on electronic databases and the Internet for the purpose of compiling the evidence published to date on this subject. The authors concluded that the administration of recombinant human growth hormone alone or together with glutamine with or without a modified diet may be beneficial when the appropriate patients are selected for treatment [60].

Enteroendocrine glucagon-like peptides GLP-1 and GLP-2 are synthesized and released

from enteroendocrine cells in the distal small intestine and large intestine. GLP-1 promotes efficient nutrient assimilation, while GLP-2 regulates energy absorption via effects on nutrient intake, gastric acid secretion and gastric emptying, nutrient absorption, and mucosal permeability [61]. Evidence that GLP-2 is important in controlling intestinal adaptation following bowel resection has come from experiments by Litvak et al. [62]. In addition, Martin et al. [63] have recently shown that luminal nutrients stimulate bowel growth and differentiation by stimulation of GLP-2 secretion and that GLP-2 levels significantly correlated with the magnitude of intestinal resection and nutrient malabsorption. Uluutku et al. [64] investigated the trophic and functional effects of bombesin on the remaining gut in rats with SBS and showed an increased absorptive capacity and improved serum protein and albumin levels following bombesin administration, even in the absence of elemental nutrition. In another recent study, treatment with bombesin resulted in a significant increase in accelerated cell turnover after massive small bowel resection in a rat [65]. The obese gene protein product leptin is a hormone that is secreted from adipocytes and acts primarily on the hypothalamus regulating energy expenditure and food intake [66–68]. Recent study has shown that treatment with leptin enhances structural intestinal adaptation, increases enterocyte proliferation, and decreases cell death via apoptosis following massive small bowel resection in a rat [69].

Because of its antisecretory properties, somatostatin has been advocated for the treatment of patients with SBS. Somatostatin decreases diarrhea and stoma output following massive small bowel resection. However, recent experimental evidence suggests that Sandostatin decreases cell proliferation and inhibits structural intestinal adaptation following massive small bowel resection in a rat model [70]. In light of these results, somatostatin should be avoided following massive small bowel resection in order to prevent its inhibitory effects of bowel regrowth.

Little is known about the effects of gender and sex hormones in short bowel syndrome. A growing body of literature points to gender differences

in many diseases as well as gender dimorphism in the response to trauma, shock, and sepsis. Current theories for the different responses to these events between genders are based on gonadal, hypothalamic, and pituitary hormone levels. In a recent study, the effects of gender and sex hormones on structural intestinal adaptation were investigated following massive small bowel resection in a rat [71]. This study confirms that bowel regrowth following massive small bowel resection is not gender related. Depletion of androgen by castration inhibited intestinal adaptation, and testosterone showed a strong stimulating effect on bowel regrowth.

Adaptation and Peptide Growth Factors

Over the past decades, several proteins produced by different cells and tissues, designated peptide growth factors, have been reported to play an important role in stimulating enterocyte turnover. Our understanding of the structure and function of the peptide growth factors has advanced rapidly in recent years. Peptide growth factors appear to mediate many of the processes required for normal intestinal growth and differentiation. Every growth factor modulates growth through autocrine, juxtacrine, or paracrine mechanisms and usually acts as a mitogen through the stimulation of specific cell surface receptors. It has been reported that growth factors stimulate cell proliferation through the alteration of transcription of various genes [72]. Peptide growth factors are often divided into several groups based on their structure and mode of induction and include the epidermal growth factor (EGF) family, the transforming growth factor- β (TGF- β) family, the insulin-like growth factor (IGF) family, and the fibroblast growth factor (FGF) family. In addition, a smaller number of peptide growth factors having different structural properties compared to the main families also have been identified within the gastrointestinal tract. These include hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), trefoil peptides, hematopoietic stem cell factors, and many more [73].

Certain peptide growth factors have been evaluated for their role in modifying cell proliferation and in stimulating the enterocyte functional activities in animal models of short bowel syndrome. The effect of other factors has not been evaluated following bowel resection, and further work is required to study its effect on intestinal adaptation. EGF was initially isolated by Cohen in 1962 from mouse submandibular salivary glands as the factor responsible for promoting premature eyelid opening in neonatal mice. EGF is a multifunctional, 53-amino-acid peptide that acts through stimulation of specific cell surface receptors. EGF exerts a variety of biological influences in numerous cell populations. Among these, EGF was shown to regulate proliferation of gastrointestinal epithelium through interaction with the enterocytes at the luminal surface as well as increases functional capacity of the gastrointestinal tract mucosa. EGF has been shown to augment the intestinal adaptation in animal models of SBS. Multiple studies have suggested a positive effect of EGF on both structural [74] and functional [75] parameters of intestinal adaptation. The second member of the EGF family, transforming growth factor- α (TGF α), is a 50-amino-acid polypeptide which was first identified in nontransformed fibroblast indicator cells in soft agar and was found to promote anchorage-independent growth of these cells [76]. TGF α shares many structural homologies to EGF and appears to act through the same receptor as EGF. Since its isolation from transformed cell lines, TGF α has been demonstrated to directly promote cell proliferation and to exert a trophic effect on intact gastric, intestinal, and colonic mucosa. Recently, the effect of TGF α on intestinal adaptation has been evaluated in a mice model of SBS. Falcone et al. [76] have reported that in mice with SBS, intestinal adaptation occurs despite the absence of TGF α expression in the remaining bowel; however, exogenous TGF α stimulated enterocyte proliferation and intestinal adaptation. The insulin-like growth factor family includes three peptides: insulin, insulin-like growth factor I (IGF-I), and insulin-like growth factor II (IGF-II). The positive effect of IGF-I and IGF-II in stimulating bowel regrowth after

intestinal resection has been reported by many investigators [77, 78]. In a recent study, oral insulin supplementation dramatically enhanced structural intestinal adaptation after massive bowel resection in a rat [79]. This effect was much more significant than the one observed previously following parenteral insulin administration and was correlated with insulin receptor expression along the villus-crypt axis [80]. Based on these studies, a pilot study was performed to examine whether oral insulin supplementation decreases the need for parenteral nutrition in pediatric patients with SBS. In this trial, clinical improvement was observed in a subset of children, and two of ten infants were successfully weaned off parenteral nutrition [81]. In the intestinal mucosa, numerous cytokines were shown to affect epithelial cell differentiation and proliferation through epithelial-mesenchymal and epithelial-immune cell interaction. Transforming growth factor-beta family includes TGF- β 1 and several peptides exhibiting various degrees of homology to this prototypic member. TGF- β 1 was first isolated from human platelet as a large propeptide of 391 amino acids with the characteristics of secretory polypeptide. TGF-beta has been found to inhibit proliferation of all epithelial cell proliferation of all epithelial cell populations through prolongation of the G1 phase. Therefore, probably, there are no works studying the effect of TGF- β on intestinal adaptation following massive small bowel resection. The most interesting possibility, but one that is speculative at present, is that TGF-beta in conjunction with TGF-alpha can contribute to the regulation of the dynamic turnover of the intestinal epithelium in adapting gut. Additionally, TGF-beta may affect bowel growth through its stimulating effect on extracellular matrix. Fibroblast growth factors play key roles in controlling tissue growth, morphogenesis, and repair in animals. Recent study has shown that keratinocyte growth factor (fibroblast growth factor VII) plays a positive role in intestinal regrowth in a mouse model of SBS [82]. The effects of other fibroblast growth factor family members, transforming growth factor- β family, and platelet-derived growth factor on bowel growth have been examined in normal intestine, but have not been

evaluated in an animal model of short bowel syndrome. Future experiments will, therefore, be needed to examine the role of these factors and to elucidate the potential mechanisms by which they affect the adaptive response. Hepatocyte growth factor (HGF) is a distinctive growth-modulating peptide, which has been identified in primary hepatocytes and is also expressed in the stomach, small intestine, and colon. HGF was found early in all human fetal digestive tissues, suggesting its morphogenic role in digestive system development during embryogenesis [83]. It has been reported that intestinal mesenchyme secretes HGF which stimulates the growth of attaching epithelial cells by a paracrine mechanism [84]. Comparing the effect of TGF- α , TGF- β , keratinocyte growth factor, and hepatocyte growth factor on restitution of intestinal epithelial cells, Nishimura and collaborators have shown that HGF was the most potent of the cytokines in accelerating repair of the damaged monolayer of the intestinal epithelium [85]. Further experiments demonstrated that HGF can increase intestinal epithelial cell mass and function in vivo. After reviewing the evidence for the role of HGF as a pro-adapting agent after bowel resection, it should be mentioned that recent work by Schwartz and colleagues [86] has demonstrated dramatic response in mucosal mass and enterocyte functional capacities following bowel resection in rats exposed to HGF.

Enhancing Adaptation in the Treatment of Short Bowel Syndrome

Early management of SBS in reference centers by multidisciplinary groups is certainly the key issue to recognize, as early as possible, irreversible intestinal failure, to improve its outcome, and to perform intestinal transplantation in an appropriate time. Management of SBS has traditionally been divided into three phases: an acute phase, an adaptation phase, and a maintenance phase. Phase I, the acute phase, occurs during the immediate postoperative weeks and may last 1–3 months. This phase is marked by poor absorption

of almost all nutrients, including water, electrolytes, proteins, carbohydrates, fats, vitamins, and trace elements [87]. Fluid loss from the gastrointestinal tract tends to be greatest during the first few days after massive small intestinal resection; ostomy outputs may exceed 5 L/day. Aggressive fluid and electrolyte replacement therapy is necessary to reduce life-threatening dehydration, hypotension, and electrolyte imbalances. Frequent measurements of vital signs, intake and output, and central venous pressures are required because of rapid metabolic changes and possible hemodynamic instability [88]. Phase II, the adaptation phase, generally begins within 24–48 h after resection and may last from 1 to 2 years. During this period, 90–95 % of the bowel adaptation potential (including nutritional and metabolic stability) has been realized, and only 5–10 % of additional improvement in bowel adaptation and absorption is possible [89]. Adaptive changes also take place in the stomach, pancreas, and colon. Clinical manifestations of intestinal adaptation include weight change and stabilization of fluid and electrolyte levels [87]. By phase III, the maintenance phase, the absorptive capacity of the gut is at a maximum. Although some patients still require parenteral nutrition, others do well on diet alone. Attempts should be made to compensate for continued malabsorption by increasing the quantity of small meals and supplementation with vitamins and minerals [90]. At this point, the patient has either adapted maximally so that nutritional and metabolic homeostasis can be achieved entirely by oral feeding, or the patient is committed to receiving supplemental or complete nutritional support for life, either by ambulatory home TPN or specialized enteral or oral feedings.

An increasing number of factors have been identified that can promote epithelial growth, increase epithelial absorptive function, and affect intestinal growth. Recent clinical trials offer the potential of a new modality to care for such patients. Selection of appropriate patients for these new therapies and ensuring efficacy of these factors will be important objectives over the next several years [91, 92]. In a pilot study, enteral treatment with epidermal growth factor in pediatric SBS improves

nutrient absorption, increases tolerance with enteral feeds, and improves the infection rate [93]. Two clinical studies in adult SBS patients show extremely encouraging results of glucagon-like peptide 2 (GLP-2). In a non-masked study of eight SBS patients, a number of positive effects of GLP-2 were noted [94]. These patients lacked a distal small bowel and colon and thus had very little endogenous GLP-2 and were without the normal postprandial elevation in GLP-2 levels. Nutrient absorption was carefully measured in this study and was found to increase by 3.5%. A significant increase in protein absorption, and a nonsignificant increase in carbohydrate absorption, was noted; however, no significant change was found in fat absorption.

Morphometric analysis of the small intestine demonstrated an increase in villus height and crypt depth in the majority of their patients. Teduglutide is a protease-resistant analog of GLP-2 for the potential treatment of gastrointestinal disease. Teduglutide has prolonged biological activity compared with native GLP-2, and preclinical studies demonstrated significant intestinotrophic activity in models of SBS, experimental colitis, and chemotherapy-induced intestinal mucositis. Patients with SBS rely on parenteral nutrition following bowel resection, and in a phase III clinical trial with teduglutide, >20% reduction in PN was observed in patients with SBS receiving teduglutide [95].

In a recent pilot study, oral insulin supplementation decreases the need for parenteral nutrition in pediatric patients with SBS with clinical improvement in a subset of children, and two of ten infants were successfully weaned off parenteral nutrition [81].

Stem Cells and Intestinal Adaptation

Intestinal stem cells (ISCs) are fundamental cornerstones in intestinal biology, ensuring homeostatic self-renewal of intestinal mucosa and presenting a reserve pool of cells that can be activated after tissue injury (ischemia-reperfusion) or after bowel resection. Intestinal stem cells are

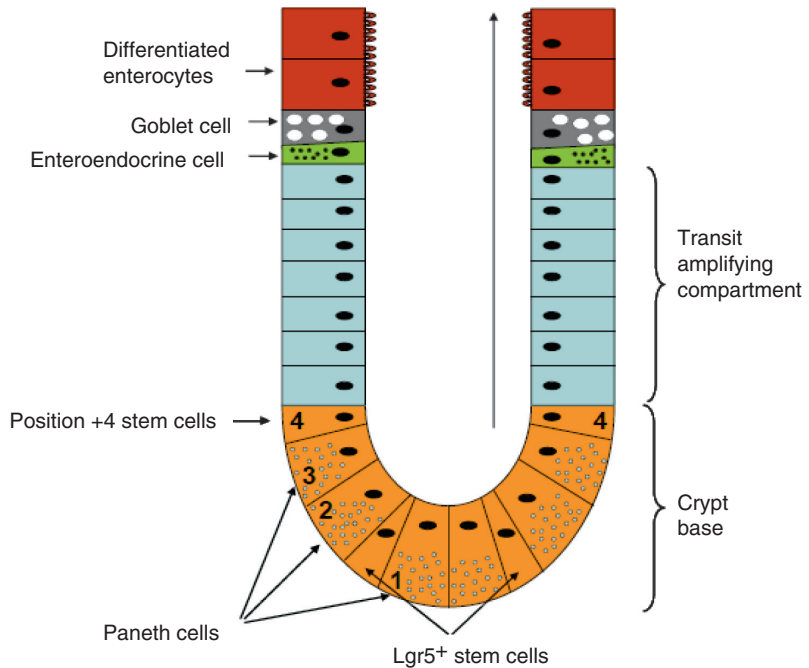
characterized by their ability to self-renew as well as to differentiate into specialized cells, properties critical for tissue maintenance and regeneration. ISC compartment has long been known to reside near the crypt bottom; however, the definitive identification of ISCs has been hampered by a lack of unique molecular markers (Fig. 2.2).

Two hypotheses exist regarding the exact identity of the ISCs: the +4 position model and the SC zone model. Both concepts are based on the assumption that every crypt contains approximately 4–6 independent ISCs. According to the +4 position hypothesis, the ISCs reside at position 4 relative to the crypt bottom, while the first three positions are occupied by the terminally differentiated Paneth cells. Potten and colleagues reported that these +4 cells retain DNA labels throughout long periods of time [96] and are extremely radiation sensitive [97]. The second (SC zone) hypothesis was put forward after the identification of a unique small cycling cells interwedged between the Paneth cells (so-called crypt base columnar (CBC) cells). Bjerknes and Cheng proposed that these CBC cells represent the true intestinal SCs [98].

+4 stem cells (which occupy the fourth position from the crypt base) reside at position 4 relative to the crypt bottom, while the first three positions are occupied by the terminally differentiated Paneth cells. Multipotent LGR5+ (Leu-rich repeat-containing G protein-coupled receptor 5-expressing) crypt base columnar stem cells drive regular epithelial renewal.

Until recently, there had not been consistently reliable markers to identify these intestinal stem cells. However, several intestinal stem cell markers including *Musashi1*, *Lgr5* (leucine-rich repeat-containing G protein-coupled receptor 5), and *DCAMKL-1* (doublecortin and CaM kinase-like-1) have been identified. *Musashi1*, an RNA-binding protein, was originally thought to be a neural stem cell marker. However, subsequent studies demonstrated that *Musashi1* was also present on intestinal and colonic stem cells [99]. Utilizing this marker, the isolation of an unpure culture of intestinal stem cells from the jejunum was achieved.

Fig. 2.2 Model of epithelial regeneration in the small intestine



However, additional markers were clearly needed to purify this culture. Wnt signaling has been implicated in different stages of mammary development as well as in mammary oncogenesis [100]. *Lgr5* has recently been discovered and has been shown to exist exclusively in crypt base cells within the intestine. Studies examining intestinal stem cell signaling have also suggested that *Wnt/Ephrin*, *BMP* (bone morphogenic protein), *Notch*, and *PI3K/PTEN* (P-phosphatase and tensin homologue) signaling cascades are dramatically involved with intestinal stem cell proliferation and lineage commitment.

Experiments designed to further purify intestinal stem cells are certainly required prior to their widespread use. Once the mechanisms of stem cell proliferation are elucidated, intestinal stem cells may be deemed the most optimal stem cell to seed tissue-engineered grafts or to apply to injured tissues during therapy.

Stem cells represent a novel treatment modality with increasing therapeutic potential. The extensive proliferation and differentiation capacities of stem cells make them optimal for seeding tissue-engineered grafts. Stem cell-engineered bioprosthetic neointestine may prove beneficial in

conjunction with these techniques to increase the absorptive capacity of the intestine in short bowel syndrome. In this regard, supplying an adequate number of functional stem cells to affected patients, either through tissue-engineered neointestine or via stem cell transplantation, may increase overall enteric function, promote intestinal restitution, and relieve disease symptoms. Such procedures have already shown benefit in animal models and may decrease the need for long-term parenteral nutrition or multivisceral organ transplantation [101]. In addition, the release of protective factors (paracrine effects) has also been shown to be beneficial to growing intestine.

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