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REVIEW

New approaches to increase intestinal length: Methods used for intestinal regeneration and bioengineering

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Abstract

Inadequate absorptive surface area poses a great challenge to the patients suffering a variety of intestinal diseases causing short bowel syndrome. To date, these patients are managed with total parenteral nutrition or intestinal transplantation. However, these carry significant morbidity and mortality. Currently, by emergence of tissue engineering, anticipations to utilize an alternative method to increase the intestinal absorptive surface area are increasing. In this paper, we will review the improvements made over time in attempting elongating the intestine with surgical techniques as well as using intestinal bioengineering. Performing sequential intestinal lengthening was the preliminary method applied in humans. However, these methods did not reach widespread use and has limited outcome. Subsequent experimental methods were developed utilizing scaffolds to regenerate intestinal tissue and organoids unit from the intestinal epithelium. Stem cells also have been studied and applied in all types of tissue engineering. Biomaterials were utilized as a structural support for naive cells to produce bio-engineered tissue that can achieve a near-normal anatomical structure. A promising novel approach is the elongation of the intestine with an acellular biologic scaffold to generate a neo-formed intestinal tissue that showed, for the first time, evidence of absorption *in vivo*. In the large intestine, studies are more focused on regeneration and engineering of sphincters and will be briefly reviewed. From the review of the existing literature, it can be concluded that significant progress has been achieved in these experimental methods but that these now need to be fully translated into a pre-clinical and clinical experimentation to become a future viable therapeutic option.

Key words: Bioengineered intestine; Tissue engineered; Scaffolds; Organoids; Stem cells; Intestinal elongation techniques

Core tip: Several methods were used to elongate the short and insufficient segment of intestine in patients suffering short bowel syndrome. These methods include transplantation of an intestinal graft, intestinal elongation, and techniques to create a bioengineered segment of intestine. Innovations in using stem cells, organoid units of intestine and bio-scaffolds allow the modern medicine to engineer segments of functional intestinal tissue in animal models. However, to reach the goal of implanting a fully functional bioengineered intestine in human improvements are still required. This article will review various methods to approach this condition from surgical techniques to elongate the intestine to the application of stem cells and bio scaffolds for creating three dimensional intestinal structure.

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INTRODUCTION

Intestinal absorptive function is the result of fine regulation between different cell types and signaling, cooperating within this organ. Intestinal failure is the consequence of various diseases that limit intestinal length or function. These include, but are not limited to: Intestinal atresia, gastroschisis, pseudo-obstruction, motility disorders, Crohn's disease, mesenteric thrombosis, intestinal necrosis, trauma and lead to short bowel syndrome. When the remaining portion of the intestine is functionally insufficient, intestinal failure results and this is characterized by fluid imbalance, electrolyte loss and altered nutrients absorption[1].Total parenteral nutrition (TPN) has been used as a treatment option, however, hepatic insufficiency, catheter related thrombosis and sepsis are the most significant limiting factors[2-5].

Intestinal transplantation offers a physiologic cure in the treatment of these patients as an alternative treatment[6]. Limitations of intestinal transplantation include sepsis and infections, chronic immunosuppression to avoid rejection and shortage in optimal organ donors[7]. Various techniques have been proposed to develop a safe and functional method to take advantages of bioengineering in the field of intestinal elongation. In this article, we will review the current knowledge on this subject, explain the limitation and benefits of each method and finally elaborate on the future direction and goals.

In general, the methods in intestinal tissue engineering can be classified into the following groups: Surgical techniques that can physically elongate the patient's intestinal length; development of intestinal tissue using stem cells (SCs) in culture; development of organoid units from intestinal cells implanted on biologic materials *in vivo* and then incorporated in continuity with the intestine; utilization of biologic scaffold *in vivo* to obtain a neo-formed intestinal segment.

SURGICAL TECHNIQUES

Early surgical procedures to address short bowel syndrome attempted to increase nutrient absorption prolonging food transit time. Those procedures included vagotomy and pyloroplasty procedures, reversing small intestine segment, pouch formation, and prejejunal or preileal colon transposition[8-14]. In the early 1980s, Bianchi[15] described a reproducible technique to increase the length of the small intestine. Briefly, the procedure consisted in dividing an intestinal loop longitudinally in the midline where the vessels alternately go to one or other side of the loop from the mesentery. Then each side would be sutured to form a hemiloop. The final step was to anastomose the newly formed loops iso-peristaltically. As a result, the length of that bowel loop would be doubled, however, the diameter was halved. The advantage of this procedure was preservation of all available mucosa while tailoring the intestine length[15,16].

An alternative approach, called serial transverse enteroplasty (STEP), was introduced in early 2000. Following intentional dilatation of the small bowel, surgical stapling would be performed in an alternating direction from side to side in a "zig-zag fashion" perpendicular to the long axis of the bowel to elongate the existing small intestine. This procedure would be basically equivalent of the Bianchi procedure, however STEP had several theoretic advantages. The procedure was easier to perform and there was no need for anastomoses. Additionally, the intestine would never be opened, and the mesentery would never be jeopardized. In contrast, the over-all theoretical increase in length would depend on the amount of bowel dilatation and the size of the created intestinal lumen[17].

However, the patients who had undergone the Bianchi procedure would wean off TPN more than those with STEP, and they eventually would require intestinal transplants more than those with STEP. In addition, STEP was shown to be associated with higher rates of complication[18]. A study describes results from 38 patients who underwent STEP procedure for different diagnosis including intestinal atresia, gastroschisis with or without volvulus and necrotizing enterocolitis. Overall, the mean intestinal length increased considerably. The percentage of total calories tolerated enterally also increased. The most common complication was: Staple line leak, obstruction and

abscess. It should be acknowledged that both these procedures have an acceptable short-term outcome while bridging the patients to intestinal transplants and do not seem to constitute a permanent treatment for intestinal failure[19].

SCS

SCs application in regenerative medicine is relatively new. The peculiarity of SCs differentiation is based on their plasticity and mainly on the microenvironment in which they are placed. Recently, it was shown that bone marrow derived hematopoietic stem cells (HSCs) after transplantation in mice, lethally irradiated with ^{60}Cobalt, induce regeneration of gastrointestinal tissues[20]. Bone marrow mesenchymal stromal cells (BMMSCs) are able to mitigate lethal intestinal injury and their intravenous injection will increase the level of intestinal growth factors in the blood and induce regeneration of the intestinal SCs niche of the irradiated host[21].

Utilizing soluble growth factors, like epidermal growth factor (EGF) and hepatic growth factor (HGF), in the culture medium of intestinal SCs improves results obtained by increasing the homing of transplanted cells[22]. Supporting stem cell application, Qu *et al*[23] reported that transplantation of BMMSCs and soluble stem cell factors cooperate in regeneration of GI mucosa in a rat model in which indomethacin-induced GI injury was performed.

Hori *et al*[24] in 2002 seeded autologous mesenchymal stem cells (MSCs) on a collagen sponge graft to evaluate intestinal regeneration. Despite a complete mucosa was developed, they did not induce regeneration of the muscle layers. To develop smooth muscle cells with peristaltic features, Yoshida *et al*[25] employed induced pluripotent stem cells (iPSCs) from mice to induce differentiation of the muscularis into active and functional intestinal smooth muscle cells. However, they were not able to control the produced differentiated cells, since they include cardiac-like cells, mucosal cells and smooth muscle cells.

The intestine is a complex organ composed by many cell types. Today, no SC sources permit the generation of all cell types. During the last years, many studies analyzed stem-cell differentiation mechanisms. Studies on population of muscle-derivedstem cells confirmed that they are capable of self-renewal and multi-lineage differentiation including the ability to differentiate into intestinal smooth muscle cells[15,16].

Neuronal progenitor cells are present both in the central nervous system as well as enteric nervous system (ENS). Advances in cell culture techniques allowed isolation of enteric stem/progenitor cells and glial precursor cells. Several groups were able to isolate the neuronal crest-derived cells by sorting according to the markers for Sox10, p75 and Nestin. Following transplantation of these cells in the aganglionic bowel of mice Ret (-/-), the ENS was rebuilt[26].

Interestingly, it has been shown that inducing the CNS-neuronal progenitor cells with gut-derived soluble growth factors, will cause these cells to acquire enteric neuronal phenotype[27]. Likewise, transfected BMMSCs with glial cell-derived neurotrophic factor (GDNF) and Neurotrophin-3 (NT-3) genes, resulted in differentiation of BMMSCs into neuron-like cells with expression of neuronal markers as MAP-2 and GFAP[28,29].

In 2011, Spence *et al*[20] mimicked embryonic intestinal development in an *in vitro* model by using a series of specific growth factors at different time points and they successfully induced human pluripotent stem cells (PSCs) to differentiate into the new intestinal epithelium tissue and crypt-villus units. In order to mimic the natural intestinal peristalsis and physiology *in vitro*, Kim *et al*[30] developed a microfluidic "Gut-on-a-Chip" technology that exposed established epithelial cell lines to physiological peristalsis motions and liquid flow. This particular condition spontaneously induced morphogenesis of three-dimensional intestinal villi. However, these studies supported SCs applications, these *in vitro* models can only partially reiterate the whole *in vivo* intestinal complexity including absorptive or enteric barrier functions, and are far from offering a complete intestinal tissue that could be utilized in an *in vivo* model.

SCS AND BIO-SCAFFOLDS

SCs use has been improved by the attempt to create a three-dimensional (3-D) gel supporting structure system *in vitro* but this remains a major challenge for translational studies. McCracken *et al*[29] enhanced the 3-D tissue culture model. They transformed the PSCs implanted on a matrigel layer for a period of one to three months into intestinal mesenchyme and epithelium.

Generation of 3-D milieu provides a microenvironment with superior cell-cell interaction and communication that mimic an *in vivo* condition. For this aim, tissue engineering has used biocompatible scaffolds. Polymeric materials have two main characteristics; they are bio inert and easily biodegradable while they support all cell functions including adhesion, proliferation and differentiation.

Many studies supported that, these scaffolds provide a matrix for the seeding of cells in high density, which promotes reorganization of a functional tissue in a shorter time-frame. Biodegradable materials must give a perfect mechanical support until cells become able to produce extracellular matrix and other cellular factors. Then they are obligated to be wiped out gradually while being replaced by cellular and extracellular components. Persistence of these materials in the body and prolonged exposition to them can trigger an inflammatory response in the implantation site. Kim *et al*[31] used biodegradable

matrices of polyglycolic acid (PGA) fibers, and seeded smooth muscle cells in tissue culture dishes (static seeding) and a cell suspension in spinner flasks (stirred seeding). They observed that seeding with dynamic model produced more uniform distribution and resulted in a neo-formed tissue with higher cellularity and greater elastin deposition. In the course of optimization of the tissue engineering methods, Qin *et al*[32] isolated intestinal smooth muscle cells from rats and seeded them in small intestinal submucosa (SIS) that is an acellular porcine-derived collagen-based matrix. SIS were implanted in an adult rat jejunal interposition model. Cell-seeded SIS displayed significantly improvement in contracting ability in respect to the SIS when no cells are seeded. However, there were no organized smooth muscle cell layers. Totonelli *et al*[33] and Maghsoudlou *et al*[34] used a detergent enzymatic treatment (DET) procedure to wash the cellular components of the rat's intestine and to construct a natural acellular intestinal scaffold for regeneration of new intestinal tissue. The yielded scaffolds preserved the native architecture and connective tissue components.

Nakase *et al*[35] used a mixture of autologous smooth muscle cells from the stomach wall of a canine model with collagen solution, which was poured into a sponge to develop a collagen scaffold. Then, these structures have been implanted into the isolated defects of ileum as a patch graft. After 12 wk, the patch turned into relatively well-developed regenerated epithelium, villi and a smooth muscle layer in the lamina propria, however, the lack of contraction of these grafts presented as a significant problem.

Autologous MSCs from bone marrow were used by Hori *et al*[24] and seeded onto collagen scaffolds to induce the regeneration of a muscular layer. One month after implantation, they observed regeneration of the intestine with a muscular layer at the reconstructed site by - smooth muscle actin positive cells; however, this layer was thin and disappeared by 16 wk.

To stimulate proliferation of smooth muscle layer and angiogenesis, Lee *et al*[36] used basic fibroblast growth factors (bFGF). They compared two different concentrations of local administration of bFGF with the control. They found that incorporation of bFGF into the collagen coating layer of scaffolds would result in a significantly higher density of cells and blood vessels. They also found that when the bFGF is incorporated in encapsulated poly D, L-lactic-co-glycolic acid microsphere, it is more effective than its simple employment in collagen scaffolds suggesting that the addition of specific growth factors improves scaffold performance.

Previously, Zakhem *et al*[37] utilized a composite chitosan/collagen scaffold three-dimensional matrix to support the smooth muscle cells to restore lost innervation. They grew the rabbit colonic circular smooth muscle cells (RCSMCs) on chitosan-coated plates with a ratio of 1:1 and observed that cells maintained their morphology and physiologic functionality over time. The muscle constructs contracted in response to acetylcholine and potassium chloride and they relaxed in response to vasoactive intestinal peptide. Furthermore, they showed that this scaffold supports neo-innervation of non-innervated smooth muscle cells[38].

In 2015, Zakhem *et al*[38] showed that neural progenitor cells derived from the appendix and small intestine, will differentiate into mature functional enteric neurons, should they be incorporated in bio-engineered internal anal sphincters. Raghavan *et al*[39,40] found that according to the extracellular matrix microenvironment of culture medium, enteric neuronal progenitor cells, will generate excitatory or inhibitory neuronal subtypes. Microenvironment enriched with collagen Ⅰ and laminin resulted in contraction pattern, collagen Ⅳ induced a nitrergic neuronal population (neurons where transmission is mediated by nitric oxide) and laminin and/or heparin sulfate resulted in a balanced expression of relaxant and contractile motor neurons.

ORGANOID UNITS ON BIO-SCAFFOLDS

Another approach to regenerate intestinal tissue employs the use of organoids. Haffen *et al*[41] in the 1980s, demonstrated that intestinal crypt cells require interacting with mesenchymal cells for survival, proliferation and differentiation. Then Organ *et al*[42] isolated progenitor cells from the intestinal crypt and seeded them onto sheets of polyglycolic acid. They observed generation of stratified epithelium suggestive of fetal intestinal development. Of the limitations of this technique was the absence of epithelial-mesenchymal cell-cell interaction, which is thought to be of importance in organogenesis. Subsequently, Tait *et al*[43] demonstrated that dissociated post-natal small intestinal epithelium of rats, will generate small intestine-like structures when transplanted in the subcutaneous plane of adult rats. They confirmed that those small aggregates of intestinal epithelium and stroma are able to generate the required signals for 3-D regeneration of intestinal tissue. Then Choi and Vacanti[44], developed a villus structure with a core of mesenchymal stromal cells overlaid with epithelium called "Organoid Unit". They believed that these units possess the epithelial-mesenchymal interaction required for mucosal regeneration. They seeded the organoid units isolated from neonatal rat intestine, and seeded them on poly glycolic acid scaffolds. They implanted them into the rats' omentum and observed that cysts were generated after 8 wk, composed of columnar epithelium, Paneth's cells, goblet cells, and crypt-villus-like structures.

To improve their previous work, Choi *et al*[45] later demonstrated that by collagen coating the scaffolds,

the cells engraftment will enhance significantly and cyst sizes will be larger. Since it was known that the small intestine is a dynamic organ and responds differently to various factors, Vacanti's lab, also investigated the effect of massive small bowel resections, partial hepatectomy and portocaval shunt on the development of organoid units. These interventions would increase the serum level of the epithelial growth factor (EGF) and hepatocyte growth factor (HGF). Interestingly, they observed that the length and diameter are larger and the villus numbers, height, area and mucosal surface are significantly greater in the group with resected small bowel[46]. As the next step, to evaluate the effect of incorporation of these organoid units in the intestine, they anastomosed the units side-to-side to the jejunum after three wk of implantation. They demonstrated that anastomosis had no complication. It also had trophic effects on the villus number, height, and surface length[47]. However, they also described a patchy distribution of the obtained neo mucosa[48].

Later, Grikscheit *et al*[49,50] adapted the organoid unit transplantation technique to develop tissue engineered colon. They produced organoid units from the rats' sigmoid colon and implanted them into the omentum. Then, these organoids were anastomosed to the ileum of the rats that previously underwent ileostomies. After 41 d, they found the rats had less stool transit time and moisture content. Histology also showed a normal large intestine architecture including epithelium, vasculature, ganglion cells, and muscularis propria.

To evaluate the function of the tissue engineered small intestine (TESI), Grikscheit *et al*[51] replaced small intestine with these TESIs. After development of TESIs, they anastomosed them side-to-side to the duodenum, when the rats had 95% of their small bowel resected. Forty days post operation, they found an appropriate architecture and a well formed muscularis mucosa with appropriately distributed Aurbach and Meissner's plexus and increased blood levels of B-12.

Following the successful results of TESI in rat model, Sala *et al*[52] transitioned this model in mice to take advantage of transgenic tools available in this species for studying the processes involved in formation of tissue engineered intestine. They found that TESI contains all four differentiated epithelial cell types present in the native small intestine including Goblet, Paneth, Enteroendocrine, and microvilli. They also confirmed that TESI contains innervated muscularis as well as presence of intact stem cell niche.

These investigators, also studied as a preclinical model an autologous-derived organoid unit transplantation in a large animal model. They generated organoid units from a short segment of jejunum of a swine model and implanted them onto omentum to the autologous host. They found that the TESIs replicated the native intestine with all epithelium, muscularis mucosa and stem cell niche[53].

Levin *et al*[54] investigated the possibility of development of organoid units from the postnatal human small intestine. They implanted organoid units, loaded on polyglycolic acid scaffolds in mice omentum. After 4 wk, they found all TESIs were of human origin with all differentiated cell types of mature human small intestine as well as muscularis and nerve tissue. This study was critical since the majority of the patients acquire the pathology after birth and the tissue engineering should be able to develop the tissues from post-natal stem cells. Then, recently they confirmed that both TESIs derived from human and mice developed intact epithelium with ultrastructural components of tight junctions, microvilli, ion transporter/channels, brush border enzymes similar to native tissue[55].

SCAFFOLDS

Observing the development of a neomucosa after patching the intestinal defects with abdominal wall or serosa of the adjacent colon, brought hope in using these methods for expanding the small bowel absorptive area[56-59]. Due to the limited availability of the tissues as well as anatomical restrictions, Thompson *et al*[60] investigated the outcome of the patching with prosthetic materials at 8 wk. They studied the outcome of patching the ileal defects of antimesenteric borders of rabbits' intestine by using a variety of prosthetic materials including knitted Dacron, PGA mesh and polytetrafluoroethylene (PTFE). They also performed an interposition in the distal ileum with a Dacron tube in another group of animals. They only observed development of thin neomucosa covering 15% of the defect with the patches and no neomucosa formation in interposition tubes. They concluded that the use of prosthetic material was not useful for clinical management of short bowel syndrome[60].

Biological Scaffolds derived from extracellular matrixes of different types of tissues are being applied in tissue engineering to replicate the organs both structurally and functionally. In intestinal tissue engineering, these biocompatible materials are thought to increase the intestinal mucosal surface area and absorption.

Chen *et al*[61] used scaffolds derived from submucosal extracellular matrix of porcine small intestine "small intestine submucosa" (SIS) to evaluate the regeneration of small bowel in dogs. SIS has been previously used to create vascular grafts, abdominal wall, bladder, tendons, and dura mater in animals[62-66]. They applied the SIS as a patch to repair a partial defect created in the small bowel wall. They observed development of mucosal epithelium, smooth muscles and serosa, however, the layers were not architecturally well organized. They also tried to interpose SIS as a tubular segment in the small intestine, which was unsuccessful and all animals died

postoperatively due to obstruction or leakage[61].

Then, Wang *et al*[67] interposed rat derived SIS between an isolated ileal loop in a rat model. They found development of a well-organized three-layer small intestine including mucosa, smooth muscle and serosa after 24 wk, however, there were no signs of innervation.

Another type of scaffolds applied is a collagen-rich membrane derived from submucosal layer of the pig's small intestine called "Surgisis". Since it is bio-compatible, resistant to infection and contains growth factors, it seemed prudent to use it as a bioscaffold for small intestine regeneration[68-74].

Cicalese *et al*[75] utilized an acellularized matrix of connective tissue obtained from the dermis of cadaveric donors to develop "acellular dermal matrix" (ADM) with preserved proteins of basement membrane, elastin and collagen fibers. We hypothesized that this matrix will be vascularized by host capillaries and stem cells either circulating or derived from the adjacent crypts would induce tissue regeneration. We implanted these ADMs into the rats' intestine either in continuity of the functioning bowel loops or as a blind-ended pouch in a defunctionalized jejunal limb. The blind-ended pouch group immediately showed full thickness ingrowth of capillaries, myofibroblasts and a fully regenerated mucosa at 6 mo. Despite the first group developing peritonitis in the first week without any signs of mucosa or muscular development, in subsequent studies, and using a ticker ADM placed immediately in continuity with the resected intestine, we were able to obtain successful generation of a neo-normal intestinal segment without obstructions or abscesses similar in morphology to the blind-end pouch group.

Similarly, Ansolani *et al*[74] utilized a three-centimeter long tubular Surgisis graft to interpose it in an isolated ileal loop in a rat model. After 24 wk, they found a neovascularized, well-developed layers of serosa, smooth muscle and mucosa. This biomaterial showed to offer a promising alternative in small intestine regeneration, however, the fact that it was not placed in continuity with the functional intestinal tract and there was no confirmation of absorption were the limiting factors.

Recently, we studied the function of such obtained bioengineered intestinal segment transplanting on the rats' proximal jejunum a Surgisis scaffold. Besides performing a detailed anatomic and functional evaluation, we measured the absorptive function of this neo intestine *in vivo*. The structural characteristics of the bio artificial intestinal segment was comparable to normal intestine while we also observed brush border development with preserved microvilli as well as the presence of water and ion transporter/channels. In order to unequivocally demonstrate absorption, the animals underwent to a laparotomy after 12 wk from the primary surgery. Upon isolated of the newly formed intestinal segment and its vascular pedicle, we evaluated the absorption of D-Xylose from that specific surface area alone, which confirmed comparable absorption with normal intestine[75]. These promising results providing absorptive functional evidence for the first time *in vivo,* offer the basis for investigation of this method in a large animal model and its possible rapid translation into the clinical settings.

FUTURE DIRECTIONS

Through the years, significant improvements have been made in the development of new methods to create neo-formed bioengineered intestinal tissue. In the last few years, we have assisted an increment of interest in the field. At this time, most of the proposed models described in the literature present several limitations to translate into human. The main limitations are due to the complexity of some models. For example, the need to perform multiple surgeries to re-implant in continuity with the intestine preformed omental organoids. Moreover, many of the methods described are still rudimental and do not offer a complete structure that can be used in a clinical application. Even more limiting, most methods do not offer evidence of *in vivo* absorptive function. We believe that constitute a minimum and fundamental requirement to embark in using any neo-formed bioengineered intestinal structure in a clinical setting to treat intestinal failure. On these bases, we believe that the simpler model that we have described and proven functional *in vivo* utilizing an acellular biologic scaffold placed immediately in continuity with the short intestinal segment appears to be more promising to translate into clinical application for patients with intestinal failure. With these new approaches, if proven successful in a preclinical model, a breakthrough could take place in development of bio-artificial organs.

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