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Stem cells and biopharmaceuticals: Vital roles in the growth of tissue-engineered small intestine

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ABSTRACT

Tissue engineering currently constitutes a complex, multidisciplinary field exploring ideal sources of cells in combination with scaffolds or delivery systems in order to form a new, functional organ to replace native organ lack or loss. Short bowel syndrome (SBS) is a life-threatening condition with high morbidity and mortality rates in children. Current therapeutic strategies consist of costly and risky allotransplants that demand lifelong immunosuppression. A promising alternative is the implantation of autologous organoid units (OU) to create a tissue-engineered small intestine (TESI). This strategy is proven to be stem cell and mesenchyme dependent. Intestinal stem cells (ISCs) are located at the base of the crypt and are responsible for repopulating the cycling mucosa up to the villus tip. The stem cell niche governs the biology of ISCs and, together with the rest of the epithelium, communicates with the underlying mesenchyme to sustain intestinal homeostasis. Biopharmaceuticals are broadly used in the clinic to activate or enhance known signaling pathways and may greatly contribute to the development of a full-thickness intestine by increasing mucosal surface area, improving blood supply, and determining stem cell fate. This review will focus on tissue engineering as a means of building the new small intestine, highlighting the importance of stem cells and recombinant peptide growth factors as biopharmaceuticals.
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Introduction

Organ failure may arise from congenital or acquired conditions and with enhanced care and increasing survival of premature infants may be an early life event. Tissue engineering has emerged within the field of regenerative medicine as a field focused on developing tissue and organ surrogates to restore, maintain, or improve biological functions.[1] The oldest example of tissue engineering is a passage from the book of Genesis in which woman is created from a rib taken from man.[2] The first report of an organ being actually transplanted dates back to the 1950s, consisting of a kidney transplant between identical twins.[3] Since then, this field has greatly matured, evolving from employing pre-existing organs to creating *de novo*, complex ones.

Due to its importance in providing the cellular and molecular building blocks for tissue growth and maintenance, the small intestine is a vital organ, especially in infants born with GI abnormalities or who undergo intestinal resection for various neonatal medical conditions. Loss of portions or the entirety of segments of the small intestine may lead to variable degrees of absorption debilities, such as short bowel syndrome (SBS) and ultimately to death. One of the main strategies to overcome loss of intestinal tissue is to increase the surface area in order to restore the absorption level to that of the healthy organ. An ideal therapeutic approach would eliminate drawbacks of current treatments, such as the need for immunosuppressive drugs and total parenteral nutrition (TPN), allowing a better quality of life, and a higher survival rate for patients.

Intestinal stem cells (ISCs) maintain the pool of precursor and differentiated cells of the dynamically proliferating intestinal epithelium. Differentiated cells are shed from the tip of the villi after a journey of 7–10 days from their production at the base of the crypt.[4] Preserving the intestinal stem cell niche with cells that produce important signaling proteins, along with the supporting mesenchyme, appears to be crucial for therapeutic approaches.[5]

Biopharmaceuticals are engineered biological molecules produced for therapy and/or diagnosis. They encompass hundreds of currently marketed products, ranging from nucleic acid sequences to complex proteins with post-translational modifications, such as growth factors, which control numerous cell and tissue processes. Several epithelial growth factors have proven to be important players in intestinal growth.[6] Every engineered organ requires

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vascular ingrowth in order to receive adequate nutrition and oxygenation, but sufficient vascularization is not frequently obtained. One of the main causes rests on the shortage of growth factors where they are most required.[7] Thus, local administration of growth factors that induce angiogenesis and other beneficial processes is logical and should be promising for the correct development and growth of organs in the context of regenerative medicine.

This review provides an overview on the advancements of tissue-engineered small intestine (TESI) research and the potentially vital combination of stem cells and biopharmaceuticals to improve the quality of life and life span of pediatric patients suffering from SBS.

Small intestine and short bowel syndrome

The small intestinal epithelium is composed of villi and crypts, which is a confluent sheet of specialized cells. Villi are luminal protrusions that increase surface area thousands of times for better absorption of carbohydrates, peptides and amino acids, lipids, vitamins, ions, and water. The absorptive capacity of the small intestine relies on enterocytes, the most abundant specialized cell type of the small intestine epithelium, bearing microvilli on their apical region and significantly increasing the intestinal surface. Goblet cells are distributed between enterocytes and secrete mucin, a family of O-glycosylated proteins, which are essential to secrete mucous and protect the luminal surface. Enteroendocrine cells release several peptide hormones that regulate satiety, energy and lipid metabolism, glucose homeostasis, and several other food ingestion-related metabolic functions. M (membranous or microfold) cells are present in close proximity to lymphoid follicles and participate in antigen-sampling.[8–11] Crypts are depressions found between the villi and are also found in the colon. The base of the crypts is occupied by Paneth cells, which secrete lysozyme and antimicrobial defensins and support the crypt base cell. Paneth cells are key to maintenance of the intestinal barrier that separates the lumen content from the sterile underlying mucosa in addition to supporting the $Lgr5^+$ intestinal stem cells (ISC) through an intimate association with these cells.[12] ISCs and progenitor cells are also found in the crypt and maintain the cell numbers of the dynamically renewing epithelium.[11,13] The surrounding mesenchyme ensures full function of the small intestine by signaling the epithelial stem cells and contributing vascular supply and an innervated muscularis for peristalsis.[14]

The onset of intestinal failure (IF) results from obstruction, dysmotility, surgical resection, congenital defect or disease-associated loss of absorption, characterized by the inability to maintain protein–energy, fluid, electrolyte, or micronutrient balance,[1] which may ultimately lead to death. Short bowel syndrome (SBS) is the most common type of IF, which was first reported in the late 1800s.[15] It is caused by intestinal loss or resection, which in the term infant is considered to occur if more than 50–75% of the small bowel is removed, with higher severity being associated with simultaneous resection of the ileocecal valve or, in addition, the colon.[11] The resulting shortened intestinal remnant leads to an inability to sustain homeostasis on a normal diet due to inadequate surface area for absorption, demanding additional nutrition supplementation via the parenteral route (PN).[15] The length of the remaining small intestine is highly associated with neonatal PN dependence even though longer bowel lengths sometimes do not correlate with weaning from PN.[16]

The multifactorial causes of pediatric SBS are not unique to a specific clinical setting or age group. Nonetheless, the main etiologies usually are necrotizing enterocolitis (NEC), intestinal atresia, inflammatory bowel disease, gastroschisis, and malrotation with volvulus. Postoperative SBS and malignancies, together with trauma and motility disorders, also gain importance in older children.[15,16] Accurate numbers of SBS cases in children are difficult to obtain, even though the incidence and prevalence of SBS in adults are estimated to be three and four per million, respectively.[16,17] Byrne et al.[18] estimated that approximately 10,000–20,000 patients received home-delivered total PN for SBS in the United States. A study in Canada involving 175 neonates admitted from 1997 to 1999 and followed up until 2001 estimated the incidence of SBS to be 24.5 per 100,000 live births, with a much higher incidence in infants born at less than 37 weeks.[19] A more recent study with infants born from January 1, 2002, through June 30, 2005, that comprised of a cohort of hospitalized neonates encompassing 16 tertiary care centers in the USA demonstrated an incidence of SBS between 0.7% and 1.1%, which correlated with birth weight.[20]

The mortality associated with SBS is seen not only in the early postoperative period, from complications associated with the underlying disease process and attendant surgery, but, also, in the long term, when patients succumb from the delayed complications of intestinal failure-associated liver disease (IFALD) and sepsis.[21] Sepsis in SBS is mainly caused by catheter-associated bloodstream infection (CABSI) and bacterial overgrowth can also affect up to 60% of children with SBS,[22] apart from the many complications which may arise from PN.[15] A large intestinal transplant center in the USA has reported a 5-year survival of 95% in SBS patients weaned from PN as opposed to 52% in patients remaining on PN.[16,23]

The remaining organ has an intrinsic adaptation in which the small intestinal epithelium partially compensates for the loss in absorptive surface through enhanced epithelial growth to maintain nutritional status.[15] Adaptation is a complex physiological response with several morphological and cellular changes to the intestinal mucosa, requiring exogenous assistance for improving patients' quality of life and survival rate. Several pharmacological and surgical approaches have been developed for the treatment of SBS.[24] One of the main therapeutic strategies consists of increasing the absorptive area, for which intestinal transplantation is a viable option, but one that may lead to graft rejection and lifelong use of immunosuppressive drugs, in addition to the problems of donor scarcity, high cost, and morbidity from surgery.[25–27] Conversely, techniques based on tissue engineering with intestinal stem cells and the regenerative capability of the intestine represent a great opportunity as potential alternative therapies for this syndrome.

Tissue-engineered small intestine

Early attempts based on serosal patching to increase the intestinal absorptive surface led to undesired physiological effects including decreases in intestinal remnant growth, villus height, body weight, and mucosal protein content. These changes resulted in overall impaired intestinal adaptation and absorption following massive enterectomy.[28,29] Seeding of conduits with isolated epithelial cells was unsuccessful due to limited growth.[30] Recent tactics to engineer the small intestine *in vitro* were successful but the surface area generated is not sufficient for human therapy and most in vitro approaches generate only intestinal epithelium without surrounding mesenchymal structures.

Salerno-Gonçalvez et al. created a system for generating organotypic human intestinal mucosa from fibroblasts, lymphocytes, epithelial cells, and endothelial cells in a 3D bioreactor under microgravity and in the presence of gelled collagen-1 mimicking extracellular matrix (ECM). Differentiated cell types and villus-like structures were obtained and function was confirmed by pathogen response. *Salmonella enterica* serovar Typhi was presented to epi-

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