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Review

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Tissue engineering and regenerative medicine approaches in colorectal surgery

Bigyan B. Mainali[1], James J. Yoo[2,3], Mitchell R. Ladd[1,2,3]

[1]Department of General Surgery, Atrium Health Wake Forest Baptist, Winston-Salem, NC, USA
[2]Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC, USA
[3]Department of Biomedical Engineering, Wake Forest University, Winston-Salem, NC, USA

Tissue engineering and regenerative medicine (TERM) is an emerging field that has provided new therapeutic opportunities by delivering innovative solutions. The development of nontraditional therapies for previously unsolvable diseases and conditions has brought hope and excitement to countless individuals globally. Many regenerative medicine therapies have been developed and delivered to patients clinically. The technology platforms developed in regenerative medicine have been expanded to various medical areas; however, their applications in colorectal surgery remain limited. Applying TERM technologies to engineer biological tissue and organ substitutes may address the current therapeutic challenges and overcome some complications in colorectal surgery, such as inflammatory bowel diseases, short bowel syndrome, and diseases of motility and neuromuscular function. This review provides a comprehensive overview of TERM applications in colorectal surgery, highlighting the current state of the art, including preclinical and clinical studies, current challenges, and future perspectives. This article synthesizes the latest findings, providing a valuable resource for clinicians and researchers aiming to integrate TERM into colorectal surgical practice.

Keywords: Tissue engineering; Regenerative medicine; Colorectal surgery

INTRODUCTION

Regenerative medicine encompasses a wide range of disciplines, including stem cell biology, biomedical engineering, biomaterials sciences, and gene therapy [1]. This field utilizes cells, biomaterials, and biological factors to develop therapeutic solutions to repair or replace damaged tissues and organs to restore normal function. The term "regenerative medicine" was coined and appeared in the literature as early as 1999; nonetheless, the field has existed for more than a century, with its history more closely intermingled with that of surgery than any other field in the health sciences [2, 3]. Early attempts at regenerative procedures, such as hip arthroplasty in the 1700s, underscore the long-standing interplay between regenerative efforts and surgical practice [4, 5].

Many regenerative medicine therapies have been developed and delivered to patients clinically. The technology platforms developed in regenerative medicine have been expanded to various medical areas; however, their applications in colorectal surgery are limited. Applying regenerative medicine technologies to engineer biological tissue and organ substitutes may address the current therapeutic challenges and overcome some complications in colorectal surgery, especially in inflammatory bowel diseases, short bowel syndrome (SBS), and diseases of motility and neuromuscular function [6]. To that end, this review provides an overview of

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Correspondence to: Mitchell R. Ladd, MD, PhD
Wake Forest Institute for Regenerative Medicine, 391 Technology Way, Winston-Salem, NC 27101, USA
Email: mrladd@wakehealth.edu

the technological platforms available for regenerative medicine, followed by tissue stem cell biology and tissue engineering approaches relevant to organs and their clinical applications. It also covers relevant surgical studies aiming to alter underlying pathophysiology and replace damaged organs, and discusses potential future outlooks in the field, including major hurdles for clinical translation [1, 5].

ESSENTIAL COMPONENTS OF REGENERATIVE MEDICINE

Regenerative medicine uses innovative technologies and tools, which can be employed alone or in concert, to develop therapies for repairing or replacing damaged tissues and organs. Thus, the strategies can range from using biomolecules or cells to promote regeneration through changing the environment to generating *ex vivo* tissue or organ constructs for subsequent implantation *in vivo*. These fundamental components include technologies using scaffolds, cells and/or organoids, and biomolecules (Fig. 1).

Scaffolds

In tissue engineering and regenerative medicine (TERM), scaffolds are the crucial building blocks that provide the necessary structural support for cell attachment, proliferation, and differentiation, mimicking the extracellular matrix (ECM) [7]. The materials from which these scaffolds are fabricated can range from natural biomaterials to synthetic polymers, depending on the physical and functional characteristics of target tissues and organs. Numerous scaffold design parameters must be considered, depending on the properties of the tissue or organ one is trying to engineer or regenerate (Fig. 2) [8]. For example, the preferred scaffolds for colorectal surgery applications may comprise degradable synthetic or naturally derived biomaterials that facilitate rapid tissue remodeling. These materials can be fabricated in various configurations to generate target tissue-like structures, such as sheets, tubes, or solid mass, to recapitulate the target tissue anatomy and function. Natural polymers such as collagen, hyaluronic acid, and chitosan have been widely used due to their biocompatibility and ability to promote cell adhesion, which is crucial for the regeneration of intestinal and colorectal tissues [9–27]. These materials are often combined with growth factors to enhance their regenerative potential. Synthetic polymers, such as polylactic acid, polyglycolic acid, polycaprolactone, and polyethylene glycol, offer controlled degradation rates and mechanical properties tailored to specific applications, such as intestinal anastomosis and rectal reconstruction. Composite materials combine natural and synthetic polymers and can optimize the mechanical properties and biological activity of scaffolds suitable for target tissue applications.

Cells and organoids

Cells are an essential component of tissue regeneration. Various cell types and sources, including autologous, allogeneic, and xenogeneic cells from preclinical and clinical sources, have been used

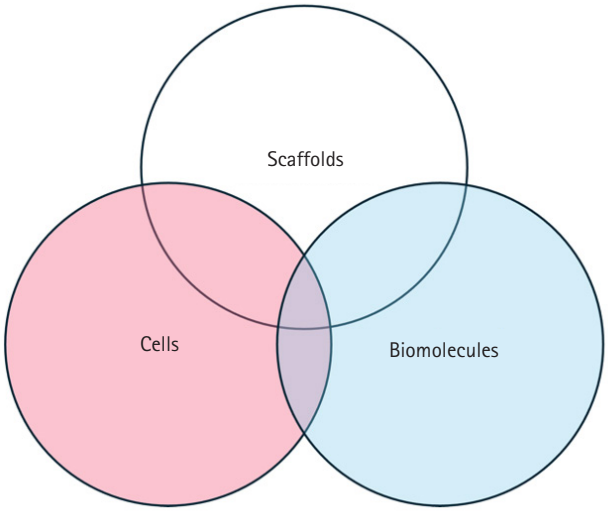

Fig. 1. Essential components of regenerative medicine. Tissue engineering and regenerative medicine is an exciting field that holds promise for colorectal surgery. The field makes use of scaffolds, cells, and biomolecules—alone or in combination—in order to restore tissue and organ function.

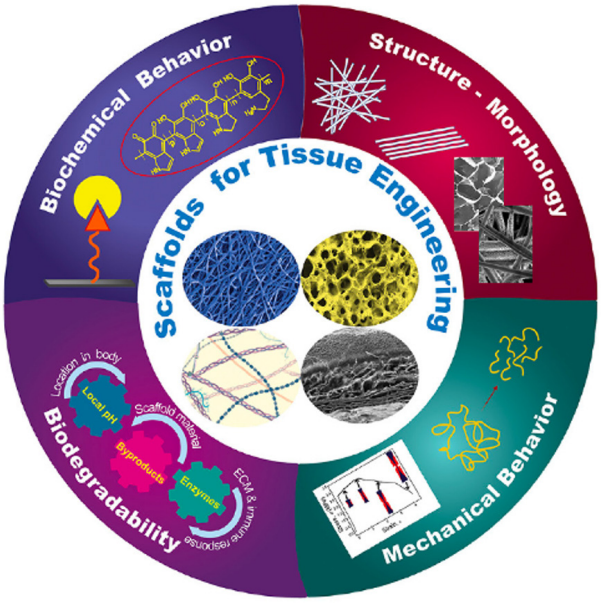

Fig. 2. Design parameters to consider when designing a scaffold for tissue engineering and regenerative medicine. Adapted from Echeverria et al. [8], available under the Creative Commons License.

in TERM research (Table 1). In addition to tissue and organ-derived somatic cells, stem cells have been used for many translational applications [28–39]. Stem cells have attracted significant interest due to their capacity to differentiate into diverse cell types and their regenerative potential [34–36, 39]. Embryonic stem cells (ESCs) are pluripotent cells derived from early-stage embryos, capable of differentiating into any cell type. However, their use is limited by ethical concerns and potential for teratoma formation [7]. Induced pluripotent stem cells (iPSCs) are generated by reprogramming somatic cells to a pluripotent state, offering an ethical alternative to ESCs with patient-specific applications. However, challenges remain in ensuring their safety and functionality. Adult stem cells include mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, and umbilical cord, which are known for their multipotency and immunomodulatory properties. MSCs are particularly valued for their versatility and application in various regenerative medicine approaches, due to their immunomodulatory effects and differentiation capabilities. Additionally, most adult tissues contain a population of progenitor cells (such as intestinal or colonic epithelial stem cells) that are capable of dividing and regenerating, to some extent, their tissue of origin. All these cell types have been employed in TERM for a range of applications, each offering specific advantages and disadvantages depending on the application.

Organoids are 3-dimensional (3D) cell cultures that essentially function as miniaturized versions of organs that replicate some of the structure and function of their full-sized counterparts. Organoids are often formed from ESCs, iPSCs, or adult stem cells under specific culture conditions that promote self-organization into organ-like structures. They exhibit cellular diversity and spatial organization similar to native organs, making them valuable for studying organ development and disease [40–45]. Organoids are used to model colorectal diseases such as cancer, inflammatory bowel disease (IBD), and congenital disorders, enabling the study of pathophysiology and drug responses in a controlled environment. Organoids derived from patient-specific cells can be used to test drug efficacy and toxicity, enabling personalized treatment approaches for colorectal diseases [46]. Organoids also hold potential for regenerative medicine, with ongoing research into their use for tissue repair, transplantation, and as cell building blocks for tissue engineering.

Biomolecules

Biomolecules play essential roles in modulating cellular activities and enhancing tissue regeneration. The biomolecules used in TERM include growth factors, cytokines, and extracellular vesicles [47–54]. Growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), have been used extensively. For example, VEGF stimulates the body to promote angiogenesis to enhance the neovascularization of engineered tissues for survival and maturation, and FGF has been used to support cell proliferation and differentiation in various tissues. Extracellular vesicles are exosomes and/or microvesicles secreted by cells into the extracellular environment. These vesicles can carry proteins, lipids, and RNAs, influencing a recipient cell's behavior and promoting tissue repair and regeneration [7]. Extracellular vesicles have been used in many tissue applications, including wound healing and IBD, and as delivery vehicles for therapeutic

Table 1. Cell sources in colorectal regenerative medicine with advantages and disadvantages

Cell	Advantage	Disadvantage
Embryonic stem cell	Self-renewing	Not autologous
	Can differentiate into all 3 germ layers	Forms tumors/teratomas when implanted
		Ethical concerns
Induced pluripotent stem cell	Self-renewing	Requires gene therapy to induce somatic cells to pluripotent cells; unclear what effects this may have on host organism
	Can differentiate into all 3 germ layers	
	Autologous	
	No major ethical concerns	
Adult stem cell	Autologous	Cannot differentiate into all germ layers
	Often secrete immunomodulatory factors (especially mesenchymal stem cells)	
	No major ethical concerns	
Progenitor cell (e.g., intestinal epithelium)	Autologous	Cannot differentiate into all germ layers
	No major ethical concerns	
Organoid	Provide 3-dimensional growth environment that more closely mimics *in vivo* conditions	Disadvantages depend on which cell type (from above) is used to make them
	Can be autologous	
	Can include multiple germ layers	

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agents for various disease processes.

These essential technological components constitute the foundation of most TERM therapies. Many TERM applications have been developed and benefited numerous patients in numerous medical areas; however, research on TERM in colorectal surgery is limited. This article provides an overview of the field's current state and how TERM technologies could be applied to colorectal diseases to develop innovative solutions for various colorectal diseases with limited treatment options, thereby improving patient care.

REGENERATIVE MEDICINE IN COLORECTAL SURGERY

While many colorectal diseases are treated with conventional medical and surgical approaches with satisfactory outcomes, some pathologic conditions present challenges requiring alternative therapeutic solutions. TERM technologies may provide opportunities to overcome the current treatment limitations and improve patient care. The platform technologies utilized in other tissue applications may be adapted to develop treatment modalities specific to diseases in the colorectal field, such as SBS, loss of colon/rectum, motility disorders, incontinence, IBD, and anorectal or rectovaginal fistulas (Table 2) [55–59].

SBS and tissue-engineered small intestine

SBS is a severe and debilitating condition that arises due to significant loss of the functional small intestine. This can be a consequence of congenital anomalies, extensive surgical resections for diseases such as necrotizing enterocolitis or Crohn disease, or traumatic injuries. Patients with SBS suffer from malabsorption, chronic diarrhea, malnutrition, and a heavy reliance on parenteral nutrition, which leads to a significantly compromised quality of life [60–62]. Moreover, long-term parenteral nutrition places pa-

Table 2. Summary of regenerative medicine applications in colorectal surgery

Clinical problem	Morbidity	Current solution	TERM solution
Intestinal failure	Sepsis/bacteremia	Total parenteral nutrition	Tissue-engineered small intestine
	Liver failure	GLP-2 analogs	
	Loss of central venous access	Serial transverse enteroplasty	
		Intestinal transplant	
Loss of colon	Diminished quality of life	Permanent colostomy or ileostomy	Tissue-engineered colon
	Electrolyte imbalances	Ileal pouch	
	Disrupted enterohepatic circulation		
Motility disorder	Chronic constipation	Resection of dysmotile bowel	Tissue-engineered intestine or colon
	Enterocolitis	Permanent ostomy proximal to dysmotile segment	Stem cell therapies to repopulate the enteric nervous system
	Intestinal failure	Cecostomy or Malone antegrade colonic enema tube	
Incontinence	Diminished quality of life	Neuromodulation [55]	Stem cell therapy
	Fecal soiling	Insertion devices [55]	Magnetic anal sphincter
		Sphincteroplasty	Tissue-engineered internal anal sphincter
		Muscle transfer [55]	
		Injection of bulking agents [56, 57]	
		Fecal diversion	
Inflammatory bowel disease	Fistula	Anti-inflammatory medicines	MSC therapy
	Stricture	Immunomodulatory biologic medications	Exosomal therapy
	Abscess/sepsis		
	Diarrhea		
	Intestinal failure/SBS		
Anorectal fistula/fissure	Pain	Fistulotomy	MSC therapy
	Fecal soiling	Ligation of internal fistula tract	Regenerative wound dressings with bioactive compounds
	Pelvic sepsis	Fissurectomy	
		Lateral internal sphincterotomy	
		TROPIS [58]	
		Cell-assisted lipotransfer [59]	

TERM, tissue engineering and regenerative medicine; GLP-2, glucagon-like peptide-2; SBS, short bowel syndrome; TROPIS, transanal opening of the intersphincteric space; MSC, mesenchymal stem cell.

tients at risk for numerous complications, such as sepsis, liver failure, and even death. Only select patients are candidates for bowel-lengthening surgery, and these generally provide only partial relief. Intestinal transplants have not been the cure they were hoped to be due to the high doses of immunosuppression required and the relatively poor overall and graft survival [63, 64]. As a result, tissue-engineered small intestine (TESI) has emerged as a promising therapeutic avenue [23, 65–71].

TESI represents an innovative approach in regenerative medicine aimed at creating functional intestinal tissue constructs *in vitro*, which can be transplanted into patients to restore intestinal function and improve nutrient absorption [6, 23, 26, 65–72]. The development of TESI involves using biodegradable scaffolds seeded with cells to form a bioengineered segment of the intestine that mimics the structure and function of the native bowel [23, 65, 68, 73–75]. Specifically, TESI must be capable of performing absorption and peristalsis to be clinically effective (Fig. 3) [13]. Cell sources have ranged from autologous progenitor cells such as intestinal epithelial stem cells to iPSCs and ESCs. Numerous scaffolds have been employed, such as nonwoven biodegradable materials (polyglycolic acid), polyglycerol sebacate, natural scaffolds (consisting of collagen and/or fibrin), decellularized material such as small intestinal submucosa, and even perfusion decellularized intestinal tissue [23, 24, 26, 46, 65, 66, 76–79]. These constructs are first implanted into the omentum to achieve an adequate vascular supply before being placed in continuity with the intestine. This method was first reported by Grikscheit et al. [73], who demonstrated the feasibility and efficacy of TESI in animal models using biodegradable scaffolds seeded with autologous cells to construct small intestine segments, which were then implanted into animals with massive small bowel resections. They observed significant improvements in nutrient absorption and reduced dependence on parenteral nutrition, highlighting the potential therapeutic benefits of TESI for SBS patients. Deguchi et al. [7] reviewed advancements in TESI for pediatric surgery, emphasizing its potential to provide long-term solutions for children with SBS. They discussed the critical factors for successful TESI, including scaffold design, cell sourcing, vascularization, and integration with host tissue, and highlighted the ongoing research aimed at overcoming existing challenges. Gardner-Thorpe et al. [75] investigated the angiogenic potential of TESI by characterizing the microvasculature and angiogenic growth factors in engineered small intestine segments. Their findings underscored the importance of angiogenesis for the success of TESI, particularly for ensuring adequate vascularization to support the survival and function of the transplanted tissue.

The integration of TESI in clinical practice for SBS patients holds significant promise. By providing a functional bioengineered intestinal segment, TESI could potentially overcome the limitations of current surgical treatments, reduce the complications associated with long-term parenteral nutrition, and improve the overall quality of life for patients with SBS. While clinically relevant TESI has eluded tissue engineers to date, much progress has been made, and with continued research, a translational solution may emerge. Ongoing research is essential to address the challenges related to scaffold materials, cell viability, and long-term functionality of the engineered intestine. The future of SBS treatment lies in the continued development and refinement of

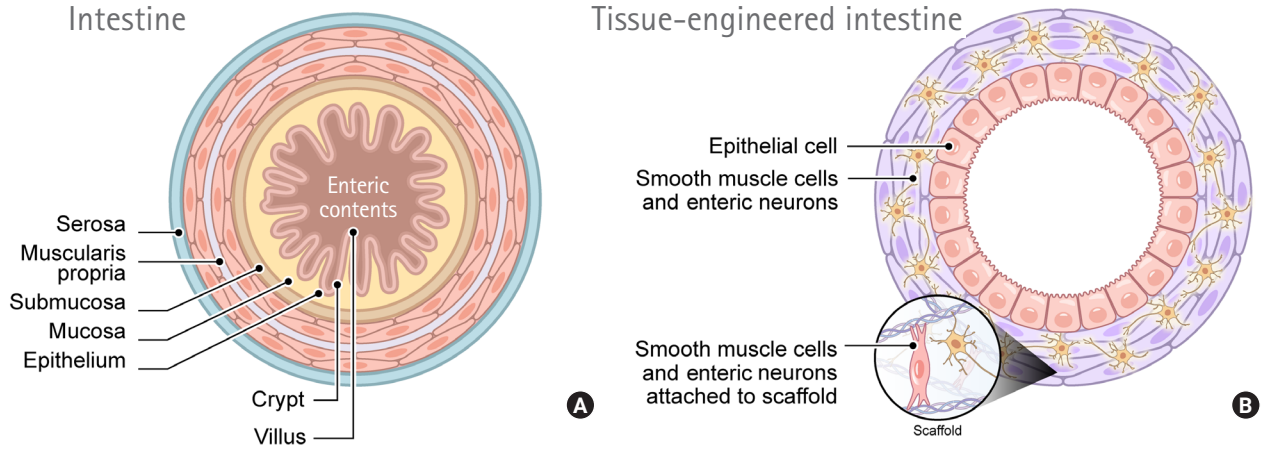

Fig. 3. (A) Native structure of the small intestine with its layers. (B) Goal of a tissue-engineered small intestine that accomplishes the minimum functions of absorption and peristalsis. The engineered intestine would consist of a scaffold containing smooth muscle cells and neuronal cells to promote peristalsis, with the inner layer lined with epithelial cells to promote absorption. Adapted from Boys et al. [13], available under the Creative Commons License.

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TESI technologies, which could ultimately lead to a curative approach to this challenging condition.

Loss of colon and tissue-engineered colon

Loss of the colon due to diseases such as IBD, colorectal cancer, or traumatic injury can lead to significant physiological disruptions, including issues with electrolyte balance, enterohepatic circulation, and water homeostasis, profoundly affecting patients' quality of life. Traditional surgical solutions, such as the creation of ileostomies, colostomies, or ileal pouches, often result in substantial lifestyle limitations and complications. Regenerative medicine, particularly through the development of tissue-engineered colon (TEC), offers innovative therapeutic approaches to address these challenges and restore normal function [9, 10, 80–82]. Admittedly, the clinical need for TEC revolves more around significant quality-of-life issues than around life-threatening problems. That is, often, patients who have colon resections for cancer or IBD can be managed reasonably well with ileostomies or colostomies. Because of this, there has been less work on TEC than on TESI.

TEC, like TESI, involves creating bioengineered colonic tissue constructs that can be surgically implanted into patients to replace lost or damaged sections of the colon [9, 10, 81–83]. This approach utilizes a scaffold seeded with cells to engineer tissue constructs that mimic the architecture and function of the native colon. Similar to TESI, scaffolds can be made from materials like polylactic acid and polycaprolactone or decellularized colon segments to provide structural support while allowing the gradual degradation of polymers or remodeling of tissue-derived decellularized colon segments as new tissue forms and integrates with native tissue. Intestinal stem cells and colonic organoid units are employed to regenerate the mucosal lining and create a functional colon [9, 10, 81, 82]. Trecartin and Grikscheit [84] emphasized the importance of stem and progenitor cells in tissue engineering for functional gastrointestinal regions, including the colon. They highlighted the critical factors in scaffold design, cell sourcing, and the role of progenitor cells in developing functional tissue constructs. For example, recent studies have discussed the importance of promoting angiogenesis to ensure the viability and functionality of the engineered colon tissue. Growth factors such as VEGF are being incorporated into scaffolds to promote vascularization.

Motility disorders

Motility disorders in the colon, including conditions such as Hirschsprung disease and functional intestinal motility disorders, present significant clinical challenges. These conditions often result in severe gastrointestinal dysfunction, impacting patients' quality of life. Traditional treatments, including surgical interventions and pharmacotherapy, often provide limited relief and are associated with various complications [85]. Regenerative medicine offers innovative therapeutic approaches to address these challenges and restore normal motility [81, 86–94].

The enteric nervous system (ENS) is a complex network of neurons and glial cells that regulate gastrointestinal motility, secretion, and blood flow. Disorders of the ENS, such as Hirschsprung disease, are characterized by the absence of ganglion cells in the distal bowel, leading to severe motility issues. Regenerative approaches aim to restore the functionality of the ENS through the use of stem cells and tissue engineering techniques [90]. Previous studies demonstrated the maintenance of intestinal smooth muscle cells by basic FGFs after implantation into the omentum, highlighting the potential for growth factors to support the restoration of motility [95, 96].

Stem cell therapy aims to repopulate aganglionic segments of the bowel with functional neurons, restoring normal motility. Stem and progenitor cells can be used to enhance neuronal density and functionality in affected bowel segments, improving motility and overall gastrointestinal function. ENS progenitor cells are necessary for re-establishing the ENS, which controls gut motility and function. This approach has shown promise in preclinical studies and is moving toward clinical applications [89, 97]. Recent studies have shown the successful differentiation of stem cells into functional neurons and their integration into the host ENS, improving motility in animal models [29]. Similarly, Pan et al. [86] demonstrated the successful transplantation of stem cells into animal models with motility disorders, showing improved gastrointestinal function. Despite many advances, hurdles remain before these therapies can be used clinically. For further detail, the reader is referred to the recent excellent review by Ohkura et al. [30], which describes the current state of the art, potential cell sources, and the challenges that still lie ahead.

Incontinence disorders

Incontinence, which can result from surgery, trauma, childbirth, or congenital conditions, poses significant challenges to patient quality of life and daily functioning. Traditional treatments, such as surgical repairs and pharmacotherapy, often provide limited relief and can be associated with complications. Newer therapies are emerging, such as injectable aluminum potassium sulfate and tannic acid as a bulking agent (for incontinence) and/or sclerotherapy (for rectal prolapse), and have shown reasonable results [56, 57]. The physiology of the internal and external anal sphincters and continence are complex. These mechanisms involve numerous biochemical pathways and reflexes to maintain resting pressure and to relax for defecation, which have been recently re-

viewed by Kim et al. [98]. Although regenerative medicine has developed new promising therapeutic approaches to restore continence via engineered anal sphincters and cell therapy, because of the immense complexity of the sphincter mechanism, much work remains to be done before these therapies will become viable clinical treatments.

The development of engineered anal sphincters involves creating bioengineered sphincter tissue that can be implanted to restore normal function. This approach again utilizes scaffolds seeded with smooth muscle cells and often neurons to replicate the structure and function of the native anal sphincter. Hecker et al. [22] developed a 3D physiological model of the internal anal sphincter bioengineered *in vitro* from isolated smooth muscle cells. That study demonstrated the potential for creating functional sphincter tissue that mimics the physiological properties of the native sphincter. Somara et al. [21] successfully bioengineered an internal anal sphincter derived from isolated human internal anal sphincter smooth muscle cells. Smooth muscle cells were isolated and cultured to populate the scaffolds, creating a tissue construct that replicated the function of the native sphincter. Their findings highlighted the feasibility of using patient-specific cells for creating functional anal sphincter constructs. Raghavan et al. [17] demonstrated the successful implantation of a physiologically functional bioengineered mouse internal anal sphincter, demonstrating the feasibility of restoring normal anal function *in vivo* with an engineered anal sphincter.

Another approach to restoring continence is the use of cell therapy. This method involves transplanting stem cells or progenitor cells to regenerate the internal anal sphincter and restore continence. The goal of cell therapy is to regenerate the smooth muscle of the internal anal sphincter, thereby restoring its tone and contractile function, which are crucial for continence. When successful, cell therapy facilitates the integration of new cells within the existing sphincter tissue, ensuring functional restoration. For a detailed review of the current state of cell therapy for treating incontinence, readers can refer to the comprehensive review by Balaphas et al. [99]. In short, numerous cell types have been used, ranging from skeletal and smooth muscle derivatives (depending on if the internal or external anal sphincter is being treated), stem cells (adipose-derived, mesenchymal, and bone-marrow-derived), and ENS progenitor cells. Some of these approaches have been used in clinical trials [99].

Inflammatory bowel disease

IBD presents significant therapeutic challenges due to its chronic, relapsing nature and the complex interplay of genetic, environmental, and immunological factors. Current treatments, including immunosuppressive agents and biologics, often provide incomplete relief and can have significant side effects. Regenerative medicine, particularly through cell and biomolecule therapy, offers innovative approaches to modulate the immune response, repair damaged tissues, and restore normal bowel function.

MSCs have shown particular promise in IBD due to their immunomodulatory properties and ability to differentiate into various cell types. MSCs modulate the immune response by secreting anti-inflammatory cytokines and growth factors, thereby reducing inflammation in the gut. MSCs can be administered intravenously, directly into the affected bowel segment, or encapsulated in biomaterials to enhance their viability and therapeutic efficacy. Ko et al. [31] reviewed the efficacy and safety of MSC therapy for IBD, highlighting their potential to alleviate inflammation and promote tissue regeneration. MSC therapy has shown promise in reducing inflammation and promoting perianal fistula healing, but the ability of MSCs to treat systemic Crohn disease is unclear, with mixed results.

Exosomes and other extracellular vesicles that carry bioactive molecules are also being investigated as potential immunomodulatory therapeutics for IBD [47]. Exosomes can contain numerous biologically active components and may derive from multiple cell types. For details, the reader is referred to the excellent review by Ocansey et al. [47]. Some of these exosome therapies have shown promise in reducing inflammation and promoting tissue repair in preclinical models of IBD [47].

Anorectal fistulas and fissures

Anorectal fistulas and fissures present significant therapeutic challenges due to their chronic nature and the complexity of the affected tissues. Traditional surgical approaches, while often necessary, can be associated with high recurrence rates and significant morbidity. Newer surgical techniques have been developed, including cell-assisted lipotransfer and the transanal opening of the intersphincteric space, and these techniques have demonstrated promising results [58, 59]. In addition, regenerative medicine offers promising new approaches, mainly through cell therapy and regenerative wound dressings, gels, and matrices, to enhance healing and reduce recurrence.

MSCs, in particular, have shown promise due to their anti-inflammatory properties and ability to differentiate into various cell types. Cell therapy has been effective in promoting the healing of perianal fistulas associated with Crohn disease (as described above), showing reduced recurrence rates and improved quality of life. MSCs have shown potential in treating chronic anal fissures that do not respond to conventional treatments. MSCs modulate the immune response by secreting anti-inflammatory

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cytokines, reducing inflammation at the site of the fistula or fissure. García-Olmo et al. [100] reported the successful use of autologous stem cell transplantation for treating rectovaginal fistulas in patients with perianal Crohn disease. This pioneering study demonstrated the potential of cell-based therapies to promote healing in complex anorectal conditions. Panés et al. [101] conducted a long-term study on the efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in Crohn disease patients, showing promising results for sustained fistula closure and reduced recurrence. Lastly, recent studies have demonstrated the effectiveness of adipose-derived MSCs—a readily available and potent source of stem cells— in treating complex perianal fistulas [32]. For a recent detailed review of cell therapies used in treating perianal and rectovaginal fistulas, the reader is directed to the superb review by Kent et al. [102].

Regenerative wound dressings, gels, and matrices are designed to create an optimal environment for healing by providing structural support, promoting cell migration, and delivering bioactive molecules. Wound dressings can be impregnated with growth factors, cytokines, and other bioactive molecules to promote tissue regeneration and reduce inflammation. Scaffolds and matrices provide a framework for cell attachment and proliferation, facilitating the regeneration of the damaged tissue. Lastly, these materials can promote wound healing by maintaining a moist environment, protecting the wound from infection, and reducing mechanical stress. Regenerative wound dressings can be used in conjunction with surgical procedures to promote healing and reduce the risk of recurrence. Bioactive gels and matrices can accelerate the healing of chronic anal fissures, improving patient outcomes and comfort. Finally, the use of fibrin glue in combination with cell therapy has shown synergistic effects, enhancing the overall healing process and reducing recovery time [103].

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

TERM is an emerging field that has led to new therapeutic opportunities by delivering innovative solutions. The development of nontraditional therapies for previously unsolvable diseases and conditions has brought hope and excitement to countless individuals globally. Despite the promise and potential of TERM, many scientific and technological challenges must be overcome before translation into the clinic. Here, we discuss these hurdles as well as the exciting prospects of TERM in colorectal surgery.

Biomaterial scaffolds

Tissues and organs are 3D structures, and as such, 3D scaffolds are needed to recreate them. While there are innumerable biomaterials, fabrication techniques, and methods for developing scaffolds, finding the ideal scaffold to provide the appropriate environment for the engineered tissue construct remains paramount. It is unlikely that a single scaffold will be suitable for all applications; thus, a scaffold often needs to be designed for each tissue application based on the tissue anatomy, characteristics, and function. For example, it is unlikely that a scaffold for colon tissue engineering would work well for engineering an anal sphincter and vice versa. Specifically, the scaffold should recapitulate the complex microarchitecture of the colorectal tissue, including the mucosal layer, submucosa, muscularis propria, and serosa. While an in-depth discussion of scaffolds for tissue engineering is outside the scope of this review, it is worth noting the general categories that scaffolds fall into [7].

The biomaterials used for scaffolds can be permanent or biodegradable, however, the majority used in regenerative medicine for colorectal surgery are degradable. Secondly, these materials can be synthetic (e.g., polylactic acid, commonly used in Vicryl sutures) or naturally derived (such as type I collagen). Synthetic polymers are easier to control, but natural materials may be more similar to the native environment the scaffolds try to recapitulate. Synthetic polymers may lack bioactivity, while natural polymers can have the disadvantage of poor mechanical strength and variability. Identifying materials that are biocompatible, biodegradable, and possess the mechanical properties needed to mimic native tissue is challenging.

Another type of scaffold is a decellularized scaffold where all the cells of the tissue of interest (e.g., a segment of the colon) are removed while preserving the native tissue ECM. This type of scaffold has the advantage of retaining the correct 3D structure as well as many of the environmental cues contained within the ECM [104]. Moreover, decellularization often results in a scaffold that could be surgically implanted. The ECM could be configured into a hydrogel for injection therapy or bioink that could be printed to generate an implantable tissue construct. Advanced 3D printing technologies offer precise control over scaffold architecture and composition, enabling the creation of patient-specific scaffolds, but these too can suffer from adequate mechanical strength [105]. Although numerous scaffold types and configuration options exist, there is no ideal scaffold for all applications. Instead, one must weigh the advantages and disadvantages of each material, scaffold fabrication technique, and scaffold size based on the organ or tissue to be regenerated.

Cell source

As with scaffolds, selecting the proper cell type and source is criti-

cal for the success of regenerative medicine, as each has advantages and disadvantages. Depending on the target tissue and expected function, various cell sources and types are considered. While stem cells are attractive as a cell source for regenerative medicine due to their ability to differentiate into multiple cell types, limitations such as consistency in differentiation into the target lineage, the large expansion capacity of terminal cell types, cell banking, and biomanufacturing processes remain to be solved. Unlike ESCs, iPSCs are recognized as an attractive cell source because they contain the pluripotent potential of ESCs but can be made from a person's own somatic cells. However, the reprogramming process remains complex, and there are concerns about genetic stability and tumorigenicity (a tendency to form teratomas) [106]. Despite this, if large-scale production becomes available, iPSCs will likely be used for many colorectal disease applications, especially those requiring all 3 germ layers.

Adult stem or progenitor cells are another potential cell source for colorectal tissue engineering; however, these cells are typically limited to one germ layer. For example, colon epithelial organoids can be created from colon epithelial stem cells; however, they can only form the endodermal layer. Thus, to recreate an entire colonic tissue, one would need progenitor cells from each tissue. This may be possible in some cases, but often, depending on the tissue type, adults may not harbor enough progenitor cells for this to be practical. Harvesting these cells from patients can also be invasive and yield insufficient quantities for therapeutic use [107]. As noted above, no perfect cell source exists that could be used universally. In addition to acquiring a reliable cell source, another consideration is cellular function. For regenerative medicine therapy targeted at mitigating inflammatory conditions (such as IBD) or promoting healing, autologous MSCs may be a good source. These cells release significant levels of anti-inflammatory mediators, which may promote healing and regeneration [33]. Therefore, it is critical to identify an ideal cell source that provides sufficient numbers of reliable and functional cells for the target applications. Due to the challenges in procuring a reliable and reproducible cell source, investigations have been pursued to develop and establish a universal donor cell manufacturing and banking system that could be used for multiple tissue applications.

Vascularization of tissue constructs

Establishing adequate vascularization to implanted engineered tissue constructs has been an unsolved challenge in TERM. Since its inception, tissue engineering has been plagued by the problem of delivering oxygen and nutrients to implanted cells within the construct. The diffusion of oxygen to implants is limited to approximately 1 mm^3 without established vascularization. Numerous strategies have been employed to encourage vascularization. The earliest attempts were to place constructs in the omentum of animals [9, 10, 75, 108]. Other strategies have included the use of growth factors such as VEGF and, more recently, bioprinting to directly incorporate vascularization within a construct [109, 110]. While promoting angiogenesis (the growth of new blood vessels from existing ones) is crucial, creating a fully functional vascular network within the construct is more complex. One promising strategy involves using decellularized tissue and organ scaffolds that retain the microarchitecture of native tissue structure with intact vasculature, identical to normal tissue anatomy [24, 26, 104]. The decellularized tissue vasculature can then be recellularized with vascular endothelial cells to the vascular wall, allowing blood to perfuse without forming thrombi. More recently, perfusable tissue constructs containing a network of vascular channels have been bioprinted for eventual surgical implantation [111, 112]. Future work will need to continue incorporating ready-made vasculature for the desired tissue constructs so that tissues of a clinically relevant size can be engineered. Without tissues of a clinically relevant size, these therapies will have minimal benefit for patients and, as will be noted in the next section, will be difficult to implant surgically. Finally, for the long-term success of engineered tissues, engineered vascular networks must support the growth and maintenance of the engineered tissue and its vascular network while integrating seamlessly with the host's circulatory system.

Scale/manufacturing

Developing a clinically relevant tissue construct for clinical use requires scale-up and streamlined manufacturing processes. This involves producing an immense number of target cells—on the order of billions—making the selection of cell sources critically important. Careful considerations related to cell isolation, expansion, and differentiation must be made to maximize the production of target cells. Scaffold fabrication and preparation protocols must be developed and validated before creating a cell-seeded construct. In addition to scale-up in size and volume, all these technologies will require consistent and safe manufacturing. While this has historically been a relatively straightforward process for devices and materials, regenerative medicine technologies involving cells and biological factors combined with biomaterials increase the complexity of safely manufacturing tissue implants by several orders of magnitude. For this reason, scale-up and biomanufacturing have been identified as challenges that need to be addressed to accelerate the distribution of TERM therapies. Toward this goal, several societies have been founded to help explore and improve the technologies required for efficient and safe man-

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ufacturing of regenerative medicine technologies. For example, the Regenerative Medicine Manufacturing Society was formed to help address many of these issues and to develop pathways for US Food and Drug Administration (FDA) approval of regenerative medicine therapies [113]. However, navigating the regulatory landscape for the approval of complex tissue-engineered products can also be time-consuming and costly.

CONCLUSION

TERM is an exciting field with great potential to treat diseases in colorectal surgery. The essential technological components of regenerative medicine, i.e., scaffolds, cells, and biomolecules, are used alone or in combination, depending on the application for which they are being used. While many developing therapeutic applications are still in the preclinical investigative stages, some cell therapies are being clinically tested, including IBD, incontinence, and healing perianal and rectovaginal fistulas. Despite the advances made over the past 2 decades, many scientific and technological challenges remain in advancing these therapies to clinical trials and developing safe and efficient ways to manufacture these technologies once they are approved for use by the FDA.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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