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Review Article

Rebuilding the Barrier: Peptide-Based Strategies for Intestinal Regeneration

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Abstract

The gastrointestinal (GI) tract is a dynamic organ system with remarkable regenerative capabilities; however, repeated or severe injury, due to inflammatory bowel disease, cytotoxic therapies, ischemia, or surgery can overwhelm intrinsic healing mechanisms. Peptide-based therapies have emerged as a promising modality in regenerative gastroenterology, leveraging the bioactivity and specificity of short amino acid chains to modulate key cellular and molecular pathways. Therapeutic peptides promote epithelial proliferation, preserve barrier integrity, modulate inflammation, stimulate angiogenesis, and prevent apoptosis, thus fostering a coordinated environment for mucosal repair. Several peptides also influence the gut microbiome and enhance host-microbial interactions critical to tissue homeostasis. Clinical translation is accelerating, with ongoing trials evaluating agents (e.g., GLP-1/GLP-2 analogues). However, novel formulations such as organ-specific Nano Organo Peptides (NOPs) and Mito Organelles (MO) peptides show promise in enhancing mitochondrial function and tissue-specific repair, offering an alternative to traditional pharmacologic therapies. Advances in proteomic techniques, including MALDI-TOF mass spectrometry, have enabled precise characterization of peptide formulations, revealing heterogeneity and guiding future standardization efforts. Despite these advances, challenges such as peptide instability, immunogenicity, and high production costs remain. Cutting-edge strategies including nanoparticle delivery, microbiome synergy, and precision medicine approaches aim to address these limitations. As the field evolves, peptide therapies are poised to become central to gut regenerative strategies, combining biological precision with therapeutic flexibility to address unmet needs in GI care. This review outlines the current landscape, innovations, and future directions of peptide-based therapeutics in gastrointestinal regeneration.

Keywords: Gastrointestinal tract dysfunction, Gut injury, GI inflammation, GI regeneration

Introduction

The gastrointestinal (GI) tract serves as a critical interface between the external environment and the internal milieu, playing essential roles in digestion, immunity, and barrier protection. Damage to the gut mucosa can severely disrupt these functions, leading to significant morbidity and mortality [1]. Common causes of gut injury include chronic inflammatory conditions such as inflammatory bowel disease (IBD), cytotoxic therapies like chemotherapy and radiation, infectious enteritis, ischemic insults from vascular compromise, and surgical interventions that disrupt intestinal integrity [2]. These injuries can compromise the epithelial barrier, alter microbiota composition, and provoke a cycle of chronic inflammation and tissue remodeling [3].

Despite the inherent regenerative capabilities of the GI tract, challenges in gut healing and regeneration persist, particularly in the setting of repeated or extensive injury [4]. Healing requires a highly coordinated interplay of epithelial cell proliferation, migra-

tion, and differentiation, along with immune modulation, angiogenesis, and extracellular matrix remodeling [5]. Factors such as persistent inflammation, microbial dysbiosis, fibrosis, and impaired stem cell function can impede the regenerative process. Clinically, inadequate gut healing manifests as chronic diarrhea, malabsorption, sepsis, strictures, or intestinal failure, significantly impacting quality of life and healthcare outcomes.

In this context, the emerging role of peptide-based therapies offers new hope for enhancing gut regeneration. Peptides, short chains of amino acids that can mimic natural signaling molecules, are uniquely positioned to promote mucosal healing by stimulating epithelial growth, restoring barrier function, modulating inflammation, and enhancing vascular repair. Therapeutic peptide are currently under active investigation, with promising preclinical and early clinical results. As understanding of gut biology deepens, peptide-based strategies are poised to become integral components of regenerative medicine approaches aimed at restoring intestinal structure and function after injury.

The GI tract possesses remarkable regenerative capacity, necessary to maintain its integrity against constant mechanical, chemical, and microbial challenges [6]. Gut healing following injury proceeds through a highly coordinated, dynamic sequence of phases: inflammation, proliferation, and remodeling [7].

i. The initial inflammatory phase is triggered immediately after mucosal injury, characterized by the recruitment of immune cells such as neutrophils, macrophages, and lymphocytes. These cells release cytokines and chemokines that orchestrate debris clearance and prime the tissue for repair. This phase also involves the activation of resident immune cells and the modulation of the gut microbiota, both crucial for regulating the inflammatory response [8].

ii. During the proliferative phase, intestinal epithelial cells at the margins of injury migrate and proliferate to reseal the mucosal barrier. Intestinal stem cells (ISCs), residing in the crypt base, are critical for replenishing lost epithelial lineages. Concurrently, fibroblasts deposit provisional extracellular matrix, endothelial cells promote neovascularization, and immune cells secrete growth factors that support tissue regrowth [9].

iii. The final remodeling phase restores tissue architecture and function. Fibroblasts and myofibroblasts reorganize the extracellular matrix, while endothelial cells mature the newly formed vasculature. Proper resolution of inflammation and restoration of epithelial diversity are essential to prevent fibrosis and chronic dysfunction.

A myriad of cellular players are integral in the three phases. For example, epithelial cells rapidly migrate and proliferate to restore barrier function. Fibroblasts and myofibroblasts produce matrix components and modulate the healing environment. In turn, endothelial cells promote angiogenesis, ensuring oxygen and nutrient delivery. The interplay of immunomodulation is essential. Immune cells fine-tune inflammation and tissue remodeling with significant interactions with gut microbiota. The gut microbiome responds to and induces response from host cells to influence immune responses, epithelial regeneration, and metabolic signaling. Critical to successful regeneration is the activation of signaling pathways that regulate ISC behavior and epithelial renewal. Further, Wnt signaling drives ISC proliferation and maintenance, whereas notch signaling governs the differentiation of epithelial progenitors into absorptive and secretory lineages. Growth factors such as transforming Growth Factor-β (TGF-β) [10,11] and epidermal Growth Factor (EGF) modulates immune responses and fibrosis during the remodeling phase and stimulates epithelial proliferation and migration during repair, respectively [12]. Collectively, these orchestrated cellular and molecular processes enable the gut to efficiently heal after injury. Dysregulation of any component can impair regeneration, leading to chronic inflammation, fibrosis, or tissue breakdown, highlighting the need for therapeutic strategies that can support and enhance these natural healing pathways.

The Emerging Role of Peptide-based Therapies

Peptide-based therapies have emerged as promising tools in regenerative medicine, particularly for promoting gut healing following injury [13]. Short chains of amino acids with diverse biological activities, therapeutic peptides can precisely target key pathways involved in tissue repair, offering advantages in specificity, bioavailability, and safety compared to larger biologic agents or small-molecule drugs [14]. A principal mechanism by which peptides facilitate gut regeneration is by stimulating epithelial proliferation and migration. Maintaining tight junction integrity is also essential for preserving the gut's selective permeability and defense against luminal pathogens. Certain peptides enhance the expression and assembly of tight junction proteins, thereby reinforcing barrier function and preventing secondary infections or chronic inflammation. The modulation of inflammation is another critical action of regenerative peptides. Anti-inflammatory peptides can suppress excessive cytokine production while promoting the release of pro-repair factors, creating a controlled inflammatory environment that supports rather than impedes healing [13]. Peptides also contribute to angiogenesis, essential for restoring oxygen and nutrient supply to regenerating tissues. Pro-angiogenic peptides upregulate vascular endothelial growth factor (VEGF) signaling, stimulating the formation of new capillaries within damaged gut tissue. The anti-apoptotic effect on enterocytes, by which peptides can inhibit pro-apoptotic pathways and enhance cell survival under stress conditions such as ischemia, inflammation, or oxidative damage, preserving the epithelial cell pool needed are also requisite for effective regeneration [15]. Finally, emerging evidence suggests that peptides can influence the gut microbiome, fostering a microbial environment conducive to healing. Certain antimicrobial peptides selectively modulate bacterial populations, enhancing the growth of beneficial commensals while suppressing pathogens that exacerbate injury and inflammation [13].

Clinical Research Landscape

The first gastrointestinal peptides discovered were gastrin and cholecystokinin [16]. They are commonly involved in digestive processes, including gastric acid secretion, pancreatic enzyme release, gallbladder motion, gut motility, and energy homeostasis. Gastrin and its receptor, cholecystokinin 2 receptor (CCK2R), are highly and widely expressed in the heart [17]. Recently, the trophic actions of gastrin were demonstrated by a sequence of in vivo studies. One previous study showed that a synergistic interaction between renal CCK2R and D1-like dopamine receptors is crucial in maintaining normal blood pressure [6]. Plasma gastrin concentration is associated with low cardiovascular mortality risk, the opposite of that found with plasma cholecystokinin level [18].

To date, there are several on-going and completed trials that aim or have aimed to leverage the unique ability of to modulate physiological processes, offering targeted treatment options. For example, an ongoing study is evaluating the combined effect of diet and tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, in patients with Crohn's disease who have a body mass index (BMI) of at least 27 is assessing improvements in disease activity and weight management with tirzepatide treatment [19]. The synthetic ghrelin receptor agonist Relamorelin (RM-131) has undergone Phase II clinical trials for diabetic gastroparesis and chronic constipation. Relamorelin aims to enhance gastric motility and alleviate symptoms associated with delayed gastric emptying [20]. Originally investigated for pulmonary conditions, aviptadil, a synthetic vasoactive intestinal peptide (VIP) analogue, has completed Phase III trials for COVID-19 treatment. Its potential applications in GI disorders are under exploration due to its anti-inflammatory properties [21]. The investigational GLP-2 analogue, Apraglutide, is being studied for short bowel syndrome with intestinal failure (SBS-IF). Clinical trials aim to assess its efficacy in enhancing intestinal absorption and reducing the need for parenteral support. Further, research suggests that peptide YY (PYY) or its analogues could be beneficial in treating intestinal malabsorption disorders or conditions following bowel resection. However, clinical trials evaluating therapeutic potential and safety profiles have not yet begun [22]. Beyond their established roles in diabetes and obesity management, GLP-1 receptor agonists are being investigated for their anti-inflammatory properties. Emerging research suggests potential benefits in conditions such as heart disease, kidney disease, and neurodegenerative disorders, with implications for GI inflammation. While these clinical trials reflect the expanding scope of peptide therapies in gastroenterology, aiming to provide more targeted and effective treatments for various GI conditions, the content of peptides is similar between cells, the function and morphology of each cell defines the contents of its biologically active substances and unique ultrastructures. Moreover, certain biologically active substances are predominantly synthesized or accumulated in specific tissues. Since the signaling activity and function of peptides is largely based on the cell type, peptide therapy utilizes organ-specific extracts to target diseased GI tissue.

The capacity of peptides as critical mediators of communication between cells and tissues has rapidly advanced therapeutic treatment, but their structural complexity and organ/tissue specificity have posed challenges for medical understanding. Some peptides exert localized or systemic anti-inflammatory and regenerative effects by binding to organ- or tissue-specific receptors, while others, as some of the aforementioned act broadly across multiple tissues. Indeed, peptides perform diverse functions, relaying information, modulating metabolism, regulating inflammation, and serving as biomarkers, highlighting their essential roles in tissue regeneration, immune response, and GI processes. Proteomic studies have detected the expression of over 150 distinct mature peptides. Through years of research and extensive global practice, MF-Plus has manufactured two products, Nano Organo Peptides (NOPs) and Mito Organelles (MO) Peptides, which are intended for use in both animals and humans as a revitalization therapy. Mito Organo (MO) peptides are biologically extracted mixtures of cellular peptides that have predominantly mitochondria-specific functions [23]. Although cells of different organ systems have similar functions, variations in cellular functions between organs create the differential expression of peptides, which can be utilized for various therapeutic purposes. MO peptides are organ-specific extracts that are aimed at revitalizing and rejuvenating mitochondrial activity, thereby regenerating cells and organisms as a whole [12,13]. Recently, MF-Plus manufactured and tested heart-oriented NOP for cardiac patients. The NOPs are organ-specific, thus making it possible to choose the range of the NOP needed for a particular patient. It could be injected intramuscularly and via noninvasive routes (sublingual, intranasal).

Analogously, just as non-cardiac organs also secrete cardiotropic peptides, non-GI organs also secrete gastrointestinal-tropic peptides. As successfully implemented in cardiac patients, combinations of the NOP taken from the intestine, kidneys and endothelial cells can be leveraged to regenerate the damaged GI tract, playing an essential role in gut regeneration. The various cells throughout the gastrointestinal tract are highly dependent upon mitochondrial biogenesis. Chronic GI conditions induce mitochondrial dysfunction, which in turn promotes ROS activation, peptide malfunction, cell damage and apoptosis. Together with a nucleus, mitochondria contain genetic information. In human cells, mitochondria are the only organelles containing DNA besides the nucleus. Mitochondrial DNA (mtDNA) comprises 37 genes, 13 of which encode proteins, and the remaining genes encode RNA molecules involved in the translation of proteins. The number of peptides and polypeptides encoded by mtDNA is very small compared to that encoded by nuclear DNA. Therefore, mtDNA and mitochondria are vital for proper cellular function. Mitochondrial RNA contains information about the organ-specific peptides secreted by enterocytes, gastric secretory cells, endothelial cells, etc. Therefore, restoration of MO peptides represents an emerging therapy in bioregenerative gastroenterology.

Yet, little is known of the exact makeup of these formulations. Matrix-assisted laser desorption/ionization time of flight (MAL-

DI-ToF) mass spectrometry has been able to identify and quantify analytes in complex solutions and allows for highly sensitive, fast and high-throughput analysis [24,25].

By comparing experimental MS data with that of well-established open-source databases, a determination can be made of the proposed identity of the molecules, peptides, or proteins found within a solution. Due to the low-cost and rapid application of MS in identifying the components of unknown solutions, our study employed MS as our primary method of identification [26]. Although our preliminary data relied upon LC-MS/MS based peptide sequencing techniques to produce chromatograms and deconvolute our data MALDI-TOF utilizes a protein fingerprinting method in which the sample is digested by a proteolytic enzyme such as trypsin and used to generate an MS spectrum that can be searched against existing databases [27]. Matched hits are ranked according to a scoring method in which the candidate protein that contains more proteolytic peptides has a higher score and generally represents the most probable protein/peptide. The desirability of MALDI-TOF also includes the speed at which each run is performed– often less than one minute to obtain– and the speed at which analysis can be performed against a database. Following deconvolution, five peptides were identified in Batch 1 with masses of 14,969 Da, 15,300 Da, 8,449 Da, 8,294 Da and 4,618 Da. Batch 2 identified four of the same peptides– 14,969 Da, 15,301 Da, 8,294 Da, 8,449 Da in size– and two additional peptides of 5,436 Da, and 6,214 Da in size. Slight differences in peptide products between batches is likely due to the heterogeneous nature of cellularly-derived solutions and differences that occurred during the extraction process.

Trends, Innovations, Challenges and Limitations

Recent trends in peptide therapy for gut regeneration reflect a surge of innovation aimed at enhancing efficacy, targeting, and patient outcomes. Advanced formulation strategies, such as oral, enteric-coated, and nanoparticle-based delivery systems, are being developed to protect peptides from degradation in the harsh gastrointestinal environment and ensure targeted release at sites of injury. Combination therapies, particularly those pairing peptides with microbiome interventions, are gaining attention for their synergistic effects on mucosal healing and immune modulation. Meanwhile, peptide engineering is focused on designing molecules with prolonged half-lives and enhanced receptor specificity, addressing the traditional limitations of rapid degradation and off-target effects. Emerging personalized medicine approaches aim to tailor peptide therapies based on an individual's gut microbiome composition or genetic profile, optimizing therapeutic responses and minimizing adverse effects.

However, despite these advances, several challenges and limitations remain. The stability and bioavailability of peptides in the gut environment continue to be significant hurdles, often necessitating sophisticated delivery technologies. There is also concern regarding the potential for immunogenicity, where therapeutic peptides may inadvertently trigger immune responses. Additionally, the high cost of peptide synthesis and therapy poses economic barriers to widespread clinical adoption. Finally, there is a pressing need for robust, validated biomarkers to reliably assess gut healing responses in clinical trials and practice, which is critical for monitoring therapeutic efficacy and guiding personalized treatment strategies. Continued research and innovation are essential to fully realize the potential of peptides as a transformative tool in gut regenerative medicine.

European Wellness

To date, European Wellness (EW) has demonstrated to application by which peptide therapies have the capacity to operate through a multifaceted network of actions that target key cellular and molecular processes in gut repair, positioning them as a powerful next-generation approach for treating gastrointestinal injuries and chronic diseases marked by impaired mucosal healing.

Future Directions

The future of peptide-based gut regeneration is rapidly evolving toward more targeted, personalized, and integrative approaches. One major direction involves the expansion of peptide libraries designed to mimic or enhance endogenous regenerative signals, such as Wnt, R-spondin, and Notch pathway modulators, offering the potential to fine-tune epithelial repair and stem cell niche function. Concurrently, the integration of peptides with stem cell and organoid-based therapies is opening new avenues for ex vivo modeling and in vivo tissue restoration, where peptides can promote engraftment, differentiation, or niche maintenance. Another emerging area is the study of peptide-microbiome interactions, which is revealing how microbial communities influence and respond to therapeutic peptides, shaping local immune responses and regenerative capacity. Looking forward, precision regenerative medicine strategies are gaining traction by leveraging genomic and proteomic profiling to match patients with optimal peptide therapies — enabling stratified interventions tailored to individual disease states or injury responses. Ongoing and upcoming clinical trials are increasingly testing these next-gen peptide constructs in conditions such as inflammatory bowel disease, short bowel syndrome, and radiation-induced enteropathy, suggesting a promising horizon for safe, modular, and biologically intelligent gut repair.

Conclusion

Peptide therapy has emerged as a promising modality for gut regeneration, with growing preclinical and early clinical evidence demonstrating its ability to promote epithelial repair, enhance intestinal stem cell function, and modulate key regenerative pathways such as Wnt, Notch, and EGF signaling. Studies have shown that specific peptides can accelerate mucosal healing, reduce inflammation, and improve barrier function in models of intestinal injury and chronic diseases like IBD, Crohn's, and short bowel syndrome. Despite this encouraging progress, robust clinical research is essential to fully establish the safety, efficacy, and cost-effectiveness of

these therapies across diverse patient populations. Well-designed trials are needed to validate therapeutic outcomes, optimize dosing strategies, and evaluate long-term effects. If these challenges are met, peptide-based interventions hold significant promise to transform current treatment paradigms, offering targeted, biologically informed alternatives to conventional immunosuppressive or surgical approaches for gut injury and chronic intestinal disorders.

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