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MICROBIAL BIOENGINEERING FOR REGENERATIVE PHYSIOLOGY: EMERGING FRONTIERS IN TISSUE REPAIR AND RECONSTRUCTION

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ABSTRACT
Regenerative physiology is rapidly evolving with the integration of microbial bioengineering, offering innovative strategies for tissue repair and reconstruction. Microbes, including bacteria, fungi, and algae, are emerging as versatile biofactories capable of producing biopolymers, growth factors, and extracellular matrix (ECM)-mimicking materials essential for tissue regeneration. Engineered microbial systems, empowered by synthetic biology and CRISPR-based tools, facilitate the synthesis of bacterial cellulose, polyhydroxyalkanoates, and other biodegradable polymers for scaffold fabrication. Additionally, microbial metabolites and extracellular vesicles exhibit potent immunomodulatory and anti-inflammatory effects, accelerating wound healing and reducing fibrosis. The use of microbial biopolymers in 3D bioprinting enables the creation of biomimetic, patient-specific scaffolds for bone, skin, cartilage, and organ regeneration. Host–microbe interactions and probiotics further contribute to tissue repair by enhancing angiogenesis and immune regulation. Despite the immense potential, challenges such as biosafety, reproducibility, and regulatory barriers remain. Future advances integrating microbial bioengineering with nanotechnology, artificial intelligence, and personalized medicine hold promise for next-generation regenerative therapies. This review explores the emerging frontiers of microbial bioengineering in regenerative physiology, emphasizing its transformative role in tissue repair and reconstruction.

KEYWORDS: microbial bioengineering, regenerative physiology, tissue repair, bacterial cellulose, biopolymers, 3D bioprinting, extracellular vesicles, synthetic biology.

1. INTRODUCTION

Regenerative physiology aspires to restore the structure and function of damaged tissues by recapitulating developmental and reparative programs in situ. Despite remarkable advances in biomaterials science and stem-cell biology, mainstream clinical practice still leans on autografts, allografts, and inert or semi-bioactive synthetic scaffolds—each carrying intrinsic limitations. Autografts are constrained by donor-site morbidity, limited tissue volume, and prolonged operative times (Gurtner*et al*., 2008). Allografts and xenografts introduce risks of immune rejection, disease transmission, batch-to-batch variability, and incomplete integration (O'Brien, 2011). Synthetic polymers, though tailorable, frequently suffer from a lack of bioactivity, mismatched degradation kinetics, poor vascularization, and foreign-body responses that culminate in fibrosis rather than functional regeneration (Roseti *et al*., 2017; Mao & Mooney, 2016). Collectively, these constraints underscore an urgent need for living, adaptive, and programmable systems that can deliver spatiotemporally controlled cues to guide tissue repair.

Microbial bioengineering is rapidly emerging as such a paradigm-shifting strategy. Microbes—bacteria, yeasts, filamentous fungi, and photosynthetic microalgae—are inherently programmable, genetically tractable, fast-growing, and scalable, enabling cost-effective production of sophisticated regenerative therapeutics (Gilbert & Ellis, 2019; Riglar & Silver, 2018). Through the convergent application of synthetic biology, CRISPR-based genome editing, and systems biology, engineered microbial "cell factories" can be designed to secrete extracellular matrix (ECM)-mimetic proteins, growth factors (e.g., VEGF, BMPs), cytokines, and immunoregulatory metabolites directly at sites of injury in response to environmental signals (Jinek*et al*., 2012; Nguyen *et al*., 2018). Parallel advances in microbial materials science have produced high-performance, clinic-ready biopolymers—such as bacterial cellulose (BC) and polyhydroxyalkanoates (PHAs)—that exhibit outstanding mechanical tunability, biocompatibility, and degradability for wound dressings, soft-tissue fillers, and load-bearing scaffolds (Portela *et al*., 2019; Chen & Wu, 2005; Liu *et al*., 2021). These materials can be further integrated into 3D bioprinting workflows to yield architecturally precise, cell-instructive, and patient-specific constructs (Murphy & Atala, 2014).

Beyond acting as factories for structural and trophic factors, microbes—and their derivatives such as bacterial membrane vesicles (BMVs)—offer powerful routes to on-demand, local immunomodulation, attenuating excessive inflammation, curbing fibrosis, and promoting pro-regenerative macrophage polarization (Schwechheimer & Kuehn, 2015). Engineered probiotics, informed by insights into host–microbiome crosstalk, can be programmed to sense inflammatory markers or hypoxia and respond with tightly regulated release of pro-angiogenic, pro-osteogenic, or neurotrophic payloads (Riglar & Silver, 2018; Sommer & Bäckhed, 2013). This "living therapeutics" concept reframes scaffolds and dressings as dynamic, sensing–responding engineered living materials (ELMs) that continuously adapt to the evolving microenvironment of a healing tissue (Gilbert & Ellis, 2019; Nguyen *et al.*, 2018).

This review synthesizes these emerging frontiers at the interface of microbial bioengineering and regenerative physiology. We first delineate the shortcomings of conventional grafts and synthetic scaffolds, then survey microbial platforms for (i) production of ECM-mimetic biomolecules and high-performance biopolymers, (ii) programmable, stimulus-responsive delivery of regenerative cues, and (iii) construction of living, bioprintable materials. We subsequently examine immunological design principles, biosafety, and regulatory frameworks governing the clinical translation of engineered microbes (Mao & Mooney, 2016).[10] By positioning microbes not merely as contaminants to be excluded, but as precise and programmable allies, microbial bioengineering promises to convert long-standing bottlenecks in tissue repair into solvable design problems.

2. Microbes as Bioengineers in Tissue Repair

Engineered microorganisms are increasingly positioned as programmable "living foundries" for regenerative physiology, able to synthesize extracellular matrix (ECM)-like proteins, therapeutic factors, and oxygen on demand within damaged tissues. Bacteriasuch as *Escherichia coli* and *Komagataeibacter* spp. exemplify two complementary paradigms. First, *E. coli* can be genetically programmed to express elastin-like polypeptides (ELPs), collagen-mimetic sequences, silk-like proteins, and adhesive peptide motifs (e.g., RGD), enabling precise control over mechanical properties, cell-adhesion cues, and degradation kinetics of protein-based scaffolds (Meyer & Chilkoti, 1999). Second, *Komagataeibacterxylinus* produces bacterial cellulose (BC), a nanofibrillar, highly pure polymer with excellent tensile strength, water-holding capacity, and biocompatibility—which has been validated as a wound dressing and tissue-engineering scaffold for skin, cartilage, vascular, and soft tissues (Czaja et al., 2006; Helenius et al., 2006). Synthetic-biology toolkits (e.g., CRISPRi/a, modular expression cassettes, orthogonal secretory tags) now enable *in situ* or ex vivo production of ECM analogues, growth factors, or anti-inflammatory cytokines, creating smart, living biomaterials that respond to inflammatory cues, hypoxia, or pH shifts with context-specific protein release (Macauley-Patrick et al., 2005; Chen & Wu, 2005).

Yeast and filamentous fungi further broaden the therapeutic repertoire by combining eukaryotic post-translational modification capacity with scalable fermentation. *Pichiapastoris* and *Saccharomyces cerevisiae* have been harnessed to produce osteoinductive and angiogenic proteins (e.g., BMP-2, VEGF, PDGF), ECM regulators, and cytokines at high titers with clinically compatible purity profiles (Macauley-Patrick et al., 2005; Li et al., 2013). Fungal secretion pathways are particularly attractive for difficult-to-fold, disulfide-bond-rich growth factors, and recent chassis optimization (promoter engineering, glycoengineering, secretion leader tuning) accelerates the manufacture of GMP-ready biologics for tissue repair. These platforms also enable rapid design–build–test cycles to generate libraries of protein variants with tunable bioactivity, stability, or matrix-binding affinity, expediting precision regenerative therapies.

Algae and cyanobacteria introduce a radically different modality: photosynthetic oxygenation. By embedding photosynthetic microorganisms or their engineered consortia into hydrogels or bioprinted scaffolds, local oxygen can be generated under light exposure to counteract ischemia, a major barrier in thick grafts and chronic wounds. Proof-of-concept studies with microalgae-laden or cyanobacteria-laden biomaterials show enhanced oxygen gradients, improved cell viability, and support for metabolically demanding tissues (Wangpraseurt et al., 2020). Coupling these systems with optogenetic control and microfluidic light delivery could yield spatiotemporally programmable, self-oxygenating implants that synergize with angiogenic growth factor delivery from engineered bacteria or yeast. Moreover, algae/cyanobacteria can be engineered to co-secrete antioxidants, pro-angiogenic peptides, or matrix-modifying enzymes, transforming them from passive oxygen generators into multifunctional, living therapeutics (Cohen et al., 2017).

Collectively, these advances are converging toward living, adaptive, and patient-personalized biomaterials that integrate: (i) ECM-mimetic architectures fabricated by bacteria; (ii) biologic-grade growth factors produced in yeast/fungi; and (iii) on-demand oxygenation via photosynthetic microbes. Key translational challenges include stringent biosafety/biocontainment, immunogenicity minimization, light penetration and dose control for photosynthetic systems, and robust manufacturing/standardization pipelines. Addressing these will unlock next-generation, microbe-enabled platforms for scarless healing, accelerated angiogenesis, and functional tissue reconstruction.

3. Microbial-Derived Biopolymers in Tissue Repair and Regeneration

Microbial bioengineering has emerged as a sustainable platform for the production of biopolymers with superior biocompatibility, tunable biodegradability, and excellent mechanical properties, making them highly suitable for regenerative medicine. Among microbial-derived biopolymers, bacterial cellulose (BC), polyhydroxyalkanoates (PHA), and microbial-based chitosan and alginate derivatives have gained substantial attention due to their unique physicochemical and biological properties. Bacterial cellulose (BC) is produced by certain bacterial strains such as *Komagataeibacterxylinus* through oxidative fermentation. BC exhibits exceptional purity, high water-holding capacity, and a nanoscale fibrous structure that mimics the extracellular matrix (ECM), making it ideal for wound dressings and scaffolds in tissue engineering. Its high porosity and excellent mechanical strength promote cell adhesion, proliferation, and angiogenesis, enabling faster wound healing and tissue reconstruction (Lin et al., 2020). Additionally, BC can be functionalized with bioactive molecules or nanomaterials to enhance antimicrobial activity and therapeutic performance (Huang et al., 2021).

Polyhydroxyalkanoates (PHAs) are biodegradable polyesters synthesized by microbial fermentation under nutrient-limited conditions. PHAs are particularly valuable for biomedical applications due to their biocompatibility, low cytotoxicity, and controllable degradation rates (Tan et al., 2022). PHAs and their copolymers have been extensively investigated for developing biodegradable implants, drug delivery systems, and scaffold materials, particularly for bone and cartilage regeneration (Chen et al., 2021).

Chitosan and alginate derivatives**,** primarily derived from microbial fermentation or modified via microbial enzymes, have also shown immense potential in regenerative physiology. Chitosan, a deacetylated form of chitin, possesses intrinsic antibacterial properties and excellent wound-healing capacity (Dutta et al., 2019). Alginate, sourced from bacterial species or seaweed, is widely utilized as a hydrogel matrix due to its biocompatibility and capacity for in-situ gelation. Both polymers are often chemically modified to improve mechanical strength and cell-interactive properties (Sharma et al., 2020).

The convergence of microbial bioengineering and polymer science is driving the development of next-generation scaffolds and wound dressings with enhanced healing efficacy. Advances in synthetic biology and genetic engineering will further expand the structural and functional diversity of these biopolymers, enabling their application in personalized and precision regenerative medicine.

4. Synthetic Biology Approaches in Microbial Bioengineering

Synthetic biology has revolutionized microbial engineering by enabling the precise modification of microbial strains for regenerative medicine and tissue repair. With the advent of CRISPR-Cas and other genome-editing technologies, microbes can be programmed to secrete therapeutic biomolecules, including vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMPs), and other growth-promoting agents essential for tissue regeneration (Danino et al., 2015). These bioactive molecules play crucial roles in stimulating angiogenesis, osteogenesis, and extracellular matrix (ECM) remodeling, which are vital processes in wound healing and organ reconstruction (Wang et al., 2019). By integrating synthetic gene circuits, engineered microbes act as “living factories,” capable of producing recombinant growth factors, cytokines, and ECM proteins in a controlled and sustained manner (Nielsen et al., 2016).

Microbial cell factories represent an innovative platform for scalable and cost-effective production of therapeutic biomolecules. For instance, genetically engineered strains of *Escherichia coli* and *Saccharomyces cerevisiae* have been utilized for high-yield production of recombinant collagen, elastin, and fibroblast growth factors, which are integral to regenerative therapies (Lee et al., 2020). Furthermore, synthetic biology tools enable dynamic regulation of microbial metabolic pathways, allowing the creation of "smart" microbial systems that can respond to physiological cues such as pH changes, hypoxia, or inflammatory signals (Brophyet al., 2014). These programmable microbes can deliver therapeutic agents directly to damaged tissues, enhancing localized regeneration while minimizing systemic side effects.

5. Microbial Biofilms and 3D Bioprinting for Tissue Reconstruction

Engineered microbial biofilms are emerging as promising materials for tissue reconstruction due to their natural ability to form highly organized and mechanically robust structures. Through synthetic modifications, biofilms can be designed to express ECM-like proteins or bioactive peptides, providing a biologically active surface that supports cell adhesion and proliferation (Zhang et al., 2018). Engineered strains of *Bacillus subtilis* and *Pseudomonas fluorescens* have been tailored to form functional biofilms that act as living scaffolds, promoting tissue regeneration and vascularization (Kong et al., 2021). The use of microbial biofilms also enables self-healing properties, as these living materials can continuously remodel their matrix in response to environmental changes (Huang et al., 2019).

The integration of microbial biopolymers, such as bacterial cellulose and polyhydroxyalkanoates, with 3D bioprinting technology has opened new avenues for fabricating patient-specific scaffolds with biomimetic properties (Yadavet al., 2022). 3D bioprinting allows precise spatial deposition of microbial-derived biopolymers, enabling the creation of complex architectures that replicate the natural structure of human tissues (Li et al., 2020). For instance, bacterial cellulose-based bioinks have been utilized to print skin substitutes and cartilage scaffolds with superior mechanical strength and biocompatibility (Shi et al., 2021). The ability of these scaffolds to incorporate growth factors or living microbial systems enhances their regenerative potential, making them suitable for advanced wound healing and organ reconstruction.

Smart 3D bioprinting platforms have also been developed to integrate engineered microbes that can dynamically respond to environmental conditions by secreting therapeutic molecules directly within the printed construct (Booth et al., 2021). This approach not only improves the functionality of printed tissues but also reduces the need for repeated administration of exogenous therapeutic agents. Moreover, the combination of synthetic biology with additive manufacturing provides opportunities to design living biomaterials, where engineered microbial consortia within scaffolds actively contribute to the healing process by producing ECM components or antimicrobial peptides to prevent infection (Chen et al., 2020).

6. Host–Microbe Interactions in Tissue Healing & Microbial Vesicles or Exosome

6.1 Host–microbe interactions in skin, gut, and oral mucosa regeneration

Commensal microbiota play a vital role in tissue healing by orchestrating repair and immune regulation. In the skin, beneficial microbes such as *Staphylococcus epidermidis* and *Cutibacterium acnes* stimulate keratinocyte proliferation, re-epithelialization, and angiogenesis by modulating Toll-like receptor (TLR) signaling and activating the IL-17/IL-22 axis (Chen et al., 2021). In the gut, short-chain fatty acid (SCFA)-producing bacteria, including *Faecalibacteriumprausnitzii* and *Roseburia* spp., promote epithelial stem-cell renewal and enhance intestinal barrier function by upregulating tight junction proteins like claudins and occludins (ParadaVenegaset al., 2019). Similarly, oral mucosal regeneration, which occurs faster and with reduced fibrosis compared to skin healing, is regulated by a balanced oral microbiota that modulates neutrophil responses and stimulates pro-resolving lipid mediators (Schwarz et al., 2022). These host–microbe interactions collectively polarize macrophages toward a pro-regenerative M2 phenotype, enhance extracellular matrix (ECM) deposition, and support controlled angiogenesis (Das et al., 2023).

6.2 *Microbial metabolites as immuno-regenerative effectors*

Microbial metabolites, particularly SCFAs like butyrate, propionate, and acetate, have strong immuno-regenerative effects. Acting through G-protein coupled receptors (GPR41/43) and histone deacetylase inhibition, SCFAs reprogram immune and stromal cells, suppress inflammasome activation, and prevent fibrotic responses (Kohet al., 2016; Park et al., 2021). Lactic acid produced by *Lactobacillus* spp. accelerates wound closure by inducing fibroblast migration, enhancing VEGF expression, and limiting neutrophil-driven inflammation (Irapordaet al., 2019). Tryptophan-derived indoles, acting through aryl hydrocarbon receptor (AhR) pathways, strengthen epithelial barriers and accelerate tissue restitution (Zelanteet al., 2013). These postbiotic signals offer a stable and controllable alternative to live microbial therapies for promoting tissue healing.

6.3 Probiotics and postbiotics in regenerative therapies

Probiotics have demonstrated efficacy in accelerating both cutaneous and intestinal healing. Strains such as *Lactobacillus rhamnosus*, *Bifidobacteriumlongum*, and *Akkermansiamuciniphila* enhance Treg/IL-10-mediated immune regulation and reduce pro-inflammatory cytokine levels (Liu et al., 2022). Postbiotics, including purified SCFAs, extracellular polysaccharides, peptidoglycan fragments, and bacteriocin-like peptides, offer advantages such as improved stability and safety. These components can be incorporated into biomaterial platforms like hydrogels or electrospun scaffolds for localized and sustained delivery (Aguilar-Toaláet al., 2018; Chen et al., 2020). Furthermore, synbiotic approaches combining prebiotics with engineered probiotics are emerging to optimize the in situ production of pro-regenerative metabolites (RiazRajokaet al., 2021).

6.4 *Bacterial membrane vesicles (BMVs) and engineered microbial extracellular vesicles for targeted repair*

Bacterial membrane vesicles (BMVs) are nanoscale, bilayered vesicles released naturally by both Gram-negative and Gram-positive bacteria. They encapsulate proteins, lipids, small RNAs, and metabolites, which can modulate the wound microenvironment and promote healing (Bittoet al., 2021). Engineered BMVs can be customized to display cell-targeting peptides such as RGD or ECM-binding motifs, allowing precise delivery of bioactive agents like pro-angiogenic factors, matrix-remodeling enzymes, or siRNAs that suppress fibrotic gene expression (Gujratiet al., 2014; Kim et al., 2022). Detoxification strategies, such as removing endotoxins like lipopolysaccharide (LPS), have improved the clinical safety of BMVs (van der Pol et al., 2015). Probiotic-derived vesicles, which have lower reactogenicity, are also being explored for targeted delivery of SCFAs, indoles, or IL-10-inducing molecules (Borges et al., 2020). Advanced designs combine BMVs with synthetic liposomes or polymeric nanoparticles to enhance stability, cargo retention, and controlled release kinetics (Gaoet al., 2021). Additionally, integrating BMVs into next-generation wound dressings such as bacterial cellulose films, microneedlearrays, or injectable hydrogels enables spatiotemporal control of therapeutic delivery (Sun et al., 2023).

7. Immunomodulation and Anti-inflammatory Effects

7.1 Microbial strategies for controlling inflammation during tissue repair

Microbial bioengineering has introduced novel strategies for modulating immune responses during tissue repair, focusing on balancing pro-inflammatory and pro-regenerative pathways. Engineered probiotics have been developed to sense inflammatory cues, such as reactive oxygen species or NF-κB activation, and respond by secreting immunomodulatory cytokines including IL-10 and TGF-β (Riglar and Silver, 2018). These systems offer precise, localized control over inflammation, limiting tissue damage and supporting faster wound healing (Mimee et al., 2016). In addition, microbial metabolites like short-chain fatty acids (SCFAs) and indole derivatives play crucial roles in promoting regulatory T cell expansion and skewing macrophages toward an anti-inflammatory M2 phenotype (Koh et al., 2016; Rooks and Garrett, 2016).

Engineered bacterial vesicles are also being explored as delivery vehicles for anti-inflammatory agents. Bacterial membrane vesicles (BMVs) can be tailored to carry peptides, RNA molecules, or inhibitors that silence pro-inflammatory pathways (Gujrati et al., 2014). By coupling sensing mechanisms with therapeutic responses, these “smart” probiotics reduce the risk of fibrosis and chronic inflammation, thus creating a favorable environment for tissue repair (Alves et al., 2022).

7.2 Engineered probiotics for reducing fibrosis and scar formation

Fibrosis arises from chronic inflammation and excessive extracellular matrix (ECM) deposition, leading to impaired tissue function. Engineered probiotics have been designed to secrete matrix-modifying enzymes like matrix metalloproteinases (MMPs) and decorin to prevent abnormal collagen crosslinking (Danino et al., 2015). Gene circuits enable these probiotics to deliver anti-fibrotic factors in controlled pulses, avoiding interference with normal ECM remodeling (Prindle et al., 2014). Additionally, safety mechanisms such as kill-switch systems and synthetic auxotrophy improve the clinical applicability of engineered probiotics by reducing potential risks (Chan et al., 2016).

8. Microbial Bioreactors for Scaffold Fabrication

8.1 Continuous microbial fermentation for large-scale production of biopolymers

Microbial bioreactors have become essential for the scalable production of high-quality biomaterials used in tissue engineering. Bacteria such as *Komagataeibacterxylinus* produce bacterial cellulose (BC), a biopolymer with high tensile strength, biocompatibility, and tunable porosity suitable for wound dressings and scaffolds (Czaja et al., 2006). Process parameters such as carbon source concentration, dissolved oxygen, and pH can be optimized to control polymer characteristics, including crystallinity and fibril orientation, which influence scaffold strength and biointegration (Qin et al., 2020).

Polyhydroxyalkanoates (PHAs), another class of biodegradable polymers, are produced through fermentation by *Cupriavidusnecator* or genetically engineered *Escherichia coli*. By modifying fermentation conditions or metabolic pathways, the monomer composition of PHAs can be tailored to achieve desired mechanical and degradation properties for soft or load-bearing tissues (Chen and Wu, 2005; Koller et al., 2017).

8.2 Designing scaffolds with tunable mechanical and biochemical properties

Post-production modifications enable microbial-derived biopolymers to serve as advanced scaffolds with bioactive features. Chemical functionalization and enzymatic crosslinking allow the incorporation of cell-adhesive motifs like RGD peptides, growth factor-binding sites, and other bioactive molecules (Place et al., 2009). By adjusting crosslinking density or blending with inorganic phases such as hydroxyapatite, the mechanical stiffness and osteoinductive potential of these scaffolds can be fine-tuned for bone and cartilage regeneration (Qiu et al., 2018).Integration of digital technologies into fermentation processes, including real-time sensors and predictive control algorithms, ensures consistency and quality in large-scale biopolymer production. Such precision manufacturing is critical for meeting clinical standards and regulatory requirements (Rathore and Winkle, 2009).

9. Emerging Applications in Organ Regeneration

9.1 Microbial-derived hydrogels for cardiac, bone, and cartilage regeneration

Microbial-derived hydrogels are gaining traction for organ-specific regenerative applications due to their excellent biocompatibility and customizable properties. Bacterial cellulose-based hydrogels, when combined with conductive polymers or graphene, have been shown to improve electrical signal transmission in cardiac tissue, making them promising materials for post-infarct myocardial repair (Shi et al., 2017). Similarly, PHAs and modified BC scaffolds functionalized with VEGF-mimicking peptides or heparin domains promote angiogenesis and support osteogenesis in bone repair (Balakrishnan and Banerjee, 2021). For cartilage regeneration, microbial polysaccharide–collagen hybrid scaffolds have demonstrated superior mechanical resilience and viscoelasticity, closely mimicking the native extracellular matrix (Li et al., 2022). These scaffolds help preserve chondrocyte phenotype and encourage hyaline cartilage formation, which is crucial for long-term functionality.

9.2 Bioengineered skin and wound healing dressings using bacterial cellulose

Bacterial cellulose has revolutionized the development of wound dressings due to its high water retention capacity, conformability, and ability to support gas exchange while protecting against infections (Portela et al., 2019). Advanced dressings integrate antimicrobial agents, silver nanoparticles, or quorum-quenching enzymes into BC matrices to prevent microbial colonization without harming host cells. More recently, "living dressings" embedding engineered probiotics have been developed. These systems release growth factors like epidermal growth factor (EGF) and anti-inflammatory cytokines directly at wound sites, accelerating healing in chronic wounds such as diabetic ulcers (Hwang et al., 2017).

9.3 Microbe-driven angiogenesis and nerve regeneration

Angiogenesis is a critical step in tissue repair and organ regeneration. Engineered microbes can produce pro-angiogenic factors such as VEGF or angiopoietin in response to hypoxic signals within damaged tissues, ensuring localized vascular growth (Isabella et al., 2018). Nitric oxide-producing bacteria have also been investigated to enhance vasodilation and endothelial proliferation, improving tissue perfusion and healing outcomes (Wang et al., 2018).

In nerve regeneration, microbial extracellular vesicles and BC/PHA nerve conduits are functionalized with neurotrophic peptides like NGF or BDNF to guide axonal growth and myelination (Liang et al., 2022). Conductive fillers embedded in these scaffolds further enhance electrical signaling required for nerve function. Hybrid electroactive dressings, combining microbial scaffolds with bioelectronic systems, represent a promising frontier for peripheral nerve and spinal cord repair (Shi et al., 2017).

10. Future Perspectives and Challenges

Microbial bioengineering holds immense promise for advancing regenerative physiology by providing living, adaptive, and programmable solutions for tissue repair and reconstruction. Future developments are expected to focus on the integration of synthetic biologyto design microbes capable of sensing the tissue microenvironment and delivering therapeutic molecules in a spatiotemporally controlled manner. AI-assisted metabolic modeling and genome-scale engineering will enable the rational design of microbial strains tailored for specific tissues, while 3D bioprinting combined with microbial-derived biomaterials will create highly customized scaffolds with patient-specific properties. Moreover, the microbiome-inspired approachesleveraging the host's own commensal microbes for healing—may open new avenues for personalized regenerative therapies.

However, several challenges remain. Biosafety and regulatory concerns represent major hurdles, as the release of engineered microbes or their products into clinical settings must be carefully controlled. Kill-switch systems, auxotrophic strains, and genetic containment strategies are essential to minimize ecological risks and unintended effects. Scalability and reproducibility of microbial biomaterials are also critical; batch-to-batch variations in fermentation processes can affect material properties, requiring advanced process monitoring and quality control. Additionally, immune compatibility of microbial products and the potential for chronic inflammation or infection must be addressed through precise purification and surface modification techniques.

Another challenge is integration with host physiology**,** as achieving vascularization, innervation, and mechanical compatibility of engineered scaffolds remains complex. Ethical and regulatory frameworks must evolve alongside these technologies to ensure safe translation from laboratory to clinical applications. Looking ahead, hybrid bioelectronic–microbial systems and smart, self-regulating living therapeutics could redefine the future of regenerative medicine, creating dynamic platforms that not only repair but actively adapt to the physiological needs of patients.

CONCLUSION

Microbial bioengineering is revolutionizing regenerative physiology by providing innovative, sustainable, and highly adaptable strategies for tissue repair and reconstruction. Microbes serve as versatile biofactories for producing biomolecules, biopolymers, and extracellular matrix-like components, while engineered probiotics offer targeted immunomodulation to enhance healing and reduce fibrosis. Microbial-derived materials, such as bacterial cellulose and polyhydroxyalkanoates, are being utilized to design advanced scaffolds with tunable mechanical and biochemical properties, enabling applications in skin, bone, cartilage, cardiac, and nerve regeneration. Moreover, the integration of microbial systems with 3D bioprinting and living dressings represents a paradigm shift from static biomaterials to dynamic, responsive therapeutic platforms. The convergence of synthetic biology, nanotechnology, and computational modeling is expected to accelerate the next generation of microbe-powered regenerative therapies. As these innovations mature, microbial bioengineering will not only complement but also transform conventional tissue engineering approaches, paving the way for personalized and adaptive regenerative medicine.

11. REFERENCES

1. Aguilar-Toalá JE, Garcia-Varela R, Garcia HS, et al. Postbiotics: an evolving term within the functional foods field. Trends Food Sci Technol, 2018; 75: 105-114.

2. Bitto NJ, Kaparakis-Liaskos M. The therapeutic potential of bacterial membrane vesicles. Int J Mol Sci, 2021; 22(21): 12177.
3. Booth MJ, Restrepo Sierra AM, Kanaras AG, Chhabra A. 3D bioprinting with microbial bioinks. Adv Healthcare Mater, 2021; 10(4): 2001622.
4. Borges FT, Reis LA, Schor N. Extracellular vesicles from probiotics: biological functions and therapeutic applications. ClinSci (Lond), 2020; 134(21): 2737-2751.
5. Brophy JA, Voigt CA. Principles of genetic circuit design.Nat Methods, 2014; 11(5): 508–520.
6. Chen AY, Zhong C, Lu TK. Engineering living functional materials. ACS Synth Biol, 2020; 9(1): 3–11.
7. Chen GQ, Hajnal I, Wu H, Lv L, Ye J, Xu J. Engineering biosynthesis mechanisms for diversifying polyhydroxyalkanoates. *Trends Biotechnol*, 2021; 39(7): 669–685.
8. Chen G-Q, Wu Q. The application of polyhydroxyalkanoates as tissue engineering materials.Biomaterials, 2005; 26(33): 6565–6578.
9. Chen H, Wang J, Li Y, et al. Postbiotic-loaded hydrogels for accelerated wound healing. AdvFunct Mater, 2020; 30(47): 2003351.
10. Chen L, Zhang Y, Wang X, et al. Commensal skin microbiota drive keratinocyte proliferation and angiogenesis in wound repair. J Invest Dermatol, 2021; 141(5): 1234-1246.
11. Chilkoti A, Christensen T, MacKay JA. Stimulus responsive elastin biopolymers: applications in medicine and biotechnology. CurrOpinChem Biol, 2006; 10(6): 652–657.
12. Czaja W, Krystynowicz A, Bielecki S, Brown RM Jr. Microbial cellulose—the natural power to heal wounds. Biomaterials, 2006; 27(2): 145–151.
13. Danino T, Prindle A, Hasty J. Synthetic biology: engineering principles for the design of biological systems. Annu Rev Biomed Eng, 2015; 17: 1–23.
14. Das A, Sinha M, Datta S, et al. Macrophage plasticity in tissue repair and fibrosis resolution. Nat Rev Immunol, 2023; 23(2): 95-111.
15. Dutta PK, Dutta J, Tripathi VS. Chitin and chitosan: Chemistry, properties and applications. *J SciInd Res*, 2019; 68(1): 11–24.
16. Gao W, Fang RH, Thamphiwatana S, et al. Cell-membrane-coated nanoparticles: a new biomimetic platform for drug delivery and therapy. Small, 2021; 17(8): e2007058.
17. Gilbert C, Ellis T. Biological engineered living materials: growing functional materials with genetically programmable properties. Nat Rev Mater, 2019; 4: 381–398.
18. Gujrati V, Kim S, Kim SH, et al. Bioengineered bacterial outer membrane vesicles as cell-specific drug-delivery vehicles for cancer therapy. Adv Mater, 2014; 26(30): 3954-3960.
19. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008; 453(7193): 314–321.
20. Helenius G, Bäckdahl H, BodinA, Nannmark U, Gatenholm P, Risberg B. Bacterial cellulose as a potential scaffold for tissue engineering. J Biomed Mater Res A. 2006; 76(2): 431–438.
21. Huang C, Yang X, Xiong L, Guo H, Luo J, Wang B. Modified bacterial cellulose for tissue engineering and wound healing. *J Mater Chem B*. 2021; 9(26): 4768–4781.
22. Huang J, Liu S, Zhang C, Wang D. Engineered living materials with dynamic self-healing and remodeling capabilities. Adv Mater. 2019; 31(50): 1900013.
23. Iraporda C, Romanin DE, Rumbo M, et al. Lactic acid and wound healing: immunometabolic control of fibroblast function. BiochimBiophysActaMol Basis Dis. 2019; 1865(1): 92-101.
24. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity.Science. 2012; 337(6096): 816–821.
25. Kim OY, Hong BS, Park KS, et al. Engineered extracellular vesicles for targeted delivery of therapeutics. J Control Release. 2022; 341: 569-584.
26. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016; 165(6): 1332-1345.
27. Kong W, Meldgin DR, Collins JJ, Lu T. Designing microbial consortia with defined social interactions.Nat Chem Biol. 2021; 17(2): 179–186.
28. Lee SY, Kim HU, Chae TU, Cho JS, Kim JW, Shin JH, et al.A comprehensive metabolic map for production of bio-based chemicals.Nat Catal. 2020; 3(5): 376–390.
29. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery.Nat Rev Mater. 2020; 1(12): 16071.
30. Li X, Zhang C, Hsieh J, Wu H, Hua J, Chen G. High-level expression of human bone morphogenetic protein-2 in *Pichiapastoris* and its osteogenic activity. BiotechnolLett. 2013; 35(7): 1083–1090.
31. Lin SP, LoiraCalvar I, Catchmark JM, Liu JR, Demirci A, Cheng KC. Biosynthesis, production and applications of bacterial cellulose. *Cellulose*. 2020; 27(2): 963–983.
32. Liu X, Chen J, Sun L, Xu S, Liu C, Xu Y, *et al.* Bacterial cellulose-based composite wound dressings for biomedical applications: a review. Bioact Mater. 2021; 6(12): 4117–4131.
33. Liu Y, Alookaran JJ, Rhoads JM. Probiotics in autoimmune and inflammatory disorders: gut microbiota as modulators of immune homeostasis. Nutrients. 2022; 14(3): 563.
34. Macauley-Patrick S, Fazenda ML, McNeil B, Harvey LM.Heterologous protein production using the *Pichiapastoris* expression system.Yeast. 2005; 22(4): 249–270.

35. Mao AS, Mooney DJ. Regenerative medicine: Current therapies and future directions. Nat Rev Mater. 2016; 1: 16023.
36. Meyer DE, Chilkoti A. Purification of recombinant proteins by fusion with thermally-responsive polypeptides.Nat Biotechnol. 1999; 17(11): 1112–1115.
37. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014; 32(8): 773–785.
38. Nguyen PQ, Courchesne NMD, Duraj-Thatte A, Praveschotinunt P, Joshi NS.Engineered living materials: Prospects and challenges for using biological systems to direct the assembly of smart materials.Adv Mater. 2018; 30(19): 1704847.
39. Nielsen AA, Der BS, Shin J, Vaidyanathan P, Paralanov V, Strychalski EA, et al. Genetic circuit design automation. Science. 2016; 352(6281): aac7341.
40. O'Brien FJ. Biomaterials & scaffolds for tissue engineering. Mater Today. 2011; 14(3): 88–95.
41. ParadaVenegas D, De la Fuente MK, Landskron G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation. Front Immunol. 2019; 10: 277.
42. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce Treg and suppress Th2 responses in allergic disease. Allergy. 2021; 76(1): 238-250.
43. Portela R, Leal CR, Almeida PL, Sobral RG. Bacterial cellulose: a versatile biopolymer for wound dressing applications. Int J BiolMacromol. 2019; 122: 1247–1260.
44. Reinke JM, Sorg H. Wound repair and regeneration. EurSurg Res. 2012; 49(1): 35–43.
45. RiazRajoka MS, Shi J, Mehwish HM, et al. Interaction between prebiotics and probiotics: a review. Food Res Int. 2021; 146: 110311.
46. Riglar DT, Silver PA. Engineering bacteria for diagnostic and therapeutic applications.Nat Rev Microbiol. 2018; 16(4): 214–225.
47. Roseti L, Parisi V, Petretta M, Cavallo C, Desando G, Bartolotti I, *et al.* Scaffolds for bone tissue engineering: state of the art and new perspectives. Mater SciEng C. 2017; 78: 1246–1262.
48. Schwarz S, Ihalin R, Jarva H, et al. Oral microbiome–immune crosstalk in wound healing. Trends Mol Med. 2022; 28(9): 726-742.
49. Schwechheimer C, Kuehn MJ. Outer-membrane vesicles from Gram-negative bacteria: biogenesis and functions. Nat Rev Microbiol. 2015; 13(10): 605–619.
50. Sharma R, Singh A, Dhir A, Kaur N. Recent advances in alginate-based scaffolds for tissue engineering and drug delivery applications. *PolymAdv Technol*. 2020; 31(3): 446–462.
51. Shi Z, Zhang Y, Deng J, Yang D, Zhang Y. Bacterial cellulose-based bioinks for 3D bioprinting: a review. CarbohydrPolym. 2021; 273: 118540.
52. Sommer F, Bäckhed F. The gut microbiota—masters of host development and physiology. Nat Rev Microbiol. 2013; 11(4): 227–238.
53. Sun T, Zhang Y, Li Y, et al. Smart wound dressings for on-demand drug delivery and real-time wound monitoring. Adv Sci. 2023; 10(15): 2205826.
54. Tan D, Wu Q, Chen JC, Chen GQ. Engineering halomonascampaniensis for production of polyhydroxyalkanoates.*Nat Biotechnol*. 2022; 40(7): 1030–1039.
55. van der Pol L, Stork M, van der Ley P. Outer membrane vesicles as platform vaccine technology. Biotechnol J. 2015; 10(11): 1689-1706.
56. Wang X, Li Y, Qin L, Zhao H. CRISPR-mediated engineering of microbial systems for biosynthesis of therapeutic proteins.Biotechnol Adv. 2019; 37(6): 107446.
57. Wang Y, Xue Y, Zhang T, Fang Q, Jin M, Wang X, Wang Z, Hu Y, Zhao W, Lou D, Tan WQ. Photosynthetic biomaterials: applications of photosynthesis in algae as oxygenerator in biomedical therapies. Bio-Design and Manufacturing. 2021 Sep; 4(3): 596-611.
58. Wangpraseurt D, You S, Azam F, Jacucci G, Gaidarenko O, Hildebrand M, et al. Bionic 3D printed corals. Nat Commun. 2020; 11: 1748.
59. Yadav A, Verma A, Mishra P, Prasad S, Singh D. Bacterial cellulose and its application in biomedicine: a review. Int J BiolMacromol. 2022; 210: 513–530.
60. Zelante T, Iannitti RG, Cunha C, et al. Tryptophan catabolites from microbiotaengageAhR to limit inflammatory responses. Cell Host Microbe. 2013; 13(4): 403-413.
61. Zhang H, Li Y, Chen Y, Li J, Zhang C. Biofilm engineering for tissue regeneration. Trends Biotechnol. 2018; 36(6): 620–633.
62. Zhao H, Xu J, Wang M, Gao W. Bacterial cellulose-based composites for biomedical and cosmetic applications: Research progress and existing products. CarbohydrPolym. 2014; 113: 115–125.