

Novel Strategies in Wound Healing: Biomaterials, Growth Factors, and Regenerative Approaches

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Abstract

Wound healing is a highly coordinated biological process involving hemostasis, inflammation, proliferation, and tissue remodeling [1,2]. Chronic wounds, including diabetic ulcers, pressure ulcers, and venous leg ulcers, remain a major clinical challenge due to impaired vascularization, persistent inflammation, microbial infection, and delayed tissue regeneration. Recent advances in regenerative medicine, biomaterials, nanotechnology, stem cell therapy, platelet-derived products, and tissue engineering have significantly improved wound management strategies. This review discusses the molecular mechanisms of wound healing and highlights emerging therapeutic approaches including hydrogels, nanofibers, growth factor delivery systems, exosomes, platelet-rich plasma, and bioactive scaffolds. Additionally, the manuscript explores translational challenges, clinical applications, and future directions for advanced wound care technologies. The integration of biomaterials with regenerative medicine has the potential to revolutionize chronic wound treatment and improve patient outcomes.

Keywords: wound healing, regenerative medicine, biomaterials, hydrogels, nanotechnology, stem cells, platelet-rich plasma, chronic wounds, tissue engineering, diabetic ulcers

1. Introduction

Skin is the largest organ of the human body and serves as the primary protective barrier against environmental insults, microbial invasion, and physical injury [1]. Damage to skin integrity initiates a complex wound healing cascade involving cellular, molecular, and biochemical pathways. Acute wounds generally progress through an orderly healing process; however, chronic wounds fail to heal within the expected timeframe due to infection, diabetes, vascular insufficiency, or immune dysfunction.

Globally, chronic wounds represent a significant healthcare burden, affecting millions of patients annually and increasing treatment costs [20]. Diabetic foot ulcers are among the most severe chronic wounds and frequently result in amputation if not effectively treated. Conventional therapies such as dressings, antibiotics, and debridement are often insufficient for complete tissue regeneration. Therefore, advanced regenerative strategies are being explored to accelerate healing and restore tissue function.

Recent developments in biomaterials, nanotechnology, stem cell biology, and bioactive molecules have created new opportunities to design next-generation wound-healing systems. These technologies aim to improve cell proliferation, angiogenesis, extracellular matrix deposition, antimicrobial activity, and tissue remodeling.

This review summarizes the phases of wound healing, factors affecting wound repair, and recent advances in regenerative wound healing technologies.

2. Physiology of Wound Healing

Wound healing occurs through four overlapping phases:

2.1 Hemostasis

Immediately after injury, vasoconstriction and platelet aggregation occur to prevent blood loss. Platelets release growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), and vascular endothelial growth factor (VEGF), which initiate tissue repair.

2.2 Inflammatory Phase

Neutrophils and macrophages migrate to the wound site to remove pathogens and necrotic tissue. Cytokines including interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and IL-6 regulate inflammation and recruit additional immune cells.

2.3 Proliferative Phase

Fibroblast proliferation, collagen synthesis, angiogenesis, and granulation tissue formation dominate this stage. Keratinocytes migrate to restore epidermal integrity.

2.4 Remodeling Phase

Collagen maturation and extracellular matrix reorganization strengthen the repaired tissue. Type III collagen is gradually replaced by type I collagen, increasing tensile strength.

3. Factors Affecting Wound Healing

Several systemic and local factors impair wound healing:

- Diabetes mellitus
- Infection and biofilm formation
- Poor nutrition
- Aging
- Smoking
- Hypoxia
- Vascular insufficiency
- Excessive inflammation
- Oxidative stress

Among these, diabetes is a major contributor to chronic wound formation due to impaired angiogenesis, neuropathy, and prolonged inflammation.

4. Conventional Wound Healing Therapies

4.1 Traditional Dressings

Conventional dressings include gauze, bandages, and cotton materials [19]. These dressings mainly provide physical protection but may not actively promote tissue regeneration.

4.2 Antimicrobial Therapy

Topical and systemic antibiotics are used to control bacterial infection. However, antibiotic resistance has limited their effectiveness.

4.3 Surgical Debridement

Removal of necrotic tissue enhances healing by reducing microbial load and stimulating granulation tissue formation.

4.4 Negative Pressure Wound Therapy

Negative pressure devices improve blood circulation and accelerate tissue granulation.

5. Advanced Biomaterials for Wound Healing

5.1 Hydrogels

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water [6]. They maintain a moist environment and support cellular migration and proliferation.

Advantages of Hydrogels

- High biocompatibility
- Moisture retention
- Controlled drug delivery
- Oxygen permeability
- Reduced pain during dressing changes

Natural hydrogels such as alginate, collagen, gelatin, and chitosan are widely investigated for wound healing applications.

5.2 Nanofibers

Electrospun nanofibers mimic the extracellular matrix and support cell adhesion [8]. Nanofiber scaffolds can be loaded with antimicrobial agents, growth factors, and nanoparticles.

5.3 Films and Membranes

Bioactive films composed of biodegradable polymers provide mechanical protection while delivering therapeutic molecules.

5.4 Foam Dressings

Foam-based dressings absorb wound exudates and maintain optimal moisture levels.

6. Nanotechnology in Wound Healing

Nanotechnology has transformed wound care by enabling targeted drug delivery and antimicrobial activity.

6.1 Silver Nanoparticles

Silver nanoparticles exhibit broad-spectrum antimicrobial properties against bacteria, fungi, and resistant pathogens [9].

6.2 Zinc Oxide Nanoparticles

ZnO nanoparticles promote epithelialization and collagen deposition.

6.3 Gold Nanoparticles

Gold nanoparticles enhance angiogenesis and tissue regeneration.

6.4 Nanocomposite Dressings

Nanocomposite wound dressings integrate nanoparticles with hydrogels or polymers to improve healing efficiency.

7. Growth Factors in Wound Healing

Growth factors regulate cellular migration, proliferation, and angiogenesis [10,11].

Major Growth Factors

Growth Factor | Function |

||| | PDGF | Fibroblast proliferation || VEGF | Angiogenesis || EGF | Keratinocyte migration ||
TGF- β | Collagen synthesis || FGF | Granulation tissue formation |

Controlled delivery systems are required to maintain growth factor stability and bioavailability.

8. Stem Cell Therapy for Wound Healing

Stem cells possess self-renewal and differentiation capabilities.

8.1 Mesenchymal Stem Cells (MSCs)

MSCs derived from bone marrow, adipose tissue, and umbilical cord enhance wound healing through paracrine signaling [12,13].

8.2 Mechanisms of Stem Cell-Mediated Repair

- Immunomodulation
- Angiogenesis stimulation
- Extracellular matrix remodeling
- Reduction of inflammation

8.3 Challenges

- Ethical concerns
- Cell survival
- Standardization
- High production costs

9. Platelet-Rich Plasma and Human Platelet Lysate

Platelet-derived products are rich in growth factors and cytokines.

9.1 Platelet-Rich Plasma (PRP)

PRP accelerates tissue regeneration and angiogenesis [14].

9.2 Human Platelet Lysate (hPL)

hPL contains bioactive proteins and growth factors including PDGF, VEGF, EGF, and TGF- β [15].

Recent studies suggest that lyophilized hPL retains regenerative properties and may improve storage stability for chronic wound treatment.

10. Exosomes and Extracellular Vesicles

Exosomes are nanosized extracellular vesicles secreted by stem cells and other cell types [16,17].

Therapeutic Benefits

- Enhanced angiogenesis
- Reduced inflammation
- Improved collagen deposition
- Cell-free regenerative therapy

Exosome-based therapies are considered promising alternatives to direct stem cell transplantation.

11. Tissue Engineering Approaches

Tissue engineering integrates scaffolds, cells, and signaling molecules to regenerate damaged tissue.

11.1 Bioengineered Skin Substitutes

Artificial skin constructs can replace damaged tissue and restore skin function.

11.2 3D Bioprinting

3D bioprinting enables precise fabrication of customized wound healing scaffolds [18].

11.3 Smart Wound Dressings

Smart dressings incorporate biosensors capable of monitoring pH, infection, and oxygen levels.

12. Challenges in Translational Wound Healing Research

Despite significant advancements, several limitations hinder clinical translation:

- Regulatory barriers
- Manufacturing complexity
- Cost-effectiveness
- Limited clinical trials
- Long-term safety concerns
- Standardization difficulties

Further multicenter clinical studies are necessary to validate the safety and efficacy of emerging regenerative therapies.

13. Future Perspectives

Future wound healing technologies are expected to integrate artificial intelligence, personalized medicine, gene therapy, nanomedicine, and bioengineered tissues. Multifunctional biomaterials capable of simultaneous antimicrobial activity, growth factor delivery, and tissue regeneration may become the next generation of advanced wound care systems.

Additionally, combining stem cell-derived exosomes with nanocomposite biomaterials may significantly improve healing outcomes in chronic diabetic wounds.

14. Conclusion

Wound healing remains a complex clinical challenge, particularly in chronic wounds associated with diabetes and vascular disorders. Advances in biomaterials, regenerative medicine, nanotechnology, stem cell therapy, and platelet-derived products have significantly improved therapeutic possibilities. Hydrogels, nanofibers, growth factors, exosomes, and tissue-engineered

constructs represent promising strategies for accelerating tissue repair and restoring skin integrity.

Although substantial progress has been achieved, further clinical validation and regulatory standardization are essential for successful translation into routine clinical practice. The integration of regenerative medicine with advanced biomaterials holds tremendous potential for the future of wound management.

Declarations

Ethical Approval

Not applicable.

Consent for Publication

Not applicable.

Funding

The authors declare that no funding was received for this work.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed equally to the preparation and review of this manuscript.

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