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Review Article

Harnessing Regenerative Medicine to Improve Wound Healing Outcomes: Cellular Therapies, Biomaterials, and Nanomedicine

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Summary

Regenerative medicine examines how to use stem cells, growth factors, cellular dressings, skin substitutes, biopolymers, hydrogels, exosome-based systems, and nanoparticle-enabled delivery platforms to improve Wound Healing. It is increasingly shaping the therapeutic and conceptual approach to wound care by shifting the goal of treatment from simple wound closure to the restoration of functional tissue. This review discusses the biological rationale of wound healing. The normal process of wound healing includes several coordinated and overlapping phases of hemostasis, inflammation, proliferation, and remodeling. This sequence often is disrupted in burns, diabetic ulcers, infected wounds, and extensive traumatic injuries, which leads to chronic inflammation, delayed vascularization, defective extracellular matrix deposition, or poor epithelial regeneration. Regenerative strategies, by providing instructive cells, paracrine signals, structural scaffolds, or controlled local delivery of bioactive molecules, try to correct these failures. Regenerative medicine has seen significant advances with the development of living skin substitutes, growth factor-loaded matrices, dynamic hydrogels, electrospun nanofibers, bioprintable bioinks, and smart wound dressings. However, the variability of biomaterial composition, poor regeneration of vascular and appendages, manufacturing complexity, cost, safety concerns, and the need for standardized potency assays still limit clinical translation. A more integrated approach that combines biological signaling, scaffold design, antimicrobial control, and patient-specific wound assessment may help bridge the gap between promising experimental systems and clinically reliable regenerative wound therapies.

Keywords: Regenerative medicine, Wound healing, Stem cells, Growth factors, Skin substitutes, Biopolymers, Hydrogels, Nanoparticles, Tissue engineering

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Introduction

Regenerative medicine is an interdisciplinary field that focuses on endogenous or exogenous stem cells, with the ultimate goal of transplanting stem cell-derived tissues and organs into the human body. Regenerative medicine-based therapies are being studied to treat diseases of the skin and bone, and to repair, replace, and strengthen tissues in the human body. Primarily, stem cells are undifferentiated cells capable of self-renewal and multidirectional differentiation. In some cases, they also possess the ability to engraft and maintain their potential, playing a crucial role in this process. Stem cells can differentiate into various cell types—such as nerve cells, cardiomyocytes, and hepatocytes—that are essential for tissue regeneration and respond to physiological needs. Stem cells are divided into pluripotent, totipotent, multipotent, and unipotent stem cells.[1,2] Pluripotent stem cells show remarkable tissue repair capacity. Mesenchymal stem cells have anti-inflammatory properties, promote epithelial cell proliferation, and inhibit wound scarring. In addition, stem cells and their exosomes play a significant role in bone tissue regeneration and neural repair. Hence, the potential of stem cells for skin and bone tissue regeneration has attracted considerable attention in the field of regenerative medicine. However, challenges such as the difficulties in culturing and transferring stem cells, their inherent tumorigenicity, and the complexities of exosome extraction have made their study a significant research focus.[3,4]

Skin - the largest organ of the body- plays a protective role against external damage. Skin regeneration faces significant

challenges due to its exposure to external chemical and physical factors and its poor self-healing capacity. Skin repair is a complex and dynamic process and consists of four stages: hemostasis, inflammation, proliferation, and regeneration. The healing process is relatively long, and underlying diseases make the healing more complicated, potentially leading to negative psychological effects as well as further health limitations. Large, chronic, and slow-healing skin wounds caused by severe trauma or extensive burns can lead to physiological dysfunctions. These wounds are more susceptible to infection and significantly impact the patient's quality of life.[5] In this article, we have reviewed the main mechanisms of stem cells and their exosomes for the regeneration of tissues damaged by trauma or burns in the field of regenerative medicine.

Natural Stages of Wound Repair and Regeneration

Wound healing is a complex physiological process that occurs immediately after the loss of skin integrity. This process typically involves four sequential and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling (Figure 1).[6]

Hemostasis

Hemostasis mechanisms are activated in response to trauma as the first stage of wound healing and can last up to two days. Coagulation is the main driving factor of this stage. Activation of the coagulation cascade initiates the hemostatic process and leads to vasoconstriction, platelet aggregation, and the deposition of a fibrin mesh. This formed clot is composed of aggregated platelets, which prevents further loss of fluids and electrolytes. Also, it provides the first line of defense against external pathogens at the wound site. The wound environment at this stage consists of aggregated platelets and their secretory factors, such as PDGF and TGF-β, which recruit various cells, including fibroblasts and inflammatory cells, to initiate the healing process.[7,8]

Inflammation

The hallmarks of inflammation include pain, increased temperature, redness, and swelling of the inflamed tissue, which are driven by the migration of inflammatory cells to the site of injury. A variety of vasoactive compounds (including serotonin, bradykinin, prostaglandins, and histamine) together with chemotactic factors are secreted by inflammatory cells during this process. Activation of local immune cells, including mast cells, δ and γ T lymphocytes, and Langerhans cells, at the tissue site results in the secretion of chemokines (such as extracellular matrix protein fragments, TGF-β, PDGF, and MCP-1) and cytokines (such as CSF-1, TNF-α, TGF-α, and IGF-1). Tissue-resident macrophages then initiate a local inflammatory response, leading to the influx of large numbers of neutrophils. Neutrophils play a crucial role in phagocytosing dead or damaged cells, bacteria, and foreign bodies to clean the wound. After that, neutrophils undergo programmed cell death (apoptosis) and are subsequently cleared through macrophage-mediated phagocytosis. In this situation, platelets and macrophages secrete cytokines and growth factors that promote the migration, proliferation, and angiogenesis within the connective tissue of the wound.[9,10]

Proliferation

The proliferation phase is characterized by the migration

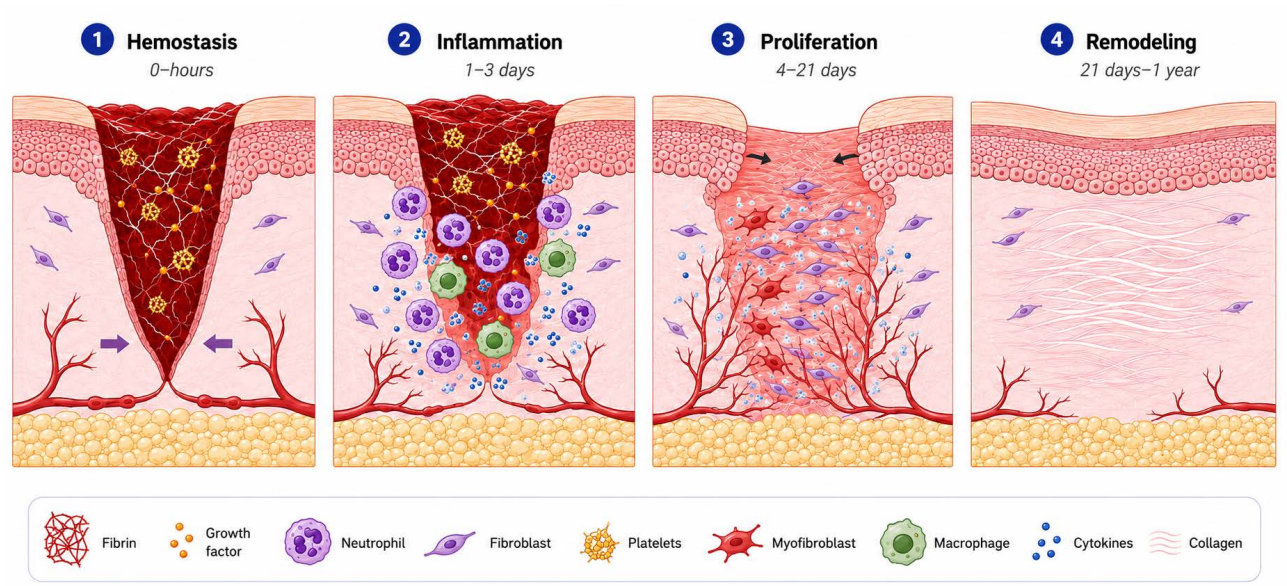

Figure 1. Stages of wound healing. Schematic overview of the four overlapping phases of cutaneous wound repair: hemostasis, inflammation, proliferation, and remodeling. The figure illustrates the temporal progression from clot formation and platelet activation to immune-cell recruitment, fibroblast and endothelial cell activity, granulation tissue formation, collagen deposition, wound contraction, and final tissue remodeling. Key cellular and molecular components involved in the process, including fibrin, platelets, growth factors, neutrophils, macrophages, fibroblasts, myofibroblasts, cytokines, and collagen, are shown in the legend. Original schematic illustration created by the authors using AI-assisted generation tools. No external sources were used for reproduction or adaptation

and proliferation of fibroblasts and vascular endothelial cells, the deposition of the extracellular matrix, and the formation of granulation tissue. This phase begins about three days after injury and lasts 2 to 4 weeks. Fibroblasts and keratinocytes play an important role in this phase. Upregulation of cell surface integrins strengthens fibroblast adhesion to fibronectin and fibrin in the provisional wound matrix, thereby promoting directed cell migration during the proliferative phase of wound healing. Factors such as fibronectin, PDGF, TGF-β, and EGF promote fibroblast migration. The early stages of wound healing are also characterized by hypoxia, which activates hypoxia-inducible factor-1α (HIF-1α). HIF-1α stimulates the expression of vascular endothelial growth factor (VEGF-A). This results in endothelial cell proliferation, increased wound capillary density, and restoration of blood flow.[11,12] Matrix metalloproteinase (MMP) secretion is essential and facilitates cell migration within the extracellular matrix and developing tissue. The formation of a granulation-tissue layer represents the final phase of the proliferation stage. Newly formed connective tissue (granulation tissue) replaces the clot made of fibrin and fibronectin. The predominant cell line in granulation tissue is fibroblasts, which produce significant amounts of fibronectin, hyaluronic acid, and collagen types I and III. These cells are essential in the later stages of the healing process. Eventually, fibroblasts differentiate into myofibroblasts, which play a key role in wound contraction.[13,14]

Remodeling

As the last and longest stage of skin repair, in the remodeling phase, tissue structure and function return to their normal state. This stage is pivotal in shaping both the ultimate quality of the repair process and the degree of scar formation that may occur. Type III collagen, produced by fibroblasts in the previous stages, is replaced by type I collagen in this stage, which increases the mechanical strength of the skin. By rearranging collagen fibers and regulating the extracellular matrix, Fibroblasts rebuild the tissue structure. Unnecessary blood vessels are removed by VEGF and matrix metalloproteinases to restore vascular density to normal levels.[14,15] The activity of M2 macrophages increases in this stage, contributing to extracellular matrix remodeling and helping to prevent fibrosis by secreting anti-inflammatory and regulatory factors. In chronic wounds, a disrupted repair phase leads to excessive collagen accumulation, thick scar formation, or incomplete tissue regeneration. Consequently, many novel therapies are designed to enhance this phase by stimulating fibroblasts, regulating the extracellular matrix, and controlling inflammation.[16]

Regenerative Medicine in Dermatology

Regenerative medicine in dermatology shifts wound care from simple coverage and closure toward functional restoration of skin structure, barrier integrity, vascular support, and mechanical strength. Effective healing depends on coordinated inflammation, angiogenesis, extracellular matrix remodeling, re-epithelialization, and control of scar formation. Regenerative strategies combine living cells, extracellular vesicles, growth factors, biomaterials, hydrogels, skin substitutes, and nanomedicine-based delivery systems to guide the wound microenvironment actively.[16] This is especially important in burns, diabetic ulcers, infected wounds, ischemic injuries, and chronic non-healing lesions, where inflammation, microbial burden, oxidative stress, impaired vascularization, and defective matrix repair disrupt normal healing.[5,6] Therefore, regenerative dermatology should be viewed as an integrated therapeutic framework in which biological signals, structural scaffolds, and controlled delivery platforms work together to improve functional skin regeneration rather than merely accelerate wound closure.[1,17,18]

Stem Cells and Their Applications

Stem cells are central to regenerative medicine because they combine self-renewal with the capacity to generate specialized cell types or regulate tissue repair through bioactive signaling. Depending on their developmental potential, they may be classified as totipotent, pluripotent, multipotent, or unipotent cells.[1]

In therapeutic research, pluripotent stem cells and adult stem-cell populations have been explored for tissue replacement, disease modeling, and repair of damaged organs.[3] However, in cutaneous wound healing, mesenchymal stem/stromal cells (MSCs) have attracted the greatest attention because they are comparatively accessible, immunomodulatory, and biologically active in damaged tissue environments.[2] MSCs can be isolated from several tissues, including bone marrow, adipose tissue, umbilical cord, dental pulp, and placenta. Their relevance to wound healing is not limited to differentiation into skin-associated cells. MSCs can influence inflammation, angiogenesis, fibroblast activity, keratinocyte migration, extracellular matrix deposition, and scar modulation through paracrine communication.[19] In a phase I pilot study, Zhang et al. administered human umbilical cord MSCs topically and intravenously to patients with diabetic foot ulcers and peripheral arterial disease; 14 of 15 ulcers closed within 1.5 months, while the remaining ulcer showed more than 95% closure.[20] Localized cell delivery has also produced encouraging signals. Mrozikiewicz-Rakowska et al. used allogeneic adipose-derived stem cells within a fibrin-gel platform for diabetic foot ulcers and reported a shorter time to 50% wound-area reduction compared with fibrin gel alone, 17.6 ± 1.5 days versus 25.5 ± 4.2 days.[21] At the evidence-synthesis level, Mei et al. reported that MSC therapy improved complete healing in diabetic foot ulcers, with an overall risk ratio of 1.63, although outcomes remained influenced by ulcer size, cell source, and delivery protocol.[22] In skin repair, these effects are particularly important because successful healing depends on the coordinated behavior of immune cells, endothelial cells, fibroblasts, and epithelial cells rather than on one cell type alone.

The therapeutic logic of MSC-based wound repair has

changed substantially over time. Earlier interpretations emphasized direct engraftment and replacement of damaged tissue, but current evidence suggests that many beneficial effects arise from transient signaling rather than durable cell integration.[23] MSCs release cytokines, chemokines, growth factors, and extracellular vesicles that can reduce excessive inflammation, stimulate neovascularization, promote granulation-tissue formation, and enhance epithelial closure, which explains why even limited cell survival after transplantation may still produce measurable biological effects in the wound bed.[24]

Stem-cell applications in dermatology include local injection of MSCs, topical application, incorporation into hydrogels, seeding onto scaffolds, integration into engineered skin substitutes, and combination with biomaterials designed to improve cell retention and survival. In diabetic foot ulcers, stem-cell therapy has been investigated as an adjunctive approach to improve ulcer closure, perfusion, and tissue repair, although clinical protocols remain heterogeneous in terms of cell source, dose, route of administration, and follow-up duration.[25]

Cell-free stem-cell-derived products have become an important extension of this field. MSC-derived extracellular vesicles, including exosome-enriched preparations, can transfer miRNAs, proteins, lipids, and other signaling molecules that regulate inflammation, angiogenesis, fibroblast migration, collagen organization, and re-epithelialization.[4] These systems may offer practical advantages over live-cell transplantation, including lower risks related to uncontrolled cell survival, easier storage, and better compatibility with biomaterial-based delivery. Nevertheless, extracellular-vesicle terminology and characterization must be used carefully because exosome-enriched products can contain mixed vesicle populations; current EV-reporting guidance emphasizes reproducible identity, purity, dose definition, and storage conditions.[25]

Growth Factors and Stimulation of Regeneration

Growth factors are endogenous signaling molecules that regulate cellular responses involved in the wound-healing process. These proteins are capable of stimulating cell proliferation, promoting wound repair, and, in some cases, inducing cellular differentiation. Growth factors are typically secreted proteins or steroid hormones. Their expression is regulated in response to tissue injury and varies according to the wound environment, healing phase, and local conditions. They are secreted by various cell types, including platelets, leukocytes, fibroblasts, and epithelial cells. Once released, growth factors exert their effects through autocrine, paracrine, or endocrine mechanisms by binding to specific membrane-bound or cytoplasmic receptors. Receptor activation initiates a cascade of intracellular signaling events that regulate cellular processes essential for wound repair. Even at low concentrations, growth factors can significantly influence the wound microenvironment, leading to enhanced cellular migration, proliferation, and differentiation.[26-28]

Among the various growth factors involved in wound repair, platelet-derived growth factors (PDGFs) play a critical role in tissue injury management and contribute to numerous cellular events during the healing process, including the recruitment of inflammatory cells, fibroblast proliferation and migration, intraepithelial collagen deposition, and granulation tissue formation.[29] During normal wound healing, platelets are among the first cell types to respond at or near the site of injury and are essential for the initiation and progression of tissue repair.[26,30] As a rich reservoir of growth factors, platelets release a variety of bioactive molecules, including PDGF. In addition to platelets, PDGF is also produced by macrophages, endothelial cells, fibroblasts, and keratinocytes, highlighting its central role in coordinating multiple aspects of the wound-healing response.[26,31]

Platelet-derived growth factor (PDGF) is the first and, to date, the only recombinant growth factor approved by the U.S. Food and Drug Administration (FDA) for topical administration, and it has been used clinically for the treatment of diabetic foot ulcers (Table 1).[26,31] PDGF participates in a variety of reparative processes, including soft tissue repair, bone healing, and epithelial regeneration.[32] Some of these effects may result from its interactions with other growth factors through additive, synergistic, or antagonistic signaling pathways that collectively regulate cellular activities involved in tissue repair.[32] Furthermore, PDGF has been shown to regulate cell growth and proliferation, and plays an important role in angiogenesis.[26,33,34] It is considered a potent mitogen and chemoattractant for mesenchymal cells, thereby contributing significantly to tissue regeneration and wound healing.[26,35] In patients with nonhealing lower-extremity

Table 1. Different products based on recombinant PDGF-BB that are currently under development, investigation, or clinical use

Recombinant Platelet-Derived Growth Factor (PDGF BB)	Stability & release in Chitosan	39,40
	Stability & release in gelatin biopolymer	41,42
	Stability & release in alginates biopolymer	43
	Stability & release in hyaluronic acid biopolymer	44,45
	Stability & release in cellulose biopolymer	46
	stability & release in collagen biopolymer	47,48
	stability & release in hydrogel polymer	49
	stability & release in polyvinyl alcohol (PVA) polymer	50
	stability & release in poly lactic-co-glycolic acid (PLGA) polymer	51
	stability & release in polylactide (PLA) polymer	52
	stability & release in polyglycolic acid (PGA) polymer	53
	stability & release in polyurethanes (PUs) polymer	54
	stability & release in polyethylene oxide (PEO) polymer	17
	stability & release in polyethylene glycol (PEG) polymer	55
	stability & release in polyhydroxyethyl methacrylate (PHEMA) polymer	56
	stability & release in polyvinyl pyrrolidone (PVP) polymer	57

diabetic ulcers, Smiell et al. reported that becaplermin, a recombinant human PDGF-BB gel, increased complete healing compared with placebo, approximately 50% versus 36%, and reduced time to closure.[36] EGF provides another clinically relevant example, especially for epithelial repair. Park et al. evaluated topical recombinant human EGF spray in a phase III multicenter, double-blind, randomized placebo-controlled trial and reported higher complete wound healing with rhEGF than placebo, 73.2% versus 50.6%.[37] For more advanced diabetic foot ulcers, Fernandez-Montequin et al. tested intralesional recombinant human EGF and reported improved granulation and healing outcomes, showing that delivery route can strongly influence biological exposure inside the wound bed.[38]

Clinical application of regenerative medicine

Regeneration of Burn Wounds

Burn-type skin injuries can cause permanent damage to the skin by thickening it. In less deep burns, grafting is often not necessary; if the wounds are treated with debridement and antimicrobial dressings, they heal spontaneously by regrowth of epithelial processes (hair follicles, sebaceous glands, and sweat glands) to cover the wounds. However, deep burns that do not heal within about 3 weeks and deep and extensive burns require replacement of the epidermal barrier with autologous keratinocyte grafts. Grafting can be performed by Split Thickness Skin Grafts (STSG), using solutions, keratinocyte sheets, or dermal-epidermal substitutes.[58] Transplanted autologous keratinocytes may remain in the wound for a long time, providing permanent wound closure, whereas allogeneic keratinocytes do not remain in the wound for more than a few days to weeks, during which time they exert their effects, secreting growth factors and extracellular matrix, and are then destroyed.[59] Studies indicate that the application of autologous tissue grafts or micrografts to deep and extensive burns is associated with delayed wound healing. This delayed healing is often characterized by the formation of excessive granulation tissue and a propensity for scar contracture. Conversely, grafts constructed from non-mesh sheets and rapidly applied to critical areas—such as the face, hands, feet, and perineum—are associated with reduced granulation tissue formation and minimized scarring. This method offers superior functional and aesthetic outcomes for patients.[60,61]

Achieving wound closure in cases of full-thickness burns at least requires the regeneration of a stable epidermis layer. The stability of the epidermis depends on the regeneration of the basement membrane and vascular connective tissues that connect the outer skin to the body. The skin is capable of self-repair, but it cannot replace epidermal appendages (hair follicles, sebaceous glands, sweat glands) or all sensory or motor nerves.[62,63] Table 2 summarizes the anatomical features of the skin in various repair conditions.

Cellular wound dressings

Numerous reports document the transplantation and replacement of skin cells, both temporary and permanent, for wound healing. Temporary cellular dressings have been developed through the direct harvesting of human cadaveric skin (either fresh or frozen) and porcine skin (which is preserved using chemical fixation or freeze-drying). In addition, allogeneic human fibroblasts or keratinocytes have been combined with biodegradable scaffolds partially denatured collagen, such as Apligraf, StrataGraft [64,65] or polyglycolic/polylactic acids such as DermaGraft [63] that deliver growth factors and extracellular matrix to the wounds for autologous healing. However, these scaffolds exhibit limited stability, typically lasting only a few days to weeks. On the other hand, autologous keratinocytes have been used as cultured cell sheets (e.g., the EpiCel) [66] and as spray cell suspensions (e.g., the ReCell).[67] They have also been used together with cultured fibroblasts as a dermal component, or in combination with a polymeric dermal scaffold containing autologous cultured fibroblasts.[68]

These approaches have helped improve outcomes in extensive burns, particularly by supporting wound coverage and reducing morbidity in patients with large

Table 2. Comparison of cell types in natural, engineered, and transplanted skin [59]

Tissue	Cell type or structure	Healthy tissue	STSG	Engineered skin substitutes	Healing after transplantation
Epidermis	Keratinocytes	+	+	+	+
	Hair follicle	+	-	-	-
	Sebocytes	+	-	-	-
	Sweat gland	+	-	-	-
	Melanocytes	+	±	±	±
	Immune cells	+	+	-	+
	Nerve	+	+	-	±
Dermis	Fibroblasts	+	+	±	+
	Endothelial cells	+	+	-	+
	Extracellular matrix	+	±	±	±
	Smooth muscle	+	+	-	±
	Immune cells	+	+	-	+
	Nerve	+	+	-	±

skin defects. However, currently available grafts and engineered skin substitutes still fail to fully restore native skin architecture, especially appendages such as hair follicles, sebaceous glands, sweat glands, and complete sensory structures.[59] Further progress is expected through advances in cellular and molecular sciences, biomaterial engineering, automated tissue fabrication, and three-dimensional bioprinting technologies; Future regenerative strategies should therefore aim not only to achieve wound closure but also to restore skin anatomy and physiology more completely, improve manufacturing efficiency, reduce treatment costs, and enable more precise wound assessment using non-invasive biophysical tools.[69]

New technologies in skin regeneration

Currently, tissue engineering in the skin is focused on the use of keratinocytes. In this method, these cells are isolated from the skin by enzymatic digestion and implanted on bioactive scaffolds. These scaffolds, which are either synthetically porous or biological, allow for adequate nutrition via injection and enhance cellular proliferation and differentiation to produce tissue that mimics the structural and biological properties of the skin. The incorporation of a dermal layer or biomimetic scaffold supports the elasticity and structural properties of the skin for lymphatics, vessels, and nerves, thereby improving skin function.[69,70] One of the problems with cellular scaffolds is the distance between their epidermal component and the site of diffusion of materials in the wound bed, which may prevent proper nutrition of these cells. To overcome this issue, mesenchymal stem cells and growth factors have been implanted into skin scaffolds to increase blood supply by stimulating angiogenesis. Other exogenous factors, such as negative pressure therapy (vacuum therapy), can increase endothelial cell migration and thus angiogenesis in situ, which leads to better skin regeneration by increasing oxygen and nutrient delivery and thus reducing the risk of infection.[71,72] Commercially available bilayered skin substitutes exist, but they do not fully reproduce native full-thickness skin, especially vascularization, immune cells, melanocytes, hair follicles, sweat glands, sebaceous glands, and normal appendage regeneration. Apligraf's FDA description specifically states that it lacks Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels, and hair follicles.[73]

Biopolymers in tissue engineering

Biopolymers are essential components in tissue engineering and wound healing, playing a vital role in the design of scaffolds, dressings, and localized drug delivery systems. It is biocompatible and biodegradable, mimics the extracellular matrix, and can be engineered to modulate physical and chemical properties. These characteristics create an ideal environment for cell adhesion, proliferation, migration, and differentiation, thereby accelerating the regeneration of damaged tissue.[74,75] Biopolymers are the basis of advanced skin tissue engineering and wound repair systems that have evolved in recent years from passive support matrices to bioactive platforms able to simultaneously modulate the wound microenvironment, modulate the inflammatory response, stimulate angiogenesis, and guide the structural remodelling of the epidermis and dermis. Meanwhile, natural biopolymers like collagen, gelatin, chitosan, alginate, hyaluronic acid, bacterial cellulose, and silk fibroin are still dominating biomedical research due to their similarity to the extracellular matrix, bioactive motifs for cell adhesion, and maintenance of the moisture balance and gas exchange (Table 3).[76] Nevertheless, the intrinsic limitations of these biomaterials, such as poor mechanical strength, fast degradation rate, and limited control over the release of therapeutic agents, can be significantly overcome by the development of composite systems and interpenetrating networks with synthetic polymers such as PCL [62], PLGA [77], PLA [78], PEG [79], and biodegradable polyurethanes.[80]

In recent years, dynamic hydrogels based on Schiff-base bonds, boronate ester linkages, and supramolecular interactions have attracted increasing attention for the treatment of chronic wounds, especially diabetic wounds, because of their injectability, self-healing ability, and response to wound-related stimuli such as pH, glucose, reactive oxygen species (ROS), and enzymes.[81] These smart hydrogel systems can modulate the controlled delivery of therapeutic agents, growth factors, antimicrobial peptides, metallic nanoparticles, and exosomes according to the pathophysiological condition of the wound microenvironment.[81] However, electrospun nanofibers based on gelatin/PCL, chitosan/PEO, silk/PLA, and other multicomponent systems have been widely developed due to their close structural similarity to the fibrous ECM of the skin, appropriate porosity, high surface-to-volume ratio, and ease of surface functionalization. These properties stimulate the adhesion and migration of keratinocytes and fibroblasts, allowing targeted delivery of antibiotics, anti-inflammatory agents, and regenerative biomolecules. Moreover, recent reports are showing an increasing interest in gelatin methacryloyl (GelMA)-based bioinks [82], modified alginate [83], methacrylated hyaluronic acid [84], and collagen-based blends [85] for three-dimensional skin bioprinting. Such systems have enabled the fabrication of multilayered scaffolds with more precise spatial organization of cells and preliminary vascular networks and controlled distribution of biological cues.[86]

Additionally, recent studies have indicated that the incorporation of mesenchymal stem cell-derived exosomes into biopolymeric platforms is one of the most promising therapeutic strategies for wound healing. These exosomes can reduce inflammation, enhance macrophage polarization toward the reparative M2 phenotype, increase angiogenesis, and accelerate epithelialization through the delivery of miRNAs, regenerative proteins, and paracrine signaling molecules.[87-89] However, their limited stability and rapid clearance have generated considerable interest in the use of biopolymeric hydrogels, microspheres, and nanofibrous scaffolds as protective reservoirs and localized delivery systems. Concurrently, there is a

Table 3. Characteristics of key biopolymers utilized in skin tissue engineering

Type of Biopolymer	Origin	Role in Skin Tissue Engineering	Advantages	Limitations	References
Collagen	Natural (Bovine/ Porcine)	Main structural component of ECM; promotes cell adhesion.	Excellent biocompatibility; low antigenicity; promotes hemostasis.	Poor mechanical strength; rapid biodegradation; risk of disease transmission.	92
Chitosan	Natural (Crustacean shells)	Antibacterial agent; promotes granulation tissue formation.	Hemostatic properties, high mucoadhesion; biodegradable.	Low solubility at neutral pH; poor mechanical stability in wet states.	93
Alginate	Natural (Brown Algae)	Hydrogel for exudate absorption; drug/cell delivery.	High porosity; easy to form hydrogels; non-toxic.	Lack of cell-binding sites (needs functionalization); slow degradation.	94
Silk Fibroin	Natural (Silkworm)	Structural scaffold for deep wounds.	High mechanical strength; tunable degradation; low inflammatory response.	High processing cost; batch-to-batch variability.	18,95
PLA / PLGA	Synthetic	Mechanical support; long-term scaffold stability.	High mechanical strength; predictable degradation rate; FDA-approved.	Hydrophobic (low cell attachment); acidic degradation products (can cause inflammation).	96
PCL	Synthetic	Long-term structural reinforcement.	Highly flexible; slow degradation; excellent processability (3D printing).	High hydrophobicity; very slow degradation (years); poor bioactivity.	97
Gelatin	Natural (Denatured Collagen)	Bio-ink for 3D printing; cell carrier.	Retains RGD sequences for cell binding; low cost; thermosensitive.	Low thermal stability; requires cross-linking to improve durability.	98

growing trend in the development of multifunctional smart wound dressings based on biopolymers that not only possess biocompatible and regenerative properties but also antimicrobial, antioxidant, tunable adhesive, and electrically conductive properties, and the capacity for continuous monitoring of wound-related parameters such as pH, temperature, and infection biomarkers. A review of recent studies in general indicates that the progress of biopolymers in skin tissue engineering has ranged from basic covering materials to sophisticated multifunctional, responsive, and customizable systems in combination with nanotechnology, exosome-based treatments, and bioprinting technologies. However, there are still some challenges, such as standardization, scalable production, and long-term stability, the inherent variability of natural materials, and demonstration of efficacy in human clinical studies. However, the current evidence is suggestive that these types of biomaterials will play an ever more important role in the near future in the treatment of complex wounds, burn injuries, and functional skin regeneration.[90,91]

Nanoparticles in drug delivery

Regenerative medicine is a leading field in medical science and contributes significantly to the development of new strategies for wound healing. It aims not only to close or heal wounds but also to restore the structure and function of damaged tissues to their original state, especially in chronic wounds that are difficult to treat using conventional methods. In this regard, nanotechnology, especially the application of different types of nanoparticles, has opened up new pathways for the improvement of the wound healing process.[99] Lipid nanoparticles are highly biocompatible, can encapsulate sensitive therapeutic agents, and are used to deliver growth factors or antibiotics to the wound site. Lipid nanoparticles can improve therapeutic efficacy while minimizing drug-related side effects.[100] Polymeric nanoparticles (e.g., PLGA and chitosan) can be used in the scaffolds for tissue engineering to allow bioactive agents and even stem cells to be released in a controlled manner to enhance the migration and proliferation of newly formed cells.[101]

In recent years, metallic nanoparticles such as silver, gold, and zinc oxide have attracted considerable attention, particularly due to their potent antibacterial properties and beneficial effects in preventing wound-site infections (Table 4). The incorporation of these nanoparticles into smart wound dressings has not only reduced microbial burden but also promoted angiogenesis and tissue regeneration.[102,103] Targeted and controlled delivery of regenerative drugs or growth factors such as VEGF has also been achieved using nano-liposomes and mesoporous silica nanoparticles as carriers. Furthermore, dendrimers are promising platforms for the delivery of genes or therapeutic proteins to specific target sites due to their highly branched architecture and extensive surface functionality. Another important feature is the development of stimulus-responsive smart systems. In this type of system, nanoparticles are activated under specific conditions of the environment, such as pH variation, presence of enzymes or reactive oxygen species in the wound microenvironment, and then the therapeutic agents are released at the right time and place. By combining these nanoparticles with biodegradable scaffolds or tissue-engineered hydrogels, the rate and quality of skin and soft tissue regeneration have been greatly enhanced (Figure 2). In conclusion, nanotechnology-powered regenerative medicine offers promising avenues for treating acute wounds, burns, diabetic ulcers, and other skin injuries, but further clinical studies and overcoming safety and biocompatibility challenges are still needed.[104,105]

Challenges and future aspects

Regenerative wound therapy has advanced rapidly, but translation remains uneven. Many platforms accelerate closure in small animal models; the same performance is harder to reproduce in older patients, diabetic wounds, infected ulcers, ischemic tissue, or extensive burns. The gap is biological, but it's also methodological. Preclinical

Table 4. Nanoparticles in Regenerative Medicine for Wound Healing

Nanoparticle type	Composition	Main mechanism in wound healing	Delivery system	Wound model	Therapeutic outcomes
Silver nanoparticles (AgNPs)	Metallic silver, Ag-loaded composites	Strong antibacterial activity, biofilm inhibition, and inflammation reduction	Hydrogels, films, nanofibers, dressings	Infected wounds, diabetic ulcers, burns	Reduced microbial burden, accelerated re-epithelialization, enhanced collagen deposition
Gold nanoparticles (AuNPs)	Gold nanospheres, nanorods	Anti-inflammatory effects, improved fibroblast proliferation, and angiogenesis support	Topical gels, scaffolds, composites	Full-thickness wounds, chronic wounds	Faster wound contraction, improved granulation tissue formation
Cerium oxide nanoparticles (CeO2 NPs)	Nanoceria	ROS scavenging, antioxidant effect, anti-inflammatory response	Hydrogels, scaffolds, gels	Chronic wounds, diabetic wounds	Reduced oxidative stress and enhanced tissue regeneration
Copper nanoparticles (CuNPs)	Cu or CuO nanoparticles	Pro-angiogenic activity, antimicrobial action	Dressings, hydrogels, electrospun matrices	Ischemic wounds, infected wounds	Increased neovascularization and faster healing
Mesoporous silica nanoparticles (MSNs)	Porous silica nanocarriers	High drug/growth factor loading, controlled release	Scaffolds, injectable hydrogels, coatings	Full-thickness and chronic wounds	Improved regenerative signaling and tissue repair

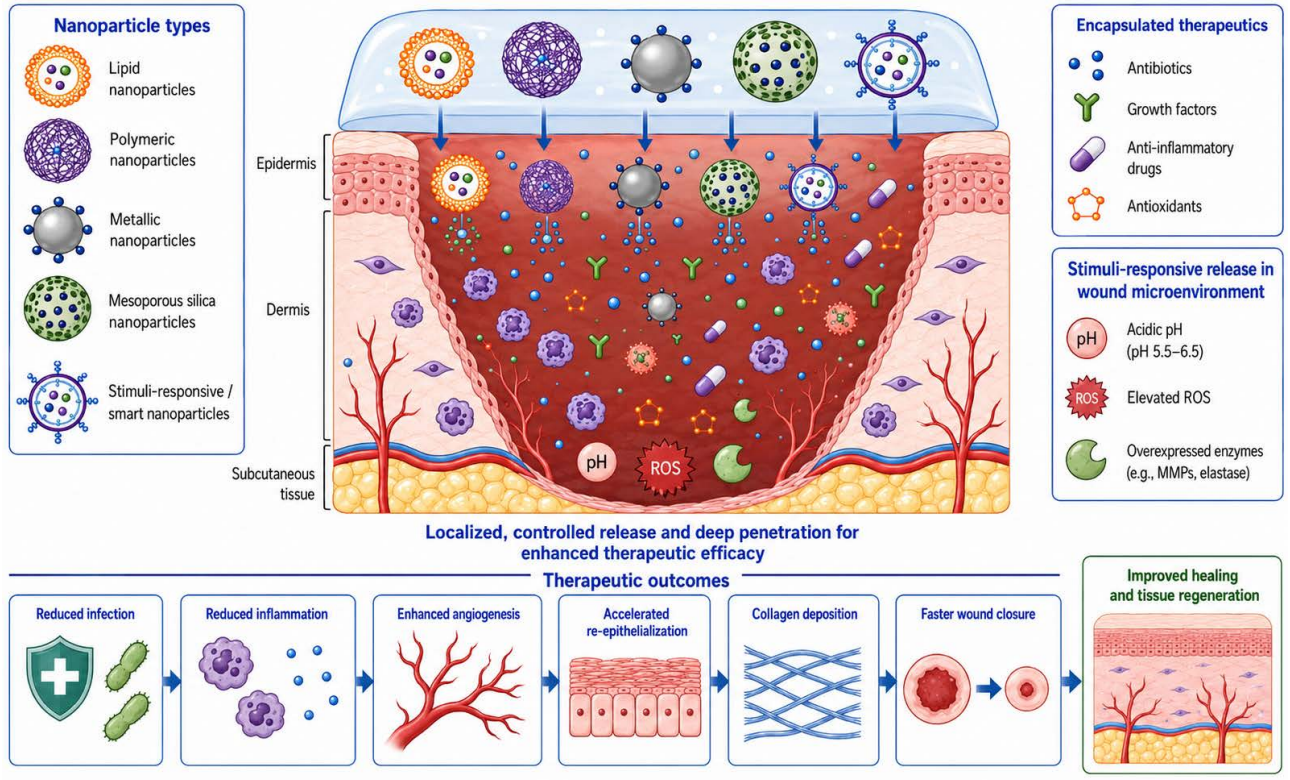

Figure 2. Schematic illustration of nanoparticle-mediated targeted drug delivery strategies in skin wound regeneration. Original schematic illustration created by the authors using AI-assisted generation tools. No external sources were used for reproduction or adaptation

closure data need to be supported by reproducible product attributes and functional potency assays [106] before they can be interpreted as clinically meaningful evidence. Standardization remains a major barrier because product identity is unstable across platforms. Stem-cell products vary with donor, tissue source, culture conditions, passage number, and storage.[2] Exosome-enriched preparations differ by cell type, isolation method, vesicle purity, and cargo composition; current EV-reporting guidance therefore emphasizes rigorous characterization, dose definition, and cautious terminology.[107] Natural biopolymers vary by source and processing, while nanoparticles add further variables such as size, surface charge, coating chemistry, degradation, biodistribution, and clearance.[74,99] Together, these sources of variability make cross-study comparison difficult and highlight the need for clearer release criteria, standardized characterization, and clinically relevant functional endpoints.[108]

Release criteria and potency assays should be aligned with the proposed mechanism of action rather than limited to descriptive characterization. For example, an angiogenic dressing should be evaluated differently from an antimicrobial hydrogel or an exosome-loaded scaffold intended to modulate macrophage polarization. In cell- and gene-therapy contexts, potency assurance is increasingly viewed as a science- and risk-based strategy rather than a single end-product assay.[106] When manufacturing changes occur, comparability planning should also consider critical quality attributes and their relationship to product performance.[108]

Safety has to be integrated into the design process rather than appended after efficacy testing. Pro-angiogenic

therapies may help ischemic or diabetic wounds, but uncontrolled vascular stimulation is not automatically desirable. Antimicrobial nanoparticles can reduce infection yet may harm mammalian cells at inappropriate concentrations. Growth factors can improve repair, but they require careful dosing and spatial control. For living skin substitutes, cell-based products, and extracellular-vesicle preparations, the evolving regulatory landscape means that sterility, immunogenicity, preparation time, cost, and product classification strongly influence clinical adoption.[109]

Future therapies will likely be more integrated and more patient-specific. A dry ischemic wound, an infected exudative ulcer, and a deep burn do not require the same dressing. Combining wound diagnostics with smart biomaterials, controlled release, exosome-based signaling, antimicrobial protection, and bioprinted tissue architecture could more closely align treatment with wound biology. Nanoparticle-infused hydrogels illustrate this direction because they can combine moisture balance, local retention, and tunable drug release within one platform.[110] The strongest future systems will be those that are not only biologically active but also manufacturable, safe, affordable, shelf-stable, and practical in routine wound-care settings.

Conclusion

In recent years, regenerative medicine has attracted the attention of many researchers and clinical experts as one of the leading fields in the treatment of various types of wounds. This branch of therapy has been able to significantly improve the repair process of damaged tissues and promises a good future for the treatment of patients using new technologies such as stem cells, bioscaffolds, and growth factors. Mesenchymal stem cells play a key role in tissue regeneration due to their ability to differentiate into skin, muscle, and vascular cell types. Studies have shown that injection of these cells into the wound area stimulates angiogenesis, reduces inflammation, and accelerates the healing process. In contrast, the use of bioscaffolds such as hydrogels and nanoparticles provides a suitable environment for cell growth and migration. They can also act as a platform for the transfer of growth factors and drugs. These scaffolds provide the necessary physical structure for tissue regeneration and optimize the repair process by interacting with host cells. Also, growth factors such as VEGF, PDGF, and EGF play an important role in chronic wound healing by stimulating cell proliferation and the formation of new blood vessels. The combination of these factors in the form of multimodal therapies has achieved better clinical results than traditional methods and has reduced scar formation, infection, and healing time. The future outlook for regenerative medicine in wound healing is moving towards personalized treatments based on patients' genetic data or patient history. Technologies such as 3D bioprinting, gene therapy, and nanomedicine have enabled the design of precise and targeted treatments that can meet the specific needs of each patient. Considering the available scientific evidence, it can be concluded that regenerative medicine has not only provided new hope for the treatment of chronic and refractory wounds but also opened a new path for improving the quality of life of patients.

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Competing Interests

References 27 and 28 were authored/co-authored by the corresponding authors and published in the same journal series; they are cited solely for scientific relevance.

Ethical Approval

Not applicable.

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