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Review

Advances in Stem Cell Applications for Wound Healing

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Abstract

With the growing use of stem cells in burn treatment, their notable therapeutic effects, ease of accessibility (e.g., peripheral blood stem cells), and broad availability have significantly elevated their research value. This review explores the role of stem cell-based strategies in advancing drug discovery for wound healing, with emphasis on their underlying mechanisms, therapeutic potential, and translational applications. Wound healing proceeds through haemostasis, inflammation, proliferation, and remodelling-processes mediated by cellular events, cytokines, and key pathways such as NF-κB, PI3K/Akt/mTOR, and Wnt/β-catenin. Stem cells play a pivotal role in this process by promoting angiogenesis, extracellular matrix (ECM) formation, and collagen remodelling, while also modulating inflammation and enhancing tissue regeneration through the secretion of TGF-β and VEGF. Stem cell-based interventions represent a promising avenue for drug development in wound healing, offering solutions to unmet clinical needs through innovative therapies and personalized medicine. This review highlights recent progress and outlines future directions in this rapidly evolving field.

Keywords

Stem cell therapy, Wound healing, Skin regeneration, Inflammation, Injury

Article History

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1. Introduction

Stem cells are unspecialized cells with the ability to self-renew and differentiate into various lineages and specialized cell types [1]. This creates an opportunity for scientists to study drugs using stem cells, as they can expand and differentiate into specialized cells that serve as platforms for in vitro disease treatment, while avoiding the ethical concerns associated with animal models [2].

Firstly, stem cells possess multipotency, enabling them to generate specific cell lines through differentiation. Researchers can harness this potential by differentiating stem cells into specialized cell types. This enables the study of cellular mechanisms in response to novel drugs, including effects on cell behavior, cytotoxicity, viability, and potential genotoxicity [3,4]. Moreover, stem cells can be used to generate disease-specific cell lines by introducing genetic mutations through engineering techniques [5]. By reprogramming the genetic architecture of the cell, some genetic diseases can be replicated in the cell line. This enables researchers to assess the efficacy of novel drugs in treating or suppressing the target disease [5]. For instance, scientists have reprogrammed somatic cells into induced pluripotent stem cells (iPSCs) carrying genetic mutations associated with specific diseases through genetic editing [6]. These iPSCs can differentiate into disease-relevant cell types, such as neurons for neurodegenerative disorders or cardiomyocytes for heart disease, enabling researchers to test drug efficacy directly in these cells [7,8].

Next, the stem cell-based model is also applied in the study of toxicology to understand how the drug interacts with the cells in the body [9]. For drug toxicity screening, stem cell models can be differentiated into mature cell types. These differentiated cells can then be used to determine drug toxicity, including the half-maximal inhibitory concentration (IC50) and lethal dose 50 (LD50), prior to in vivo animal studies and clinical trials [10]. Conducting preliminary studies to identify lethal concentrations can help ensure the safety of subsequent in vivo models. Moreover, organoids and tissues made from stem cells can be used by researchers to assess the safety and effectiveness of possible medication candidates in a setting that is more physiologically appropriate [11]. By identifying viable drug candidates earlier in the development process, this method cuts down on the time and expense involved with standard drug discovery pathways. Furthermore, stem cells derived from the patient can also be used as cell models for personalized medicine [12]. Personalized drug screening and treatment strategies are enabled by creating patient-specific cell lines using stem cell technologies. Using patient-derived iPSCs, researchers can evaluate drug effectiveness in vitro and tailor treatment plans to each individual's genetic background and disease characteristics [13]. By choosing the most appropriate medicines for each patient, this individualized strategy may enhance treatment outcomes and decrease adverse medication responses.

2. Signaling Mechanism

Wound healing is a fundamental biological process that occurs when tissue integrity is disrupted. It encompasses the entire progression from wound formation to the restoration of healthy, functional tissue [14]. The wound healing process is typically divided into four phases: hemostasis, inflammation, proliferation, and remodelling [14,15]. Cytokines, chemokines, and growth factors play essential roles in regulating and promoting wound healing [16]. Figure 1 summarizes the four phases of wound healing.

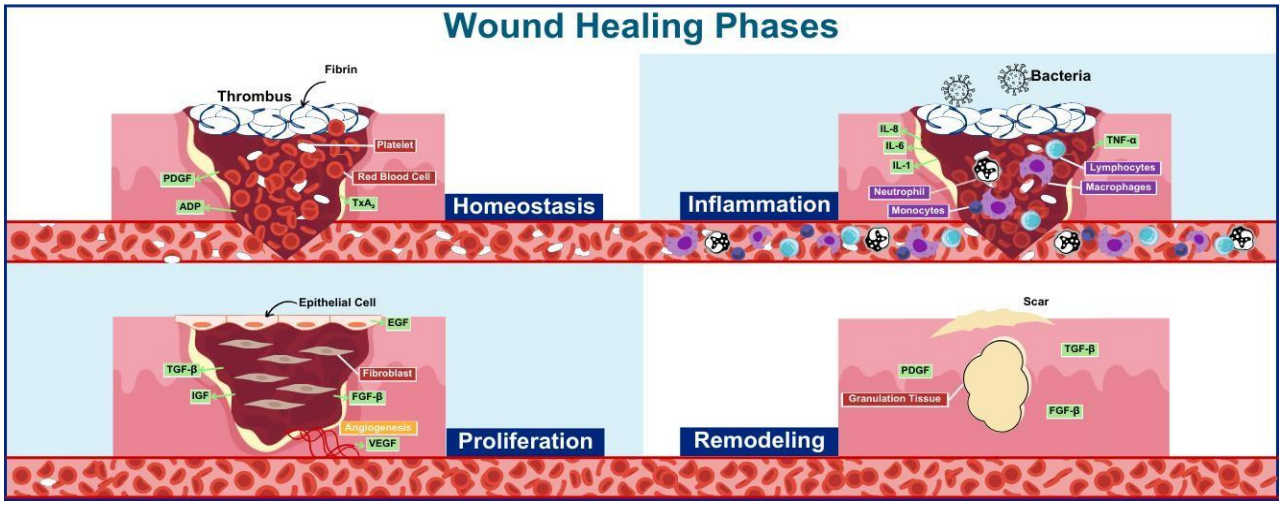

Figure 1. Indicates the four phases of the wound healing process.

Overview of the four phases of wound healing: hemostasis, inflammation, proliferation, and remodeling. Key cells and signaling molecules involved in each phase are illustrated, including platelets, immune cells, fibroblasts, and growth factors such as PDGF, VEGF, TGF-β, and ILs.

Table 1. Summary of wound healing phases and their associated cellular and physiological events, growth factors and inflammatory cytokines involved, and signalling mechanisms.

Wound healing phase	Cellular and physiological event	Growth factor and inflammatory cytokines	Signaling mechanism	Ref
Hemostasis	• Vascular constriction • Platelet aggregation and degranulation • fibrin formation	• PDGF • TF • Thromboxane A2 (TXA) • Endothelin-1 (ET-1)	• Platelet activation pathways, such as Glycoprotein VI (GPVI) pathway, Thromboxane A2 (TXA2) pathway • ADP pathway	[14] [16] [17]
Inflammation	• Neutrophil infiltration • Monocytes infiltration • Macrophage differentiation • Lymphocytes infiltration	• TNF-α • IL-1 • IL-6 • IL-8 • PDGF	• NK-κB signaling pathway • MAPK signaling pathway	[13] [16] [18]
Proliferation	• Re-epithelialization • Angiogenesis • Collagen synthesis • ECM formation	• TGF-β • VEGF • FGF-β • EGF • IGF	• TGF-β signaling pathway • PI3K/Akt/mTOR signaling pathway	[14] [19]
Remodeling	• Collagen remodelling • Vascular maturation and regression	• TGF-β • FGF-β • PDGF	• Wnt/β-catenin Signaling Pathway	[14] [20] [21]

In the hemostasis phase**,** the process begins rapidly upon wounding, involving vascular constriction and fibrin clot formation [14]. Platelet aggregation also occurs at this stage to promote blood clotting. Key growth factors and cytokines involved include PDGF, tissue factor (TF), thromboxane A2 (TXA2), and endothelin-1 (ET-1) [17]. The signalling mechanism in this phase primarily involve platelet activation pathways, including the glycoprotein VI (GPVI) pathway which involves in the platelet activation and aggregation result from an interaction between the GPVI receptor on platelets and the collagen that is exposed at the site of injury; Thromboxane A2 (TXA2) that involves in the platelet aggregation and vasoconstriction, and ADP pathway that enhances platelet aggregation and recruits extra platelet to the site of injury [16]. Next is the inflammation phase, during which leukocytes-including neutrophils, lymphocytes, and monocytes-infiltrate the wound tissue. Monocytes differentiate into macrophages at this stage [13]. Cytokines involved include TNF-α, IL-1, IL-6, IL-8, and PDGF [16]. For the signaling pathway, the NK-κB signaling pathway that used to activate B cells to promote the expression of proinflammatory cytokines, and the MAPK signaling pathway, which mediates cellular responses to inflammatory cytokines [18].

The next phase is the proliferative phase, during which re-epithelialization takes place. Epithelial cells proliferate and migrate across the provisional matrix within the wound site [14]. Concurrently, angiogenesis occurs to supply sufficient oxygen and nutrients to the wound area, thereby promoting tissue repair [14]. Extracellular matrixes such as collagen also start forming and synthesizing in this phase. TGF-β, VEGF, FGF-β, EGF and IGF are produced in the proliferative phase [19]. The signaling pathway involves the TGF-β signaling pathway to promote fibroblast proliferation, ECM synthesis, and angiogenesis, and PI3K/Akt/mTOR signaling pathway that is used to promote cell survival, proliferation, and protein synthesis during tissue repair and regeneration in the proliferative phase [20]. The final phase is the remodelling phase that may persist for months to years following intense cell proliferation and ECM deposition [14]. During this phase, the regression of newly formed capillarie**s** helps restore vascular density to baseline levels. The central event of this stage is ECM remodeling, which reorganizes the tissue matrix to more closely resemble normal architecture [14]. The physical contraction of the wound during the entire wound-healing process is believed to be mediated by contractile fibroblasts, also known as myofibroblasts, which develop within the wound [14]. Growth factors and signaling pathways involved in this phase include TGF-β, FGF-β, PDGF, and Wnt/β-catenin, which regulate ECM synthesis, myofibroblast differentiation, and tissue remodeling. Activation of these pathways promotes fibroblast function and collagen deposition [21].

3. General Summary For Stem Therapy Towards Wound

3.1 Mesenchymal Stem Cells (MSCs) Approach

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes, and are sourced from tissues including adipose tissue, bone marrow, and Wharton jelly of the umbilical cord [22]. Their regenerative potential has garnered significant attention in tissue repair and wound healing [23]. MSCs exhibit several key properties that make them valuable in the field of regenerative medicine:

- Self-Renewal: MSCs possess the ability to replicate indefinitely while retaining their undifferentiated state, enabling long-term therapeutic applications [24].
- Differentiation Potential: Under specific conditions, MSCs have the ability to differentiate into multiple cell

types from the mesodermal origin, such as bone, cartilage, and fat cells [22].

- Immunomodulatory Effects: MSCs modulate immune responses by secreting anti-inflammatory cytokines, thereby reducing tissue inflammation and facilitating repair [25].

The therapeutic mechanisms of MSCs in wound healing are multifaceted, beginning with their ability to modulate the local inflammatory environment [26]. MSCs secrete anti-inflammatory cytokines to suppress the inflammatory condition of the wound by releasing cytokines that include interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which mitigate excessive inflammation that can delay healing [26]. Moreover, MSCs influence immune cell behavior, particularly by polarizing macrophages from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype. This transition supports the progression from the inflammatory phase to the proliferative phase of wound healing [27,28].

Additionally, MSCs were proven to promote angiogenesis as these cells are capable to release of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which stimulate the formation of new blood vessels [29]. Enhanced vasculature is essential for improving nutrient and oxygen delivery to the wound site, thereby accelerating tissue repair [30]. MSCs also stimulate endothelial cell proliferation and migration, further contributing to neovascularization at the site of injury [31]. Moreover, MSCs facilitate epidermal regeneration by promoting the proliferation and migration of keratinocytes, the key cells involved in re-epithelialization [32]. Their secretion of matrix metalloproteinases (MMPs) supports extracellular matrix (ECM) remodelling, allowing for the integration of newly formed tissue with the surrounding healthy tissue [33]. These combined properties underscore the therapeutic potential of MSCs in enhancing wound healing through their immunomodulatory, pro-angiogenic, and tissue-regenerative functions.

Treatment using MSCs is often combined with other therapeutic modalities and has shown promising results. For example, biodegradable scaffolds can provide structural support while delivering MSCs directly to the wound site. They can be designed to release growth factors gradually, enhancing tissue regeneration [34]. Hydrogel has also been widely used as a wound treatment intervention [35]. Hydrogels that are infused with MSCs or their exosomes can create a moist wound environment conducive to healing while providing sustained release of therapeutic agents [36-38].

Future research may focus on optimizing delivery methods to enhance the therapeutic efficacy of MSCs at the wound site. This includes investigating various delivery routes (e.g., local injection vs. systemic administration) to maximize efficacy while minimizing risks [39]. Personalized medicine approaches, such as tailoring treatments based on individual patient characteristics or specific wound types, could further enhance therapeutic outcomes [40]. By harnessing their unique properties and mechanisms of action, researchers are paving the way for innovative therapies that could revolutionize how we approach chronic wounds and tissue repair.

3.2 Induced Pluripotent Stem Cells (iPSCs) Approach

The induced pluripotent stem cells (iPSCs) are a revolutionary discovery pioneered by Shinya Yamanaka. They have transformed the field of medical biotechnology by offering innovative approaches for treating previously intractable diseases [41]. iPSCs are generated by reprogramming mature somatic cells into immature cells with pluripotency, thereby enabling them to differentiate into any cell type in the body [42]. This remarkable versatility has positioned iPSCs at the forefront of regenerative medicine, with potential applications spanning the treatment of neurodegenerative disorders such as Parkinson's disease, cardiovascular diseases like heart failure, diabetes, and spinal cord injuries [43,44]. Beyond these areas, iPSCs are also being actively investigated in personalized medicine, where patient-derived cells can be used to model disease pathology, tailor treatments, and advance drug discovery and toxicology screening [45].

With recent advances in medical biotechnology, iPSCs have emerged as a promising tool for addressing the complex mechanisms of wound healing [46]. One of the key mechanisms by which iPSCs contribute to wound repair is through the modulation of inflammation. iPSC-derived cells secrete a series of cytokines and growth factors that help regulate the inflammatory response, which is often dysregulated in chronic wounds [47]. These factors facilitate the macrophages to recruit and activate, thus transitioning the wound from the inflammatory to the healing phase [46].

Furthermore, iPSCs exhibit the capacity to stimulate angiogenesis, a crucial process for wound healing [48]. iPSC-derived endothelial cells (iPSC-ECs) have shown significant potential in promoting the formation of new blood vessels, which is essential for delivering oxygen and nutrients to the wound site [49]. Studies have shown that iPSC-ECs enhance perfusion recovery in ischemic conditions and promote wound closure by facilitating vascularization [49].

Another key aspect of iPSC-mediated wound healing depends on the iPSCs' capability to differentiate and develop into a wide range of specialised mature cells that are required for tissue regeneration [50]. iPSCs can give rise to keratinocytes, which are essential for re-epithelialization, as well as fibroblasts, promote extracellular matrix deposition, collagen synthesis, and granulation tissue formation [50]. Additionally, iPSC-derived smooth muscle cells contribute to the stabilization and functional integrity of the vasculature during the healing process [51]. The paracrine effects of iPSC-derived cells also enhance tissue regeneration by releasing signalling molecules that stimulate surrounding cells involved in wound repair [47].

Despite the significant therapeutic potential of iPSCs, several challenges remain, particularly in terms of safety. One of the primary concerns is the risk of tumorigenesis due to the presence of residual undifferentiated cells following transplantation [52]. Ensuring complete differentiation and eliminating any undifferentiated cells is crucial to mitigate this risk. Additionally, although iPSCs offer advantages—high versatility, fewer ethical concerns than embryonic stem cells, and potential autologous use in personalized medicine—these safety issues must be carefully addressed to fully realize their clinical applications [13,53].

3.3 Extracellular Vesicles or Exosomes

Exosomes are small membrane-bound vehicles (30-150 nm in diameter) secreted by various cell types into the extracellular space. They play a key role in intercellular communication by transferring bioactive molecules such as proteins, lipids, mRNAs, and microRNAs (miRNAs) between cells [54]. This transfer of information can modulate the behaviour of recipient cells, making exosomes vital in processes like wound healing [55]. Exosomes originate from the inward budding of endosomal compartments known as multivesicular bodies (MVBs). When these MVBs fuse with the plasma membrane, they release exosomes into the targeted cells [56]. Exosomes can carry a wide range of molecular contents and may vary significantly depending on the cell type and its physiological or pathological state.

In facilitating wound healing, exosomes have been found to regulate inflammatory responses by delivering anti-inflammatory cytokines and miRNAs to immune cells [57]. This action helps to reduce excessive inflammation, which is often a barrier to effective healing [58]. For instance, exosomes derived from mesenchymal stem cells (MSCs) have been shown to downregulate pro-inflammatory cytokines and promote an anti-inflammatory environment conducive to healing [58]. Furthermore, exosomes also promote angiogenesis, which is critical for supplying nutrients and oxygen to healing tissues. Exosomes have been demonstrated to promote angiogenesis by enhancing endothelial cell proliferation and migration [59]. For example, MSC-derived exosomes can stimulate vascular endothelial cells, leading to increased capillary formation in wound sites [60]. Moreover, exosomes enhance the proliferation and migration of key cell types involved in wound healing, such as fibroblasts and keratinocytes [61]. Studies indicate that exosomes derived from induced pluripotent stem cells can significantly increase fibroblast migration and collagen synthesis, which are essential for tissue repair [62]. Exosomes are also important components in contributing to the remodelling of the extracellular matrix (ECM), facilitating tissue regeneration [63]. They carry enzymes and factors that regulate ECM components, promoting a balanced deposition of collagen and other matrix proteins necessary for structural integrity during healing.

The use of exosomes as a stem cell-free therapy offers several benefits, including the minimization of potential risks associated with cell transplantation, such as immune rejection and tumorigenesis [64]. Moreover, exosome therapy can be administered without the complexities involved in stem cell handling. In addition, current research focuses on engineering exosomes to enhance therapeutic effects by modifying their cargo or surface properties to improve targeting and efficacy. For instance, genetically engineered exosomes can be designed to carry specific therapeutic agents or enhance their binding to target cells [65,66].

Although exosome therapy offers several benefits in disease treatment, its widespread application is hindered by challenges such as a lack of standardization and quality control. There is currently no standardized method for isolating and characterizing exosomes, which leads to variability in therapeutic efficacy [67]. Establishing protocols for consistent production is essential for future clinical applications. Besides, while exosomes have inherent targeting capabilities due to their biocompatibility, improving their specificity for particular cell types or tissues remains a challenge [68]. From a future perspective, exosome studies should focus on optimizing isolation techniques to develop more efficient methods for isolating high-purity exosome populations. Moreover, scientists should aim to fully understand the underlying mechanisms by which exosomes exert their effects on different cell types during wound healing. Well-designed clinical trials are also needed to evaluate the safety and efficacy of exosome-based therapies across diverse patient populations.

In conclusion, exosomes represent a promising frontier in wound healing therapies due to their ability to modulate inflammation, promote angiogenesis, enhance cell proliferation, and facilitate ECM remodelling. As research progresses towards addressing these existing challenges, exosome-based therapies could become integral components of clinical strategies for managing chronic wounds effectively.

3.4 3D Bioprinting

3D bioprinting combined with stem cells is revolutionizing wound healing strategies by enabling the creation of customized, bioactive scaffolds that can enhance tissue regeneration [69]. This strategy makes use of cutting-edge 3D printing technology in conjunction with the special qualities of stem cells, especially their capacity to differentiate into multiple cell types and secrete advantageous substances. Ensuring adequate vascularization in the newly formed tissue remains one of the most critical challenges in wound healing [70]. 3D bioprinted constructs can be designed with vascular channels or embedded with endothelial cells to promote angiogenesis and re-epithelization [71]. Studies have shown that ADSC-laden scaffolds significantly enhance neovascularization in wound models, leading to improved healing outcomes [72,73].

The mechanism by which 3D bioprinting facilitates wound healing can be summarized as follows. The first key step

involves the customization of scaffolds. 3D bioprinting enables the precise fabrication of scaffolds tailored to the specific dimensions and shape of a wound [74]. Using computer-aided design (CAD), clinicians can create structures that closely mimic the natural architecture of the skin, including features such as pores for nutrient exchange and vascularization [75]. This customization is crucial for effective integration with the host tissue. The layer-by-layer printing technique enables the deposition of multiple bioinks, which can include living cells, growth factors, and extracellular matrix (ECM) components [76]. This method ensures that different cell types are placed in specific locations within the scaffold, promoting optimal cellular interactions and functionality necessary for healing. Stem cells, such as adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (iPSCs), are often incorporated into 3D-printed scaffolds [77–79]. These cells contribute to wound healing through several mechanisms, including their differentiation potential. The stem cells can differentiate into various cell types required for skin regeneration, such as keratinocytes and fibroblasts [33]. Additionally, through paracrine effects, these cells release growth factors and cytokines that enhance angiogenesis, reduce inflammation, and promote cell migration and proliferation [47].

3.5 Advanced Therapy to Facilitate Wound Healing - Organoids

In recent years, organoids-three-dimensional, miniaturized versions of organs grown from stem cells or somatic cells in vitro-have gained prominence in the field of regenerative medicine [80,81]. These organoids mimic the cellular architecture and functions of their corresponding tissues, making them valuable models for studying disease processes and tissue regeneration [82]. When applied to wound healing, organoids can be engineered to replicate skin, epithelial layers, or even more complex tissues, providing a rich source of cells that can accelerate the healing process [47,83].

A recent study by Wang et al. (2024) reported that skin organoids generated from iPSCs were applied to wound sites caused by frostbite [84]. These organoids served as a scaffold for new tissue growth, significantly accelerating wound healing by reducing early inflammation and increasing the proportion of epidermal stem cells. This contributed to the restoration of both dermal and epidermal layers of the skin. Furthermore, the organoids also helped regenerate the wound site into normal skin tissue by lowering the overall proportion of fibroblasts, reducing fibroblast-to-myofibroblast transition, regulating the integrin α5β1–FAK signaling pathway, and remodeling the extracellular matrix (ECM) through coordinated degradation and reassembly. These effects ultimately promoted the restoration of normal ECM architecture and reduced excessive matrix accumulation associated with abnormal scar formation [84].

In a recent study, Choudhury et al. (2024) bioengineered mesenchymal stem cells (MSCs) to overexpress the cognate receptor of CXCL2, CXCR2 [85]. The bioengineered MSCs were cultured and induced to differentiate into keratinocytes, which subsequently formed 3D organoids. Grafting the 3D organoids onto relatively avascular, non-healing wounds in aged type 2 diabetic db/db transgenic mice significantly improved wound closure, with enhanced epithelialization of the epidermis and increased endothelialization in the dermis.

In addition, Zhang et al. (2024) reported that their team developed 3D-bioprinted artificial skin using organoids derived from adult stem cells to evaluate its effectiveness in repairing skin defects in mice [86]. Researchers cultured a mixture of human skin cells (keratinocytes, fibroblasts, and vascular endothelial cells) to form cell spheres that mimicked the structure of real skin, with an outer layer of epidermal cells and a core containing dermal and blood vessel cells. These cell spheres were then used to print artificial skin through 3D bioprinting. The artificial skin was applied to mice with full-thickness skin defects, and its healing performance was compared to that of traditional hydrogel dressings. Over 16 days, the organoid-treated wounds healed faster, showing better skin layer formation, stronger attachment between the epidermis and dermis, and more compact collagen fibres. In contrast, the hydrogel group showed slower healing and weaker skin structure. These findings suggest that 3D-bioprinted organoid-based artificial skin holds significant potential for future applications in skin repair therapies.

Researchers have developed a new type of skin substitute, called epidermal organoids (EpiOs), from induced pluripotent stem cells (iPSCs) to improve wound healing and skin regeneration [86]. Unlike traditional models based on two-dimensional (2D) cultures of primary cells such as keratinocytes and fibroblasts, these three-dimensional (3D) organoids more closely replicate native skin architecture and function. These iPSC-derived epidermal organoids (iEpiOs) grow easily and can be expanded through several cycles while maintaining the characteristics of normal skin. They contain stem cells capable of differentiating into various skin cell lineages, including hair follicle cells. This makes them a more physiologically relevant model for skin research. iEpiOs also produce extracellular vesicles (EVs), nanoscale particles that transport essential biomolecules such as growth factors (e.g., VEGF) and microRNAs (miRNAs). These EVs can promote wound healing by encouraging cell growth, migration, and the formation of new blood vessels (angiogenesis).

Thus, iEpiOs represent a promising platform for regenerative medicine, with the potential to support cell-free therapeutic approaches based on their secreted EVs.

Table 2. General summarization of Stem Therapy to Promote Skin Regeneration

Type of stem cell therapy	Strategy
Mesenchymal stem cells (MSCs)	Promote angiogenesis, support endothelial cell proliferation and migration, ECM remodelling.
Induced pluripotent stem cells (iPSCs)	Stimulate angiogenesis, differentiate into a wide range of specialized cells (e.g., keratinocytes, fibroblasts, smooth muscle cells) to facilitate tissue regeneration.
Direct use of exosome or extracellular vesicles	Regulate inflammatory response, promote angiogenesis.
Stem cells incorporated by 3D printing	Layer-by-layer deposition of stem cells in printed structures, acting as scaffolds promoting stem cell differentiation into mature cell types for skin regeneration.
Stem cells derived organoids	Serve as scaffolds, increase epidermal stem cells to restore both dermal and epidermal layers, reduce fibroblast-to-myofibroblast transition, preventing scar formation and promoting normal ECM formation.

4. Conclusion

Wound healing is a highly complex and dynamic process that involves a series of well-coordinated phases, each governed by specific cellular events and signalling pathways. The hemostasis phase initiates rapidly upon injury, involving platelet aggregation and clot formation, setting the foundation for subsequent healing. Inflammation follows, where immune cells infiltrate the wound site, clearing debris and releasing cytokines that mediate the inflammatory response. The proliferative phase is characterized by reepithelialization, angiogenesis, and extracellular matrix formation, which is essential for tissue regeneration. Finally, the remodelling phase, which can last for years, refines the wound's architecture, reducing vascular density and achieving a tissue structure that closely resembles the original. The intricate interplay between growth factors such as TGF-β, VEGF, and PDGF, and signaling pathways including PI3K/Akt/mTOR and Wnt/β-catenin, plays a critical role in orchestrating these phases and ensuring effective tissue repair.

Future research will likely continue to focus on understanding the molecular mechanisms driving each phase of wound healing in greater detail. Stem cells have been shown to enhance tissue regeneration, while modulation of inflammation holds significant potential for therapeutic intervention. Moreover, with advances in the field of tissue engineering and regenerative medicine, there is growing hope that we can develop more effective, personalized treatments for wounds that are resistant to healing, such as chronic ulcers and burn injuries.

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