Current Research in Pharmacology and Drug Discovery 4 (2023) 100145

Contents lists available at ScienceDirect

Current Research in Pharmacology and Drug Discovery

journal homepage: www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery

Guiding stem cells for cutaneous repair

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ARTICLE INFO

Keywords:
Cutaneous repair
Clinical efficacy
Mesenchymal stem cells
Stem cell guiding
Stem cell niche

ABSTRACT

The significance of mesenchymal stem cells (MSCs) for tissue repair and regeneration is widely recognized. The pleiotropic nature of MSCs is demonstrated by their potential for proliferation and differentiation, and paracrine secretions, thereby making them ideal candidates for cell replacement therapy. Tissue resident MSCs are engaged in homeostasis under normal wear and tear. However, stem cell therapy may be applicable if damage cannot be repaired by normal homeostatic mechanisms. The safety of MSCs has been clearly established in clinical trials but their efficacy remains questionable. The efficacy of MSCs depends on several factors, such as their viability, functional status in terms of secretome secretions, and the in-vivo scenario after transplantation. The performance of MSCs is regulated by their micro-environmental conditions and cues. The so-called MSC niche comprises physical, chemical, and biological components, which play key roles in determining the fate of MSCs. MSCs scaled up for transplantation purposes comprise a disorganized mass of cells, which needs to be directed to perform the required function. Thus, MSCs need to be directed toward an expected target activity in human patients. This review focuses on the various methods that can be used to guide stem cells for cutaneous repair.

1. Introduction

The skin is the largest organ and it has various essential functions in the human body, including protecting from foreign pathogens, sensation, body temperature regulation, and maintaining hydration of the body (Proksch et al., 2008). Hence, it is necessary to protect this significant part of the body. Unfortunately, the skin is adversely affected by cutaneous wounds, which can be defined as an injury that causes a cut, tear, or puncture of the skin to disrupt the normal skin anatomy and physiology (Kanji and Das, 2017). Therefore, healing these wounds is highly important. Cutaneous wound healing is a highly orchestrated process involving cell migration, proliferation, and deposition of the extracellular matrix (ECM) during three phases of inflammation, followed by proliferation and maturation (Gurtner et al., 2008). Some conditions such as infection, diabetes, or radiation exposure can disrupt cellular and molecular signals to further hinder the tissue repair process. The skin can be damaged by surgical laceration, accidental cuts, pressure ulcers, burns, venous ulcers, and diabetic ulcers. According to current medical practice, chronic cutaneous wound healing requires long-term medical attention and it incurs high expenses (Boulton et al., 2005). As a consequence, regenerative medicine, especially using stem cells, has emerged as a promising therapy for positively managing the healing process and reducing the economic burden (Kanji and Das, 2017).

Wounds are broadly categorized as acute and chronic. Wound healing is an active and complex procedure where cytokines, chemokines, and growth factors are released (Grubbs and Manna, 2020), and it follows four phases comprising hemostasis, the inflammatory phase, proliferative stage, and remodeling stage, as summarized in Fig. 1 (Li and Guo, 2018; Li and Guo, 2018; Schultz et al., 2011).

Cutaneous repair is important to avoid further deterioration and affecting the quality of life of patients, and hence standard treatment options are available in practice. Some recently developed wound management options include growth factors and cytokines, skin grafts, and hyperbaric oxygen therapy. Most chronic wounds heal very slowly or they do not heal at all in some cases. Therefore, more effective methods need to be developed to manage the external intricacies of the wound,

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https://doi.org/10.1016/j.crphar.2022.100145
Received 30 June 2022; Received in revised form 20 November 2022; Accepted 5 December 2022

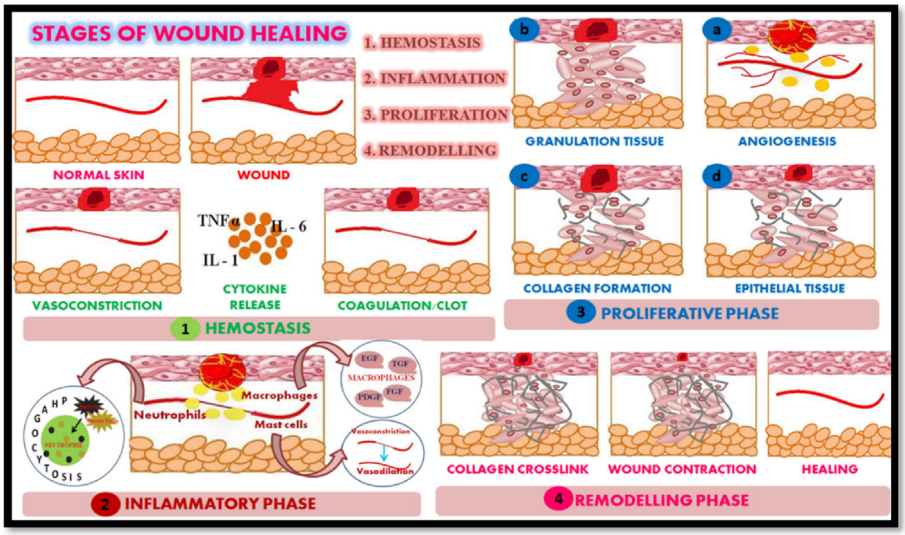

Fig. 1. Phases of wound healing.

and by systemically acting via multiple modalities to facilitate wound healing. Regenerative medicine, especially using stem cells, may be important for healing chronic wounds.

2. Mesenchymal stem cells (MSCs) in cutaneous repair

Stem cells are undifferentiated self-renewing cells that can differentiate into any type of mature specialized cell type. MSCs are present in every organ as reserved cells that can be mobilized when required for repair, regeneration, and homeostasis. MSCs can be isolated from various tissues, such as adipose tissue, bone marrow, and umbilical cord, without the risk of teratoma formation and they are promising candidates for stem cell-based therapies. MSCs can also be multiplied in vitro (Pourjafar et al., 2017). MSCs have been shown to enhance wound healing and skin regeneration by enhancing re-epithelialization, promoting granulation tissue formation, increasing angiogenesis, modulating inflammation, and regulating ECM remodeling, thereby accelerating wound closure. These advantageous effects on wound healing appear to be facilitated by paracrine signaling (Lee et al., 2016).

Various studies have examined the roles of MSC exosomes in wound healing and they are promising for mediating wound healing. MSC exosomes enhance the proliferation and migration of fibroblasts, tube formation by endothelial cells, activation of signaling pathways related to wound healing, expression of growth factors, collagen synthesis, and angiogenesis to accelerate soft tissue repair and wound closure (Shabbir et al., 2015; Hu et al., 2016; Zhang et al., 2015). Exosomes from adipose-derived stem cells were shown to have a significant effect on wound healing in a high glucose animal model due to the overexpression of Nrf2, and thus exosomes may be applied clinically in the management of diabetic foot ulcers (Li et al., 2018).

However, despite the promising effects of MSCs on wound healing, some critical obstacles hinder the clinical application of stem cells, such as the death of transplanted stem cells, reduced stem cell migration, decreased homing to the damaged tissue due to reactive oxygen species, inflammatory responses, apoptotic cascade activation, insufficient trophic factors, poor vascular supply, and loss of survival factors in the injured area (Pourjafar et al., 2017). Therefore, it is beneficial to guide MSCs by using various agents to optimize their efficiency in cutaneous wound healing in patients.

3. Guiding MSCs before transplantation to enhance their clinical efficacy in cutaneous repair

MSCs that can differentiate into adipocytes, osteocytes, and chondrocytes have important applications in regenerative medicine (Mathew et al., 2017), and thus they have great therapeutic potential in cutaneous wound healing. As mentioned above, MSCs have certain limitations, so they need to be treated with appropriate physical, pharmacological, or co-culturing agents to obtain the desired effects in cutaneous wound healing. Moreover, issues such as cellular aging, declining maintenance of stemness, and genome instability can occur, thereby necessitating the priming of stem cells to obtain improved therapeutic effects. In the following, we discuss various guiding agents that can be used to optimize the application of MSCs and improve their reparative abilities.

3.1. Preconditioning of MSCs

The fates of stem cells can be guided by preconditioning with appropriate agents. Preconditioning MSCs with precise biological and pharmacological agents is one of the main approaches used to improve their therapeutic potential. Preconditioning, also known as priming or licensing, is a method for eliciting short-term memory and improving various functions of MSCs, such as differentiation, migration, and regeneration, by directing toward phenotypic variations, genetic modification, and activating signaling pathways (Seo et al., 2019). The following preconditioning agents can elevate the cutaneous healing responses of MSCs.

3.1.1. Metformin

Diabetes mellitus is a chronic metabolic condition and the development of diabetic foot ulcers is a major complication. Metformin is considered to help wound healing via several mechanisms. In particular, a previous study investigated the efficacy of bone marrow-derived MSCs (BM-MSCs), metformin, and a combination of both in cutaneous wound healing in a streptozotocin-induced diabetic rat model (n = 40). Critical examination of the results showed that the combined therapy was more effective than each individual therapy. BM-MSCs and metformin obtained effective results, but the outcome was best when the MSCs were pharmacologically preconditioned with metformin (Shawky et al., 2019). The blood supply is reduced at the site of injury and metformin augments angiogenesis and accelerates wound closure, so it may be a preferred clinical option as a wound healing regimen.

3.1.2. Insulin

A previous study investigated the preconditioning effects of insulin and other treatment options on the healing of diabetic foot ulcers in 107 patients. In 52 cases that received insulin as the treatment, the wound healing rate increased significantly and there was a greater likelihood of complete wound healing (Vatankhah et al., 2017). Wounds treated with

insulin were also characterized by the progressive infiltration and resolution of macrophages, and thus accelerated cutaneous wound healing (Yu et al., 2017). Therefore, insulin is a valid pharmacological preconditioning agent for the management of diabetic wounds because of its regulatory effect on the inflammatory response.

3.1.3. Endothelin-1 (ET-1)

The effects of pre-treating stem cells with ET-1 on the survival and migration of MSCs as well as angiogenesis were evaluated in an in vitro study. MSCs were preconditioned with different concentrations of ET-1 and the expression levels of hypoxia-inducible factor-1 (HIF-1), cyclooxygenase-2, C–C chemokine receptor type 2, C-X-C chemokine receptor type 4, angiopoietin-2, vascular endothelial growth factor (VEGF), matrix metalloproteinase-2 (MMP-2), and angiopoietin-4 were examined. The activities of prostaglandin E2 and caspase 3 were also determined using ELISA. A positive correlation was found between preconditioning with ET-1 and the enhanced viability of MSCs, where all of the detected parameters increased compared with the control group (Pourjafar et al., 2016). Hence, it was shown that preconditioning MSCs with ET-1 could accelerate wound healing because ET-1 has strong cytoprotective effects, and it may be beneficial for clinical application in patients with chronic wounds.

3.1.4. All-trans retinoic acid (ATRA)

ATRA is also an effective tool for promoting cutaneous wound healing. A previous study investigated the effects of ATRA on the survival and migration of MSCs, as well as angiogenesis both in vitro and in a rat excisional wound healing model. The results confirmed the efficacy of ATRA as a tool for improving the wound healing effects of MSCs by activating survival signaling pathways, the release of pro-angiogenic molecules, and trophic factors (Pourjafar et al., 2017). Therefore, guiding MSCs with ATRA prior to their transplantation into patients with wounds can enhance their therapeutic efficacy in wound healing by enhancing angiogenesis.

In addition to preconditioning MSCs, other physical, chemical, and co-culturing techniques can improve the efficacy of MSCs in cutaneous healing, as described in the following. Table 1 summarized the methods used for guiding MSCs to improve their clinical efficacy in cutaneous healing. These different priming agents are classified according to their targets and the mechanism of action involved in their use.

3.2. Other agents for guiding MSCs

3.2.1. Hypoxia

Trauma at any site is promptly followed by regional hypoxia due to microvascular injury and the increased consumption of oxygen. This acute hypoxia has a positive role in accelerating cutaneous wound healing (Tang et al., 2018). Several studies have demonstrated the enhanced efficacy of MSCs in cutaneous wound healing under hypoxia. In particular, Jun et al. compared the effects of human amniotic fluid MSCs cultured in hypoxic conditions and MSCs cultured in normoxic conditions in a murine wound-healing model. They found that the MSCs cultured in hypoxic conditions exhibited increases in proliferation and the expression of VEGF compared with MSCs cultured in normoxic conditions. In addition, increases were found in the rate of migration by dermal fibroblasts and the expression levels of type III collagen, fibronectin, and elastin to enhance wound closure (Jun et al., 2014). Similar results were obtained in a study with human adipose-derived MSCs, human BM-MSCs, and human placenta-derived MSCs (P-MSCs) (Lee et al., 2016). Another study aimed to understand how P-MSCs adapt to endure hypoxic conditions. They showed that hypoxia did not hinder the secretion of insulin and it upregulated glucose transporters to increase the uptake of glucose by cells to meet their metabolic demands. The retention of cells at the site of injury was favorable for wound healing and it occurred due to the upregulation of adhesion molecules under hypoxic conditions. Angiogenesis also increased at the wound site under the presence of P-MSCs and hypoxia. Hence, hypoxic conditions can enhance the efficacy of P-MSCs and improve their suitability for wound healing applications (Mathew et al., 2017). The increased expression of HIF-1α is one of the mechanisms responsible for the beneficial effects of acute hypoxia on wound healing. HIF-1α may act by inducing angiogenesis, ECM synthesis, metabolism, and the remodeling process. A previous study demonstrated the role of stabilized HIF-1α causing hypoxia in accelerated wound healing (Tang et al., 2018). Thus, hypoxia may have great therapeutic potential for enhancing the ability of MSCs to promote an appropriate wound healing response and skin repair. Hence, the

Table 1
Methods for guiding MSCs in wound healing.

Sr. No.	Target	Treatment (Guide for MSCs)	Mechanism (Treatment activity)
Physical Assistance			
1	Diminished growth factors	Hypoxia; Hypoxia-inducible factor-1 (HIF-1α)	Increased proliferation and expression of VEGF; Increased migration rate of dermal fibroblasts, and expression levels of collagen, fibronectin, and elastin; Increased angiogenesis
Pharmacological Agents			
2	Compromised angiogenic pathway	Desferrioxamine	Neovascularization
3	Reduced blood circulation	Metformin; All-trans retinoic acid; Endothelin-1	Increased angiogenesis; Neovascularization
4	Inflammation	Insulin	Regulation of inflammation response
Co-Culturing			
5	Tissue damage	Plasma rich in growth factors (PRGF), Hepatocyte growth factor (HGF)	Tissue growth required for wound closure
6	Compromised angiogenesis	Platelet-rich plasma (PRP)	Increased proliferation and proangiogenic properties of MSCs
7	Scar formation	Conditioned media derived from umbilical cord MSCs, human amniotic fluid, and adipose tissue; α-melanocyte-stimulating hormone (α-MSH); Fibroblast growth factor 9 (Fgf9)	Lower capacity for forming myofibroblasts and decreased accumulation of collagen; Anti-inflammatory activity
Preconditioning stem cells with plant extracts			
8	Multiple pathways in wounds	*Aloe vera*, *Mimosa tenuiflora*, *Salvia miltiorrhiza*, *Alchemilla vulgaris*, *Origanum vulgare* L., *Angelica sinensis*, *Lavandula stoechas* L., Rehmanniae radix, Radix astragali, *Calendula officinalis*, *Ageratina pichinchensis*	Diverse mechanisms for cutaneous repair

The table shows the target associated with wounds and solutions using various techniques. Techniques for guiding MSCs to enhance wound healing are categorized as physical assistance, pharmacological agents, and co-culturing with MSCs.

expression of HIF-1α and hypoxia may accelerate wound healing by increasing the migration rate of dermal fibroblasts and expression levels of collagen, fibronectin, and elastin to enhance wound closure.

In some cases, the functionality of MSCs may be impaired due to defective HIF-1 as a result of diabetes. Desferrioxamine is a hypoxia mimetic agent and a previous study explored its effect on enhancing wound healing via a hypoxic mechanism. Adipose tissue stem cells from a streptozotocin-induced type 1 diabetic rat model were pharmacologically primed with desferrioxamine to investigate its effect on restoring the compromised angiogenic pathway. Desferrioxamine conditioned the MSCs to restore neovascularization and potentiate wound healing, and it may be useful in treating diabetic foot ulcers (Mehrabani et al., 2015). Another study showed that exosomes derived from preconditioning BM-MSCs with desferrioxamine enhanced the proangiogenic property in wound repair (Ding et al., 2019). Hence, desferrioxamine may be a suitable candidate for use as a pharmacological priming agent for MSCs to enhance the wound healing activity due to its mechanistic effect on restoring neovascularization.

3.2.2. Growth factors

As mentioned above, various growth factors can improve wound healing. A previous study investigated the effects of plasma rich in growth factors (PRGF), adipose derived stem cells (ASCs), and the combination of both on cutaneous wound healing in 144 rabbits. The combined treatment (PRGF + ASCs) significantly accelerated cutaneous wound healing. Hence, priming ASCs with PRGF may be a suitable choice for enhancing cutaneous wound healing and improving the healing of acute wounds (Chicharro et al., 2018). Another study found a positive correlation between hepatocyte growth factor and the enhanced effectiveness of MSCs in wound healing (Neuss et al., 2004). These growth factors may help wound healing by promoting the growth of tissues required for wound closure, and thus they can be used to guide MSCs to promote wound healing in patients.

3.2.3. Platelet-rich plasma (PRP)

PRP is another agent that is attracting interest for accelerating the wound healing process. The growth factors and cytokines found in PRP have significant roles in this process (Chicharro-Alcántara et al., 2018). The individual effects of MSC and PRP on skin regeneration are inefficient, but combining PRP with MSCs as a co-culturing agent enhances tissue repair. A previous study evaluated the wound healing efficacy of mouse MSCs when co-cultured with PRP. In vitro and in vivo results showed that PRP improved the survival and proliferation of MSCs, as well as their proangiogenic properties to enhance the wound healing efficacy (Hersant et al., 2019). The use of autologous PRP is also a major innovation for the management of non-healing and diabetic foot ulcers. The safety and efficacy of PRP for managing chronic non-healing ulcers present on lower extremities were evaluated in a case series of 24 patients. The results indicated the safety and potential efficacy of using autologous PRP for the management of chronic non-healing ulcers (Suthar et al., 2017). PRP contains various growth factors, cytokines, and thrombocytes, and it can accelerate the wound healing rate with appropriate wound closure.

3.3. Preconditioning stem cells with plant extracts

Ayurveda is a form of traditional Indian medicine and many herbal drugs are effective in promoting wound healing. The extracts and active constituents can be used from medicinal plants such as *Aloe vera*, *Mimosa tenuiflora*, *Salvia miltiorrhiza*, *Alchemilla vulgaris*, *Origanum vulgare* L., *Angelica sinensis*, *Lavandula stoechas* L., Rehmanniae radix, Radix astragali, *Calendula officinalis*, and *Ageratina pichinchensis*. The extracts from these medicinal plants may be used for priming MSCs to enhance their wound healing efficacy, and clinical trials have also validated their beneficial and adverse effects (Lordani et al., 2018). Further studies can be conducted to confirm the enhanced wound healing activity of MSCs after treatment with these plant extracts.

3.4. Scarless wound healing

MSCs can be used to treat refractory wounds but their potential for promoting the scarless healing of wounds has not been clearly established in vivo, which may restrict their application for scarless wound healing. However, a study demonstrated the potential utility of conditioned media derived from umbilical cord MSCs. This culture exhibited a low capacity for forming myofibroblasts and the increased expression of MMPs, which are the enzymes required for ECM remodeling, as well as accelerated faster wound healing and decreased accumulation of collagen. Human amniotic fluid-derived MSC conditioned media and adipose tissue derived conditioned media obtained similar results but to a lesser extent (Leavitt et al., 2016). Scarless wound healing occurs due to reduced inflammation and pathological scarring is caused by an unregulated inflammatory response. Therefore, modulating the inflammatory processes with anti-inflammatory molecules may help with scarless wound healing. Neuropeptide α-melanocyte-stimulating hormone (α-MSH) could be considered for use in managing MSCs to heal wounds with less macroscopic scar formation and by organizing collagen fibers to mimic unwounded skin. Fibroblast growth factor 9 (FGF9) can also be considered as a priming agent because it modulates the inflammatory process and the differentiation of monocytes into M2 macrophages (Leavitt et al., 2016). Therefore, conditioned media derived from umbilical cord-MSCs, human amniotic fluid-derived MSC conditioned media, and adipose tissue derived conditioned media may facilitate scarless wound healing by decreasing the capacity for forming myofibroblasts and the accumulation of collagen. In addition, anti-inflammatory molecules such as α-MSH and FGF9 could be used to treat MSCs because they have anti-inflammatory properties, which may reduce wound scarring.

4. Conclusion

Therapy based on stem cells, especially MSCs, is an attractive approach for promoting cutaneous wound healing. MSCs may affect paracrine signaling to increase the rate of wound closure, reduce inflammation due to wounding, promote angiogenesis, control ECM events, and improve the regeneration of the skin structure and functional properties. However, the use of MSCs in wound healing still requires further optimization. In particular, MSCs can be guided with various agents before transplantation to enhance their clinical efficacy and improve the outcomes for patients. The use of guiding agents can enhance the potency of stem cells in wound healing by improving their survival, immunomodulation, angiogenic capacity, anti-inflammatory activity, and neovascularization to enhance the quality of life for patients.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

Funding

No funding was received to assist with the preparation of this manuscript.

CRediT authorship contribution statement

Shivani Desai: Writing – review & editing. **Juilee Jagtap:** Writing – review & editing. **Shivani Sainani:** Designing the figures. **Ramesh Bhonde:** Designing the concept, final review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors are thankful to Dr Hitt Sharma (Add. Director, Serum Institute of India Pvt. Ltd.) and Dr Sohan Chitlange (Principal, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research). We are also thankful to Dr. D. Y. Patil Vidyapeeth, Pune, for extending continuous support and motivation to write this paper.

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