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Review Article

Mesenchymal Stem Cells, Exosomes and Cutaneous Wound Healing

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Abstract

Mesenchymal Stem Cells (MSCs) have been widely used in tissue regeneration due to the characteristic of multi-differentiation potential, strong proliferation ability, low immunogenicity, convenient material collection, no restrictions on ethical issues, and easy industrialization. A large number of studies on MSCs -based therapy for cutaneous wound have shown satisfactory results. However, the MSCs therapy is still facing many challenges, and there is still a long way to go for clinical applications. This article briefly reviewed the role and mechanism of MSCs in cutaneous wound healing and discussed issues that should be noticed in future studies. In particular, the research progress of exosomes derived from MSCs in cutaneous wound repair is reviewed.

Introduction

Skin is the largest organ of the human body. There are many factors that can cause cutaneous damage in the clinic, such as trauma, burns, diabetes, and surgery. The process of wound healing is generally described as three sequential phases: inflammation, proliferation, and remodeling [1,2]. The mechanism of wound healing is complicated, and the loss of control at any of these stages will lead to keloids, delayed wound healing of healing difficulty, therefore making the prognosis of the patient worse, and serious, even fatal infection [3]. In recent years, major breakthroughs in the clinical application of MSCs include hematological diseases, cardiovascular diseases, liver cirrhosis, neurological diseases, partial meniscus resection and repair of knee joints, and autoimmune diseases [4-9]. Studies have shown that MSCs can be used in the cutaneous wound repair [10,11]. MSCs therapy will be the most effective therapy in this field. However, there is still a long way to go before MSCs can be used to repair cutaneous injuries in clinic. So we will discuss the progress of MSCs therapy in cutaneous wound healing.

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Mesenchymal Stem Cells

MSCs was first discovered and reported by Friedenstein in the bone marrow in 1968 [12]. In 1999, Pittenger reported on its multi-differentiation potential [13]. In addition to bone marrow, various tissues of the body contain mesenchymal stem cells, such as adipose, muscle, liver, and umbilical cord [14]. MSCs have multi-directional differentiation potential. Under different induction conditions, they can differentiate into mesoderm cells, such as cartilage, bone, skeletal muscle, and fat, and neural cells of ectoderm and hepatic oval cells of endoderm [15]. Pluripotency of MSCs allows it to have a wide range of applications for repairing many different tissues. Under certain induction conditions, MSCs can also differentiate into cutaneous cells. Experiments in vivo confirmed that MSCs can differentiate into sebaceous ductal cells and epidermal cells in regenerated skin [16].

The current definition of MSCs is still unclear. At present, MSCs cells are considered to have at least the following three characteristics: 1) MSCs must be plastic-adherent when maintained in standard culture conditions; 2) MSCs must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules; 3) MSCs must differentiate to osteoblasts, adipocytes and chondroblasts in vitro [17].

MSCs differentiate to form a variety of tissue cells, which are involved in tissue regeneration and wound repair

Although MSCs are derived from mesoderm, they can still be transformed into other germ layer cells through specific environment induction. Transplant adipose derived mesenchymal stem cells (ADMSCs) in the microenvironment of human epidermal-derived keratinocytes, and ADMSCs can differentiate into keratinocyte like cells and express keratinocyte-specific markers such as cytokeratin 14, cytokeratin 5, cytokeratin 19 [18]. By co-culturing ADMSCs with keratinocytes, cells expressing keratinocyte lineage markers i.e. cytokeratin 14, cytokeratin 5, cytokeratin 10, cytokeratin 18, cytokeratin 19 [19]. They can also directly differentiate into different kinds of cells and replace the lost tissue, such as fibroblasts and skin appendages [20-23]. Similar to in vitro studies, ADMSCs can directly differentiate into epidermal cell lines, fibroblast cell lines, and endothelial cell lines under the induction of cutaneous injury microenvironment, providing sufficient cell sources for cutaneous wound healing [24, 25].

MSCs secrete paracrine factors that play crucial roles during tissue regeneration

After being stimulated and activated in the injured local microenvironment, MSC can secrete active ingredients such as cytokines, inflammatory mediators, and antibacterial proteins, thereby exerting corresponding effects locally or throughout the body. MSCs possess powerful immune modulatory properties and are able to activate various genes that contribute to tissues repair [26,27]. Moreover, MSCs may regulate local reparatory responses by recruiting host cells, such as fibroblasts, keratinocytes, macrophages and progenitor cells migrate to the injured site [28-31]. Additionally, MSCs may also induce angiogenesis which is critical in wound healing through the secretion of all kinds of cellular factors [28,32,33].

Exosomes derived from MSCs play a critical role in tissue regeneration

In more recent findings, researchers have found that MSCs achieve the therapeutic effect in vivo mainly through paracrine signaling, they can release biologically active factors that affect the proliferation, migration and survival of the target cells [34-36]. Exosomes are the key bioactive vesicles responsible for the paracrine effects of MSCs, mimic the effects of parental MSCs.

Exosomes are small (30-100 nm in diameter) extracellular membrane-enclosed vesicles released by different cells into the extracellular space or into biological fluids. Exosomes are released by exocytosis as result of fusion of intracellular multivesicular bodies with the plasma membrane, they can shuttle various effector proteins, DNA, small interfering RNA (siRNA), messenger RNA (mRNA) and microRNAs (miRNAs) to modulate the activity of recipient cells, playing important roles in wound healing. Several studies have reported that MSC-derived conditioned medium promotes cutaneous regeneration [30,37].

Exosomes derived from human umbilical cord MSCs (hucMSC-exosome), hADMSC-exosome, and human induced pluripotent stem cell-derived MSCs (hiPS-MSC-exosome) [38-40] can facilitate cutaneous wound healing by delivering various functional proteins, RNAs and soluble cytokines [41-43]. Most researchers believe that MSC-exosomes are the main effective paracrine component of MSCs and play biological effect almost equivalent to those of whole MSCs.

Comparing with MSCs, MSC-exosomes have the following advantages: 1) MSC-exosomes exert intense biological effects because they directly fuse with target cells; 2) MSC-exosomes can be stored and transported at low degree for a long time; 3) The concentration, dose, route and time of use are easy to control; 4) There is no risk of immune rejection and tumorigenesis caused by cell transplantation therapy [44].

The process of cutaneous regeneration can be summarized as three important stages: inflammation stage, proliferation stage and remodeling stage [45]. MSC-exosomes are able to play an important role in all three stages (Table 1). They lead to proliferation and re-epithelization by enhancing proliferation and migration of fibroblasts and keratinocytes through mediating activation of several factors, MSC-exosomes enhance wound healing by delivering Wnt4 [38]. MSC-exosomes can exhibit immunosuppressive effects by regulating proliferation and differentiation of lymphocytes, MSC-exosomes can repress T-lymphocyte proliferation and they exchange T lymphocytes into the T-regulatory phenotype. MSC-exosomes also enhance repress T-lymphocyte proliferation and they exchange T lymphocytes into the T-regulatory phenotype. MSC-exosomes also enhance converting of macrophages toward the anti-inflammatory M2 phenotype in the inflammation stage [46]. MSC-exosomes can also exhibit angiogenic effects through several mechanism, they cause antivascular remodeling by suppress HIMF [47,48].

Composition of the MSC-exosomes can easily deliver the massage into target cells due to their lipid layer which can avoid proteolytic degradation [49]. Further, MSC-exosomes can activate some signaling pathways including Signal Transducer and Activator of Transcription 3 (STAT3), AKT, Wnt/β-catenin, and extracellular signal-regulated kinase (ERK) in target cells which play an important role in wound healing process [50]. Activation of these signaling pathways also can enhance the expression of several growth factors which involved in wound regeneration process by target cells, such as Interleukin-6 (IL-6), STAT3, Hepatocyte Growth Factor (HGF), Insulin-like Growth Factor-1 (IGF-1), and Stromal Cell-Derived Factor-1 (SDF-1) [39,50], these growth factors can promote the angiogenesis, cell migration, cell proliferation, and re-epithelialization [50]. On the other hand, it has been revealed that MSC-exosomes in wound environment can transfer Wnt4 to stimulate Wnt/β-catenin pathway in skin cells, and subsequently active AKT pathway to inhibit epidermal cell apoptosis. β-catenin signaling pathway can stimulate pro-angiogenic effects in endothelial cells and enhance cutaneous wound healing [38,50].

Since MSC-exosomes are an ideal therapeutic tool for their plentiful advantages, such as easy to get and storage, increased safety and efficiency and lower immune rejection, they have been widely reported to support cutaneous regeneration during the proliferation stage. hADMSC-exosomes can promote fibroblast proliferation and collagen synthesis by up-regulating the gene expression of N-cadherin, cyclin-1, Proliferating Cell Nuclear Antigen (PCNA), collagen I and collagen III in vitro. In vivo experiments have also proven that hADMSC-exosomes could home to the skin incision site and significantly facilitate cutaneous wound healing [39].

In other studies, injecting hiPSC-MSC-exosomes to wound sites facilitated cutaneous wound healing by promoting human dermal fibroblast proliferation and migration and by enhancing collagen synthesis [40]. Moreover, transplanting human amniotic epithelial cell-derived exosomes (hAEC-exosomes) to wound sites accelerated wound closure and re-epithelization [51].

Stage	Effects	Molecular in Exosomes	References
Inflammation	Induce Tregs, suppress Th1 and Th17	miR-let7b, miR181c, miR-126, miR-130a, miR-125a, miR-131	[52,53] [45,54,55]
	Promote M2 macrophages, suppress M1 macrophages		
	Enhance IL-10 production, inhibit levels of TNF-α and IL-1β		
	dampen complement	CD59	[52]
Proliferation	Promote fibroblast, keratinocyte and epidermal cells proliferation, migration and re-epithelization	Wnt4, Wnt11, miR221/222	[38,56]
	Promote angiogenesis	miR-126, miR-130a, miR-132, miR-125a, miR-31, Wnt4	[47, 56-58]
Remodeling	Antivascular remodeling	suppress HIMF	[47,48]
	Modulate collagen secretion and deposition, anti-scarring effect	miR-21, miR125b, miR-23a, miR-145, YAP	[41,51,59]

Table 1: Effects of MSC-exosomes in different stages of cutaneous regeneration.

Previous study revealed that hucMSC-exosome promotes cell proliferation and accelerates re-epithelialization; in a rat deep second-degree burn injury model, hucMSC-exosomes reversed acute heat stress-induced skin cell apoptosis and increased the expression of cytokeratin 19, PCNA and collagen I by the parallel activation of Wnt4/β-catenin and AKT signaling [38].

Conclusion

Nowadays, more and more new methods have been developed for different types of wounds. Stem cell-based therapy is one of the promising methods which have been widely used in recent years. Variety of stem cells can be used in this era specifically for reducing scars following wound healing [60]. Beside these advantages of cell therapy, it also has some serious limitations like tumorigenicity and immunogenicity. To overcome these limitations, cell-free therapies have been developed by scientists in recent years which demonstrated interesting therapeutic effects. One of the considerable cell-free methods is using exosomes which can be extracted from different sources. Exosomes that contain DNA, protein, siRNA, mRNA and miRNA can moderate and regulate gene expression in target cells [41]. Moreover, using exosomes avoids many risks associated with cell transplantation. Therefore, MSC-exosomes may be safer and more efficient than whole cell, but more preclinical and clinical studies are still needed to reveal unknown aspects of exosomes and their therapeutic effects.

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Competing Interest

The authors declare that they have no competing interests.

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