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Invited review article

Mesenchymal stem cells: The roles and functions in cutaneous wound healing and tumor growth

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ABSTRACT

Mesenchymal stem cells (MSCs) are bone marrow-derived non-hematopoietic progenitor cells. MSCs are able to differentiate into various types of cells, including chondrocytes, adipocytes, osteocytes, myocytes, endothelial cells, and keratinocytes. There is increasing evidence that MSCs might be located external to the vasculature, and that perivascular cells in the skin, generally called as "pericytes", might include MSCs. It has been suggested that MSCs localized around blood vessels might migrate into wounds and contribute to the restoration of injured tissues. Many studies have demonstrated that intravenous or intradermal administration of MSCs enhanced cutaneous wound healing, such as acute incisional and excisional wounds, diabetic ulcers, radiation ulcers, and burns in animals and humans. Several mechanisms of the acceleration of wound healing by MSCs have been identified, including the enhancement of angiogenesis by secretion of pro-angiogenic factors and the differentiation into endothelial cells and/or pericytes, M2 macrophages polarization, the recruitment of endogenous stem/progenitor cells, extracellular matrix production and remodeling, and immunosuppressive effects. Since the microenvironments of wounds and/or injured tissues are similar to those of tumors, MSCs also play similar roles in malignant tumors, such as the enhancement of angiogenesis, M2 macrophages polarization, and immunosuppressive effects. In addition, the mechanisms of homing of MSCs might have a commonality in the pathogenesis of wound healing and tumors. Thus, the regulating factors of MSCs, including MFG-E8, could be a therapeutic target and lead to the establishment of new therapeutic approaches for both intractable wound healing and tumors.

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1. Introduction

Mesenchymal stem cells (MSCs) are bone marrow (BM)-derived non-hematopoietic multipotent progenitor cells. MSCs can differentiate into various cell types, including chondrocytes, adipocytes, osteocytes, myocytes, endothelial cells, vascular smooth muscle cells, and keratinocytes [1–3]. Given their potential to differentiate into tissue-specific cell types, promote angiogenesis, and secrete the extracellular matrix (ECM), there is increasing interest in utilizing MSCs in cell-based therapy for chronic intractable cutaneous wounds or ulcers, including intractable genetic blistering skin disease and diabetic wounds [3–5]. In addition to their multipotency, MSCs have immunosuppressive effects by suppressing the allogeneic host immunosurveillance system, showing potential for the use of allogeneic MSCs in broad clinical situations [6]. To develop promising clinical therapy with the use of MSCs, further knowledge and discovery of the roles of MSCs are required.

This review highlights and discusses the recent findings on the functions of MSCs, and their therapeutic potential in chronic intractable cutaneous wounds. In addition, the potential contributions of MSCs to the growth of melanoma tumors are discussed.

2. Characterization of MSCs

MSCs reside in and can be isolated from BM and various adult tissues, such as adipose tissue, nerve tissue, umbilical cord blood, and dermis [7–10]. A small percentage (estimated at approximately 0.001–0.01%) of MSCs can be isolated from the population of BM-derived cells [1]. Since previous studies used various methods of isolation and expansion to identify MSCs, standard guidelines for MSC isolation, purification, and expansion are needed. The International Society for Cellular Therapy established the following criteria to identify human MSCs: (a) proliferation *in vitro* as plastic-adherent cells; (b) the positive expression of CD105, CD73, and CD90, and the negative expression of the hematopoietic cell surface markers CD45, CD34, and CD14, CD11b and CD79α, or CD19 and HLA-DR; and (c) differentiation into osteoblasts, adipocytes, and chondrocytes in culture conditions *in vitro* [11]. There are also several established protocols for the isolation and characterization of MSCs from the BM of experimental animals [12,13].

3. Pericytes and MSCs

Interestingly, cells with MSC characteristics have been identified in multiple adult organs, which tend to be colocalized with blood vessels. These cells include both pericytes in the microvasculature and adventitial fibroblast-like cells that surround the larger blood vessels [14,15]. Moriwaki et al. [16] also reported that platelet-derived growth factor receptor α (PDGFRα)$^+$, Sca-1$^+$ MSCs were presented in the arterial perivascular space near the inner surface of the cortical bone, adjacent to vascular smooth muscle cells in the BM of mice. Perivascular cells sorted from human skeletal muscle by alkaline phosphatase expression can differentiate into skeletal myofibers *in vivo* [17]. In addition, Crisan et al. [14] reported that perivascular cells isolated by the phenotype of surface markers CD146$^+$, CD34$^-$, CD45$^-$, CD56$^-$ from human multiple tissues, including the skin, exhibited differentiation into multiple lineages (*i.e.*, osteoblasts, chondrocytes, adipocytes, and myocytes) both *in vitro* and *in vivo*. This finding suggested that blood vessel walls might harbor a reserve of MSCs, and that perivascular cells, generally called as “pericytes”, might include MSCs in the human skin. Namely, pericytes and MSCs may be similar cell types that are located external to the vasculature and are involved in angiogenesis, repair, and tissue maintenance. Furthermore, MSCs around blood vessels in the skin may migrate into the wounds and contribute to the restoration of injured tissues. However, the peculiar localization of MSCs in the skin remain unknown.

4. MSCs and wound healing

4.1. Acceleration of wound healing by MSCs

Dysregulation of the interactive complex processes of wound healing, including the migration of inflammatory cells (neutrophils and macrophages), angiogenesis, granulation tissue formation, re-epithelialization, and ECM remodeling, results in delayed wound healing [18–21]. For example, diabetic wounds are intractable because of complex factors, such as the impairment of the migration of keratinocytes and fibroblasts, abnormal regulation of chemokine and growth factor production, abnormal response of inflammatory cells, and inhibition of angiogenesis [22–24]. MSCs play several beneficial roles in therapeutic applications in these processes, leading to the acceleration of wound healing.

Many studies have identified that intravenous or intradermal administration of MSCs enhanced cutaneous wound healing of acute and chronic skin injuries, such as acute incisional and excisional wounds, diabetic ulcers, radiation ulcers, and burns in animals and humans [4,25–27]. In animal models, exogenous application of MSCs by topical and/or subcutaneous injection into incisional full-thickness wounds in normal or diabetic animals revealed the acceleration of wound healing associated with increased angiogenesis and reepithelization, and decreased inflammation in the wounds [3,4]. In addition, increasing numbers of studies have used MSCs in clinical trials to treat non-healing wounds in humans. For example, Falanga et al. [28] reported that BM-MSCs delivered in a fibrin spray accelerated wound healing in humans. Furthermore, Lu et al. [29] performed a double-blind, randomized clinical study in humans in which they compared the effect of autologous BM-MSCs or BM-derived mononuclear cells (MNCs) injections intramuscularly on the healing of diabetic critical limb ischemia and foot ulcers. The ulcer healing rate of the BM-MSCs-treated group was significantly higher than that of the BM-MNCs group. There were no adverse events related to the treatment with MSCs. Therefore, further randomized clinical trials of BM-MSCs-based therapy for intractable cutaneous wounds are warranted.

4.2. Mechanisms of the acceleration of wound healing by MSCs

Two main mechanisms of the acceleration of wound healing by MSCs have been proposed: (I) paracrine communication with resident cells in the wounds, infiltrating inflammatory cells, and antigen-presenting cells through the release of cytokines, growth