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REVIEW ARTICLE

Mesenchymal stem cells homing to improve bone healing

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Summary Cell therapy continues to attract growing interest as a promising approach to treat a variety of diseases. Mesenchymal stem cells (MSCs) have been one of the most intensely studied candidates for cell therapy. Since the homing capacity of MSCs is an important determinant of effective MSC-based therapy, the enhancement of homing efficiency is essential for optimizing the therapeutic outcome. Furthermore, trafficking of endogenous MSCs to damaged tissues, also referred to as endogenic stem cell homing, and the subsequent participation of MSCs in tissue regeneration are considered to be a natural self-healing response. Therefore, strategies to stimulate and reinforce the mobilisation and homing of MSCs have become a key point in regenerative medicine. The current review focuses on advances in the mechanisms and factors governing trafficking of MSCs, and the relationship between MSC mobilisation and skeletal diseases, providing insights into strategies for their potential translational implications.

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Introduction

Mesenchymal stem cells (MSCs) have been a major research focus in regenerative medicine for several decades. MSC-based translational therapies hold great promise as a novel approach to cure a diverse range of diseases, such as neurological diseases [1], cardiovascular diseases [2,3], wounds [4,5], and various musculoskeletal diseases [6—8]. MSCs are multipotent stromal cells that are capable of differentiating into, and contributing to the regeneration of mesenchymal tissues such as bone, cartilage, fat, tendon, and muscle [9,10]. MSCs express multiple cell surface antigens, such as CD90, CD105, CD73, and CD44, but lack expression of CD45, CD14, CD11b, CD79a, CD19, and HLA-DR [11,12]. MSCs have been successfully isolated from various adult tissues, including bone marrow (BM) [11], adipose tissue [13], and peripheral blood (PB) [14]. MSCs possess powerful immunomodulatory properties and ability for tissue repair. In response to adverse stimuli (e.g., bacterial ligands) or injury, the inflammatory response is activated. MSCs sense these potentially damaging events via surface receptors (e.g., toll-like receptors and the inflammasome) and by alterations in local cytokine and chemokine levels, and then migrate locally and systemically to inflammatory sites. MSCs modulate both innate and adaptive immune responses; biological cues in the local microenvironment determine the activation state of MSCs to become immunosuppressive [15,16]. MSCs not only provide a source of progenitors for cell replacement, but also activate or empower other local cells (such as tissue-resident progenitor or stem cells, endothelial cells, and fibroblasts) to facilitate tissue regeneration via paracrine stimulation [17].

The trafficking of endogenous MSCs to injured tissues, also defined as endogenous stem cell homing, and their subsequent participation in immunomodulation and tissue repair, are considered a natural self-healing response. To take full advantage of the intrinsic regenerative capacity of the body, strategies to stimulate and enhance the mobilisation of endogenous stem cells are of increasing interest. Furthermore, in order to enhance the therapeutic efficiency of exogenous systemically administered stem cells, a clear understanding of the biological concepts underlying stem cell homing is crucial.

It has long been proposed that the cellular and molecular signals of bone injury are highly consistent with embryonic skeletal growth processes, which involve the mobilisation and activation of MSCs. Both tissue-resident and circulating MSCs appear to take part in the processes of bone healing [18]. Immune signals, such as inflammatory mediators and immune cells, trigger the activation and mobilisation of MSCs [19]. Therefore, a better understanding of mechanisms regulating MSC mobilisation and homing may provide novel insights into strategies for successful bone repair. Here, we present a brief summary of the latest findings on the mechanisms and factors regulating MSC trafficking, and the close association between MSC homing and the treatment of musculoskeletal diseases. Our focus is to elucidate the critical role of mobilisation of MSCs in bone healing and provide insights into strategies to accelerate bone healing.

MSCs homing and bone healing

Musculoskeletal diseases remain among the most prevalent and challenging clinical problems, especially for the elderly population. Although simple fractures often heal effectively, the fracture healing process is impaired in 10—20% of fractures, causing nonunion and severe disability [20]. Furthermore, some fractures, such as hip fractures, are threatening injuries with mortality rates of 15—25% [21]. Angiogenesis and osteogenesis are coupled during embryonic skeletal development and bone repair processes, since blood vessels precede the onset of osteogenesis by transporting circulating cells, oxygen, nutrients, and osteogenic signals [22]. Thus, the stimulation of angiogenesis appears to be an important strategy for accelerating fracture healing [23]. Moreover, there is a dynamic homeostatic interplay between bone formation and bone resorption. An imbalance of bone remodelling such that bone formation is not able to compensate for ongoing bone resorption is one of the main mechanisms leading to many bone diseases, such as osteoporosis and nonunion of bone fractures [24,25] (Figure 1).

Healing of fractures is a complex process involving the interplay of osteogenesis and angiogenesis. Natural repair of fractures comprises inflammatory, repair, and remodelling phases. The mobilisation and recruitment of circulating or resident stem cells, and systemically mobilised and recruited MSCs are involved in the fracture healing [19]. The recruitment of BM-MSCs to fracture sites is mainly mediated by the stromal cell-derived factor (SDF)1/CXC chemokine receptor (CXCR) 4 signalling axis [26]. Moreover, MSCs play critical roles in mediating the coupling of bone resorption and formation. In response to osteoclastic bone resorption, active transforming growth factor (TGF)-β released by the bone matrices induces migration and mobilisation of MSCs to the local site of repair, which is essential for coordinating bone remodelling [27]. In addition, transplanted MSCs have been found to stimulate angiogenesis, thereby leading to enhanced bone healing [28]. Conversely, impaired BM-MSCs mobilisation may lead to delayed osteoporotic fracture healing. As the numbers of BM-MSCs and PB-MSCs of ovariectomised mice are significantly lower than those of the mice with sham surgery at 12 hours, 24 hours, and 72 hours after fracture, ovariectomised mice have lower intrinsic capacity for bone regeneration [29]. Therefore, MSC homing augments bone healing mainly by regulating the bone remodelling and angiogenesis processes.