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REVIEW ARTICLE

Circulating mesenchymal stem cells and their clinical implications

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Summary Circulating mesenchymal stem cells (MSCs) is a new cell source for tissue regeneration and tissue engineering. The characteristics of circulating MSCs are similar to those of bone marrow-derived MSCs (BM-MSCs), but they exist at a very low level in healthy individuals. It has been demonstrated that MSCs are able to migrate to the sites of injury and that they have some distinct genetic profiles compared to BM-MSCs. The current review summaries the basic knowledge of circulating MSCs and their potential clinical applications, such as mobilizing the BM-MSCs into circulation for therapy. The application of MSCs to cure a broad spectrum of diseases is promising, such as spinal cord injury, cardiovascular repair, bone and cartilage repair. The current review also discusses the issues of using of allogeneic MSCs for clinical therapy.

Introduction

Mesenchymal stem cells (MSCs) are non-haematopoietic cells which can be easily isolated from bone marrow and other tissues, such as adipose, umbilical cord, and peripheral blood. The MSCs have a multipotent capacity to

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differentiate into a variety of other cell types, including osteoblasts, adipocytes, chondrocytes, myoblasts, and neurons [1,2]. In response to stimuli, MSCs have the ability of homing to the target tissue. Also, MSCs have been shown to be immunosuppressive and anti-inflammatory; they do not express major histocompatibility complex-II (MHC-II), CD80, CD86, and CD40, and minimally express MHC-I on the cell surface [1,3]. These characteristics have made MSCs a promising cell source for tissue engineering.

Circulating MSCs, also called peripheral blood-derived MSCs (PB-MSCs), were initially discovered as fibroblast-like cells and were later confirmed by many investigators as peripheral blood-borne colony-forming units [4,5]. Usually, they exist at a very low level in healthy individuals, but under some pathological conditions, the number of circulating MSCs is greatly increased [6,7]. In 2007, we reviewed some studies/knowledge about circulating MSCs and their relationship with bone marrow-derived MSCs (BM-MSCs) [8]. In this current review, we give a brief summary of the current studies about circulating MSCs and analyse the clinical application of circulating MSCs in tissue regeneration.

Biological characteristics of circulating MSCs

As there are no consistent defining characteristics of MSCs among researchers, the International Society for Cellular Therapy has proposed three criteria that have been generally accepted to categorise progenitor cells as MSCs: (1) adherence to plastic; (2) specific surface antigen expression; and (3) multipotent differentiation potential. Circulating MSCs also fulfil these requirements.

The frequency of BM-MSCs in humans under normal conditions is very low, ranging from 1 in 10^4 to 1 in 10^5 bone marrow mononuclear cells (MNCs) [9]. Compared with BM-MSCs, the frequency of circulating MSCs in humans is even lower, in the order of 1 in 10^8 peripheral blood MNCs [10]. Fernandez and co-workers [11] successfully identified cells with features of MSCs in growth-factor-mobilized peripheral blood cells from breast cancer patients. The MSCs identified by Fernandez and co-workers [11] expressed collagen I, collagen III, fibronectin, CD106, CD54, SH2, and SH3, but did not express antigens CD34, CD45, and CD14. However, they did not find any stromal cells in normal peripheral blood cells which were not mobilized by growth factors. Three years later, Zvaifler and co-workers [12] successfully identified mesenchymal precursor cells in the blood of normal individuals, and these cells were referred to as blood-derived mesenchymal precursor cells. These blood-derived mesenchymal precursor cells also did not express CD34, CD45, and CD14, but were positive for vimentin, collagen I, bone morphogenetic protein receptors IA (BMPR IA) and BMPR IB. In the stromal cells obtained from mobilized peripheral blood cells, two cell populations were observed; fibroblast-like cells and some small round cells. Zvaifler and co-workers [12] also observed that both fibroblast-like cells and some large round cells exist in the predominant cells, and they found that culture conditions are an important factor which can modify the morphology of the progenitor cells.

Despite the difficulty in detection, to date, circulating MSCs have been detected and isolated from various species, such as guinea pig, mouse, rabbit, rat, and humans [8]. We have successfully isolated and cultured PB-MSCs from adult Sprague Dawley rats under normal conditions. The BM-MSCs and PB-MSCs showed similar characteristics of cell proliferation and multi-differentiation potentials. We compared the expression of a set of surface markers, and found that CD73 may be an important indicator to distinguish PB-MSCs from BM-MSCs (as summarized in Fig. 1). PB-MSCs are also plastic-adherent and have multi-differentiation potential. They can be differentiated into adipocytes, chondrocytes, and osteocytes under certain conditions, as proved by previous publications and our unpublished study.

MSCs homing

The capacity of MSCs to home and migrate to the target tissue is an important determinant for the clinical use of MSCs. For example, for bone formation to occur, MSCs must migrate to the bone surface, where they differentiate into osteoblasts and deposit bone matrix. There is a prevailing view that circulating MSCs engraft more rapidly than BM-MSCs [13]. Although the mechanisms for MSCs homing/

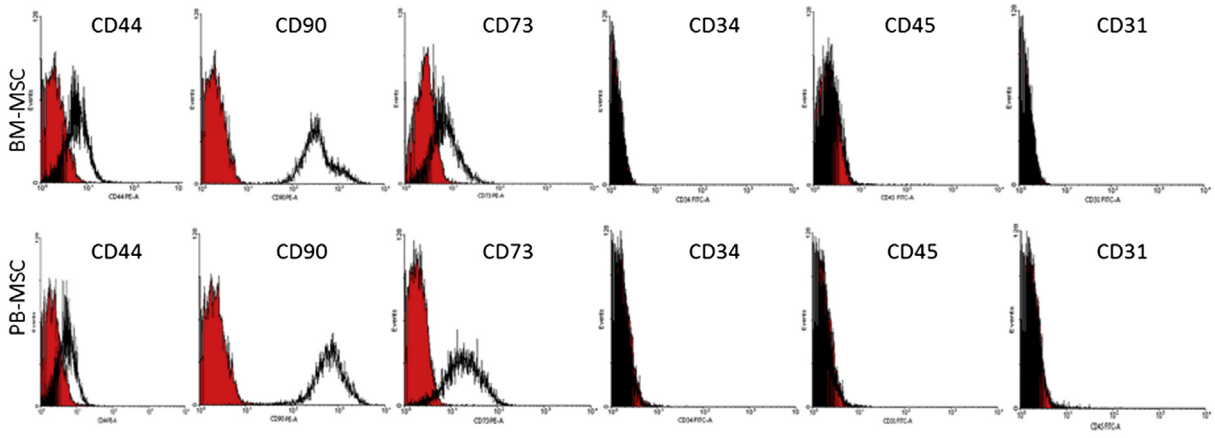

Figure 1 Surface markers of rat peripheral blood-derived mesenchymal stem cells (PB-MSCs) and bone marrow-derived MSCs (BM-MSCs), as analysed by flow cytometry. Isotype controls are represented in red, and the analysis with antibodies for cellular surface markers are represented in black. The PB-MSCs and BM-MSCs shared similar phenotypic CD markers.