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Mesenchymal stromal cells and rheumatic diseases: new tools from pathogenesis to regenerative therapies

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Abstract

In recent years, mesenchymal stromal cells (MSCs) have been largely investigated and tested as a new therapeutic tool for several clinical applications, including the treatment of different rheumatic diseases. MSCs are responsible for the normal turnover and maintenance of adult mesenchymal tissues as the result of their multipotent differentiation abilities and their secretion of a variety of cytokines and growth factors. Although initially derived from bone marrow, MSCs are present in many different tissues such as many peri-articular tissues. MSCs may exert immune-modulatory properties, modulating different immune cells in both *in vitro* and *in vivo* models, and they are considered immune-privileged cells. At present, these capacities are considered the most intriguing aspect of their biology, introducing the possibility that these cells may be used as effective therapy in autoimmune diseases. Therefore, stem cell therapies may represent an innovative approach for the treatment of rheumatic diseases, especially for the forms that are not responsive to standard treatments or alternatively still lacking a definite therapy. At present, although the data from scientific literature appear to suggest that such treatments might be more effective whether administered as soon as possible, the use of MSCs in clinical practice is likely to be restricted to patients with a long history of a severe refractory disease. Further results from larger clinical trials are needed to corroborate preclinical findings and human non-controlled studies, and advancement in the knowledge of MSCs might provide information about the therapeutic role of these cells in the treatment of many rheumatic diseases.

Key Words: *mesenchymal stromal cells, pathogenesis, regenerative therapy, rheumatic disease*

Introduction

In recent years, mesenchymal stromal cells (MSCs) have been largely investigated and tested as a new therapeutic tool for several clinical applications, including the treatment of different rheumatic diseases. MSCs are responsible for the normal turnover and maintenance of adult mesenchymal tissues as the result of their multipotent differentiation abilities and their secretion of a variety of cytokines and growth factors. MSCs are defined according to the criteria proposed by the International Society for Cellular Therapy: (i) MSCs must be plastic-adherent in standard culture conditions; (ii) They must express CD105, CD73 and CD90 but lacking in the expression of CD45, CD34, CD14 or CD11b, CD79α, CD19 and the major histocompatibility complex (MHC) class II cell surface receptor, HLA-DR; (iii) They must be able to differentiate toward osteoblasts, adipocytes and chondroblasts *in vitro* [1]. Besides these three lineages, according to environmental factors such as growth factors, hypoxia and the extracellular three-dimensional environment, MSCs may differentiate into other different cell types [2]. Although initially derived from bone marrow (BM), where they reside in a perivascular location and express markers specific for pericytes [2], MSCs are present in many different tissues. In fact, MSCs may be isolated from many peri-articular tissues including synovium, synovial fluid, cartilage, intra-articular fat and periosteum. Adipose tissue is a major source of adipose derived stromal cells (ADSCs) [3]. ADSCs are mainly located in the stroma, and only few of them display a perivascular location. Their transcriptomic and proteomic profiles show some specificities linked to their tissue origin, reflecting the influence of the microenvironment. Of note, ADSCs show angiogenic

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potential through trans-differentiation toward the endothelial phenotype; they control the evolution of scars through their antifibrotic effects and protect against apoptosis [4,5].

MSCs may exert immune-modulatory properties, modulating different immune cells in both *in vitro* and *in vivo* models [3–5], through both cell contact–dependent mechanisms and soluble factors [6,7], mainly resulting in the generation of cells with regulatory activity [8–10]. MSCs are considered immune-privileged cells: they express low levels of cell-surface HLA class I molecules, whereas HLA class II, CD40, CD80 and CD86 are not detectable on the cell surface, and this phenotype might allow escape to the immune surveillance [11]. Although many rheumatic diseases, and mainly the autoimmune diseases, reflect a pathological activation of the immune system and activation of the inflammatory cascade, the potential role of an altered microenvironment may be considered, including a disturbance of resident MSCs. Several results, available in literature, suggest that despite some functional defects of resident MSCs, they may continue to exert immune modulatory effects and many functional defects may be reverted *in vitro*, suggesting a potential role of autologous MSC transplantation in autoimmune diseases. On the other hand, their immune privilege offers the possibility of easier allogeneic transplantation, overcoming the self-recognition barrier. Thus, at present, both the possibilities—autologous and allogeneic transplantation—may be considered, and the results of future clinical trials will suggest the best choice for any different rheumatic disease. However, it must be pointed out that both their immunologically privileged phenotype and immunosuppressive skills may be considered the most intriguing aspects of their biology, which suggests that these cells may be used as effective therapy in autoimmune diseases [3,6,10,12–14].

In this review, we report the results available in the literature concerning the therapeutic role of MSCs in rheumatic diseases.

Osteoarthritis

Chronic disability in people over 50 years of age is strongly associated with disorders of the musculoskeletal system, and osteoarthritis (OA) involving the spine and diarthrodial joints is the most common condition. All joints can be affected by OA, but the hand, knee and hip represent the main targets of the disease [15]. OA has an enormous social and economic burden, increasing in parallel with population age [16]. Moreover, OA is associated not only with disability but also with other conditions, such as obesity, neuropathic pain, trauma, depression and sleep disorders, and may be an important cause of premature death [17,18].

Pathogenesis

OA is a complex condition characterized by degeneration of the articular cartilage, which is accompanied by damage of the underlying bone, sub-chondral bone sclerosis, development of cysts and osteophytes and synovial inflammation. Destruction of articular cartilage stimulates synovial lining cells and articular chondrocytes to synthesize and secrete proteolytic enzymes: matrix metalloproteinase, aggrecanase, pro-inflammatory cytokines and soluble mediators such as nitric oxide and prostaglandins, which degrade the cartilaginous matrix and accelerate articular cartilage degradation [19–21]. OA has been considered a non-inflammatory condition for some time; however, increasing evidence supports that inflammation is present in the synovial tissue of OA, raising the hypothesis that synovitis and the immune system could be active players in OA development and progression [22]. Synovial inflammation occurs in the majority of OA patients and is a predictive factor for disease progression [23–25].

Current treatments produce symptomatic rather than regenerative results and include pain control (steroidal and non-steroidal anti-inflammatory drugs), viscosupplementation (injections of sodium hyaluronate) and a variety of nutraceuticals (chondroitin sulphate, glucosamine, omega-3 fatty acids). None of these compounds has a useful impact on the progressive loss of joint tissues [26]. Joint-resident MSCs in humans were first described in synovial membrane [27], but it is well known that MSCs, or cells with properties very similar to MSCs, can be detected in different tissues of diarthrodial joints, such as the synovial fluid compartment, the synovial fat pad, the articular cartilage surface zone, ligaments and the meniscus [28–31]. These cells share the same surface markers and functions of BM-derived MSCs. However, minor phenotypic differences between different populations of joint-resident MSCs may reflect their specific tissue of origin or, alternatively, the influence of culture conditions used for their isolation [32].

The widespread distribution of MSCs in diarthrodial joints is associated with key functional characteristics that contribute to the maintenance of healthy tissues and/or their ability to respond to injury. These cells provide a reservoir of repairing cells that are activated in response to growth, remodeling or repair. Furthermore, they might act as immune system sentinels to reduce inflammation or modulating T-cell activation [25,27].