

Mesenchymal stem cells – a new therapeutic option for rheumatic diseases?



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Adult stem cells, named mesenchymal stem cells (MSCs), are multipotent cells of mesodermal origin present in diverse tissues and organs, including bone marrow and adipose tissue – the richest source of MSCs. Resident MSCs sense and respond to changes in the local microenvironment, such as injury and inflammation. Having regenerative properties and potent immunoregulatory activity, MSCs contribute to normal turnover and maintenance of mesenchymal tissues. These features make MSCs good therapeutic candidates for the treatment of various diseases. In contrast to embryonic stem cells, clinical application of which is limited because of ethical concerns and possible teratoma formation, MSCs can be used therapeutically without these restrictions.

Mesenchymal stem cells were first isolated from bone marrow in 1974, and 25 years later they were shown to possess the ability to self-renew and to differentiate toward various cell types of mesodermal lineage (adipocytes, osteoblasts, chondrocytes). Upon appropriate conditions MSCs are also able to differentiate *in vitro* into cells of ectodermal (epithelial cells, neuroglial-like cells) and endodermal (muscle cells, lung cells, gut epithelial cells, hepatocyte-like cells) origin. These progenitor cells express stromal surface markers (CD76, CD90, CD105), but not markers of hematopoietic lineage. Because MSCs do not express major histocompatibility (MHC) class II and only few MHC class I molecules, they are hardly recognized by the immune system and can be safely transplanted not only in autologous but also in allogeneic ways [1]. In addition, MSCs demonstrate interesting immunoregulatory properties. These cells exert widespread modulatory effects on cells of both innate and adaptive immunity, including inhibition of T cell proliferation and proinflammatory cytokine secretion, inhibition of B cell chemotaxis, function and differentiation, inhibition of dendritic cell development and antigen presenting function, impairment of cytotoxic capabilities of natural killer cells, as well as promotion of regulatory

T cell (Treg) development and anti-inflammatory IL-10 production. Various mechanisms mediating these immunoregulatory properties of MSC have been described, e.g. cell-to-cell contact between MSCs and target cells, release of numerous growth factors and cytokines as well as activity of enzymes (e.g. dioxygenase indoleamine – IDO, heme oxygenase 1) [1, 2].

Owing to these unique features and non-immunogenic phenotype, MSCs emerged as a promising therapeutic option for drug-refractory patients suffering from various diseases, including autoimmune, inflammatory and degenerative disorders. Currently, there are more than 200 registered clinical trial sites for evaluating MSC therapy. To date, encouraging therapeutic effects of MSC transplantation have been obtained in several pathological conditions, including graft versus host disease, heart infarction, critical limb ischemia, cirrhosis, Crohn's diseases, osteogenesis imperfecta, and the reconstruction of bone, cartilage and soft tissue [2]. Unfortunately, MSCs may cause unwanted progression of some tumors [1]. Beneficial therapeutic effects of MSC application have also been observed in patients suffering from osteoarthritis [3]. However, there is controversy about the rationale of introducing MSC-based therapy in systemic rheumatic diseases (RD), such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and scleroderma (SSc), because in these patient cohorts the pilot clinical trials evaluating MSC transplantation brought incoherent results. Heterogeneity of particular RD and application of MSCs isolated from different tissues may be the reasons for this inconsistency. However, the major problem is the limited knowledge of MSC biology in RD. It is likely that chronically inflamed tissues drastically modify immunoregulatory and regenerative properties of resident MSCs. In SLE patients bone marrow-derived MSCs have impaired renewal capacity and exhibit senescence behavior and defective IDO (indoleamine 2,3-dioxygenase) production. Based on this,

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allogeneic MSCs from either bone marrow (BM-MSCs) or umbilical cord (UC-MSCs) have recently been transplanted into SLE patients, resulting in a satisfactory clinical response. Despite this, 28% of patients relapsed and 6% of them died after MSC transplantation [4]. As for sclerodermic patients, some authors suggested the contribution of BM-MSC deficiency to fibrosing pathology and demonstrated senescence of these cells, while others failed to find any abnormalities. These discrepancies may result from the small number of enrolled patients precluding comparison of MSCs from different scleroderma subsets. Recently, two trials of MSC therapeutic application in SSc have been performed. In the first study five drug-refractory SSc patients underwent allogeneic transplantation by BM-MSCs injected intravenously, and clinical improvement (cutaneous manifestations, digital ulcers healing, stabilization of pulmonary fibrosis) was observed [5]. In the second trial autologous MSCs isolated from adipose tissue (ASCs) of six patients were transplanted to restore skin sequelae. This local treatment significantly or moderately ameliorated skin symptoms [6]. In several animal models of RA, application of MSCs of different tissue origin alleviated disease symptoms or course, mostly by inhibiting pro-inflammatory cytokine production and activating Treg cells. However, other authors reported contradictory data, suggesting that *in vivo* MSCs lost their immunosuppressive activity when infused into an inflammatory microenvironment [7]. Little is known about properties of MSCs in rheumatic patients. Consistently with data from animal studies, our recent results demonstrate that MSCs isolated from infrapatellar fat pad of RA patients retain their regenerative potential but acquire pro-inflammatory features [8–10]. The study by Swart and Wulffraat [4] has shown that as in preclinical studies, the pilot application of MSCs to RA patients brought inconsistent results. So far, the best option for RA therapy seems to be intravenous injection of UC-MSCs together with disease-modifying anti-rheumatic drug treatment [4].

The human body is equipped with MSCs possessing unique regenerative and immunoregulatory properties. These cells can be easily isolated and safely transplanted. MSC-based therapy is beneficial in some pathological conditions. However, before expanding clinical application of MSCs to systemic RD, several points should be clarified. First and foremost, it is critical to understand more deeply the physiological function of MSCs, including their survival time and homing into organs and tissues. Standardization of MSCs culture and expansion *in vitro* is also required. Second, to find out the ideal cell source (autologous, allogenic, BM-MSCs, ASCs, etc) the contribution of MSCs to the pathology of a particular

disease and its subtype should be explored and MSCs from different anatomical locations should be characterized. Third, the optimal dose, frequency and route of MSC administration should be selected. To confirm or dash hopes for MSC-based therapy of severe systemic RD, these questions have to be answered, since one must not harm patients by bringing in a “Trojan horse”.

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