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Editorial

Mesenchymal stem cells: A future for the treatment of arthritis?

1. Background

Rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) are chronic inflammatory diseases characterized by destruction of cartilage and bone. The destructive lesions result from both immune responses and non-antigen-specific inflammatory processes. Strong evidence indicates that auto-antigen recognition by specific T cells is crucial to the pathophysiology of rheumatoid synovitis. Furthermore, in addition to direct autoimmune attack by effector T cells, arthritis may result from defective homeostatic control of immunity by regulatory T cells [1]. Although an increasing number of biologicals have been added to the therapeutic options of a rheumatologist, there is still a category of patients that fails them all and suffers from progressive disease. Recently, cellular therapy by means of autologous (haematopoietic) stem cell transplantation became a treatment option for RA and JIA patients with insufficient response to conventional treatment. This requires, however a strong immune-ablative pre-treatment with high morbidity and even mortality.

An immunosuppressive subset of the non-haematopoietic mesenchymal stem cells also called mesenchymal stromal cells (MSCs) would not require such a hazardous pre-treatment. Since a few years these MSCs are a fast growing field of interest for science: 3286 (72%) of the 4584 publications found with the search term ''mesenchymal stem cells'' are written since 2005.

2. Mesenchymal stem cells

MSCs are adult (non-embryonic) stromal cells with multi-potentiality, meaning that they have the ability to differentiate into various mesodermal cell lineages which are also very important in inflammatory arthritis. Recently, it has been proved that a single-cell-derived population was capable of differentiating into different mesenchymal cell types in vivo [2]. By current definition, MSCs do at least express CD73, CD105 and CD90, but lack the haematopoietic and endothelial markers CD45, CD11b, CD31 and CD14. MSCs are capable of

in vitro formation in colonies of fibroblastlike cells (CFU-F) and the frequency of these colonies is accepted as a measure of MSC-content. Since there is no uniformly accepted method for prospective isolation of MSCs yet, their ability to adhere to plastic and their differentiation in vitro into osteoblasts, chondrocytes and adipocytes is still needed for their profile. MSCs are present in relatively low numbers in bone marrow, fat, muscle and in lower numbers in many other tissues. BM-derived MSCs (BM-MSCs) are part of the haematopoietic niche, where they support haematopoiesis. The synovial membrane has shown to be a great source for the functionality of MSCs with highest multipotentiality for adipogenesis, osteogenesis, chondrogenesis and myogenesis [3]. MSCs can be expanded ex vivo up to a billion-fold without loss of their multipotent properties and are excellent vehicles for gene therapy (e.g. for specific homing or cytokine production) since they maintain the expression of transfected genes for up to 40 divisions.

MSCs are studied widely for regenerative purposes and it has been shown that a single local delivery of adult mesenchymal stem cells to injured joints stimulates regeneration of meniscal tissue and retards the progressive destruction normally seen in a caprine model of osteoarthritis [4]. Muscle damage stimulates influx of MSCs into the muscle compartment, the influx being commensurate with the damage. The recruited MSCs differentiate into myoblasts thereby repairing the damage [5]. MSCs tend to migrate to areas with local damage. Systemic administration of syngeneic MSCs or allogeneic MSCs promoted the healing of fascial and cutaneous incisional wounds. Labeling of the MSCs with iron oxides/fluorescent dye revealed that systemically administered MSCs engrafted to the wound [6]. Recently, specific homing of MSCs to the bone marrow was accomplished without genetic modification. Cellular recruitment to bone occurs within specialized marrow vessels that constitutively express vascular E-selectin. Human MSCs do not express E-selectin ligands, but express a CD44 glycoform bearing a-2,3-sialyl modifications. By enzymatic processes the native CD44 glycoform on MSCs was converted into haematopoietic cell

E-selectin/L-selectin ligand (HCELL), which conferred potent E-selectin binding without effects on cell viability or multipotency. Real-time intravital microscopy in immunocompromised mice showed that intravenously infused HCELL + MSCs infiltrated marrow within hours of infusion, with ensuing rare foci of endosteally localized cells and human osteoid generation [7]. The engraftment in tissues of MSCs seems to be low. Only 0.1−2.9% of the human MSCs injected in the left ventricle of diabetic NOD/SCID mice were found in the pancreas after 32 days and in the kidneys this was up to 11.6% [8]. In a non-conditioned baboon however the transgene marker, enhanced Green Fluorescent Protein (eGFP), could be detected in the bone marrow 1 year after intravenous administration of gene-marked autologous BM-MSCs [9].

Another very important and largely studied feature of MSCs is the potent immunosuppressive and anti-inflammatory effects they exert in vitro and in vivo. MSCs seem to regulate lymphopoiesis and suppress the immune response as well. Bone marrow-MSCs participate in the developmental process of both T lymphocytes and B lymphocytes through growth factors, cytokines, adhesion molecules. Some crucial surface molecules are expressed on both MSCs and thymic stromal cells, indicating similarities between two different microenvironments of bone marrow compartments and thymus. Moreover, MSCs mediate immunoregulatory effects on both innate and adaptive immunity through either indirect soluble factors or direct cell−cell contact. Numerous studies convincingly demonstrate that MSCs are able to modulate the function of different immune cells in vitro, particularly involving the suppression of T-cell proliferation and the inhibition of dendritic cell maturation. This effect is dose dependent and is exerted on T-cell responses to polyclonal stimuli or to their cognate peptide. The inhibition does not appear to be antigen specific and targets both primary and secondary T-cell responses. After co-culture with MSCs, the T cells exhibited a regulatory phenotype. MSCs downregulated T cell responses through direct contact and secretion of anti-inflammatory and tolerogenic cytokines, which may involve the recruitment of regulatory T cells. The general effects are to skew the immune response towards anti-inflammatory/tolerant phenotypes, including the shift from Th1 towards Th2, downregulation of IFN-γ production from NK and reduction in the antibody productions of B cells [10]. Such immunosuppressive activity does not seem to be spontaneous but requires MSCs to be 'licensed' in an appropriate environment. IFN-γ has been shown to be a powerful inducer of such activity [11]. Immunosuppression might not be confined to MSCs only, since stromal cells (e.g. chondrocytes or fibroblasts) from different human tissues were recently shown to inhibit the proliferation of peripheral blood monocytes following polyclonal stimuli. This was in marked contrast to parenchymal cells [12].

Moreover, MSCs express low levels of human MHC class I and lack human MHC class II. In addition, MSC do not express the CD40, CD80 or CD86 co-stimulatory molecules. All these features make that MSCs are less immunogenic which enables their transplantation in an non-immunocompromised allogeneic host without rejection. However, under some experimental conditions, MSCs infused into allogeneic,

MHC-mismatched mice have been rejected after some time [13]. Thus, at least in some experimental conditions, the immune privilege of MSCs is limited.

In vivo the immunosuppressive effect was first demonstrated convincingly by the prolongation of skin graft survival after systemic administration of allogeneic MSC in baboons. The most significant results so far have been obtained by the successful treatment of severe, treatment-resistant, graft-versus-host disease (GvHD) with third party MSCs which resulted in a two prospective randomized European phase III studies to further explore the therapeutic usefulness of MSCs for the treatment or prevention of acute GVHD following allogeneic stem cell transplantation [14]. Murine MSCs have been demonstrated to ameliorate experimental autoimmune encephalomyelitis (EAE), a model of human multiple sclerosis, through the induction of peripheral T cell tolerance against the pathogenic antigen [15]. The infusion of MSCs was only effective at disease onset and at the peak of the disease, but not after disease stabilization. Central nervous system pathology showed decreased inflammatory infiltrates and demyelination in mice that received transplants of MSCs. T-cell response to the specific antigen and mitogens from MSC-treated mice was inhibited and restored by IL-2 administration. Gene-marked MSCs (eGFP) were detected in the lymphoid organs of treated mice. Many phase I and II trials with the use of MSCs are going on at the moment such as for treatment of acute myocardial infarction, end-stage ischemic heart disease, or prevention of vascular restenosis through stem cell mediated injury repair. Trials for treatment of osteogenesis imperfecta, amyotrophic lateral sclerosis, periodontitis, heart failure, bone fractures, osteonecrosis and lysosomal storage diseases. Unfortunately, some of these studies are performed before the proper use of existing animal models and most of them are without randomized controls.

3. Arthritis and MSCs

The frequency of MSCs in human synovial fluid (SF) of osteoarthritis (OA) patients is higher than in patients with early or established RA [16]. MSCs with immunomodulatory capability are present in the SF of JIA patients as well. MSCs have been shown to be capable of adhesion-independent survival and expansion as floating single cells. Furthermore, individual MSCs can survive in the viscous, antiadhesive medium of the SF of RA patients in vivo and, in spite of their pathologic environment, can maintain their multipotentiality in vitro. It was postulated that synovial fluid recruits mesenchymal progenitor cells derived from the subchondral spongious bone marrow. In collagen-induced arthritis there is an antigen-independent (innate) prearthritic phase requiring the presence of TNFα which involves the early arrival of marrow-derived mesenchymal cells [17]. At the onset of antigen-induced arthritis MSCs were attracted from the bone marrow to the joint, some of which might form fibroblastlike synoviocytes (FLS) [18]. FLS and MSCs isolated from the joint and bone marrow of RA patients provided survival factors to T and B cells in vitro. So the role of MSCs in arthritis might be contributory to