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Review Article

Mesenchymal stem cells in osteoarticular diseases: an update

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Multipotent mesenchymal stromal cells or mesenchymal stem cells (MSCs) are mainly isolated from bone marrow or fat tissue. Because of their potential of multilineage differentiation towards bone, cartilage and fat tissue, they were initially evaluated to develop innovative strategies for tissue engineering applications. More recently, they have gained interest based on their immunomodulatory properties and have been tested in various clinical trials aiming at modulating the host immune response in graft-versus-host disease or autoimmune diseases. MSC-mediated immunomodulation occurs through the secretion of soluble mediators.

The clinical applications of MSCs for rheumatic diseases are focusing on their potential to help tissue repair/regeneration and to prevent inflammation. The aim of the present review is to focus on the mechanisms by which MSCs might exhibit a therapeutic potential in rheumatology and present an update on the mechanisms involved in the therapeutic effect of MSCs. Special attention is given to their possible modulation for future innovative strategies.

Key words: Mesenchymal stem cell, immunosuppression, arthritis, cartilage regeneration, cell therapy

Multipotent mesenchymal stromal cells or mesenchymal stem cells (MSCs) are adult stem cells exhibiting functional properties that have open the way for cell-based clinical therapies. Primarily, their capacity of multilineage differentiation has been explored in a number of strategies for skeletal tissue regeneration (1). More recently, MSCs have been reported to exhibit immunosuppressive as well as healing capacities to improve angiogenesis and prevent apoptosis or fibrosis through the secretion of paracrine mediators. This has led to the development of innovative applications for the treatment of inflammatory and degenerative rheumatic diseases including rheumatoid arthritis (RA), osteoarthritis (OA) as well as bone and cartilage genetic disorders. To date, most of the data have been obtained in pre-clinical models. However, some clinical applications have been initiated that address the potential of MSCs for skeletal tissue repair. New developments on the therapeutic applications of MSCs aim at interfering with immune responses of patients in various inflammatory auto-immune disorders or inhibiting progress of the clinical symptoms in degenerative

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diseases. Besides current researches on the understanding on the mechanisms regulating the therapeutic efficacy of MSCs, more knowledge on migration, biodistribution, survival and safety of MSCs after systemic infusion or local implantation need to be achieved for the generalized therapeutic use in rheumatic diseases. Characteristics of multipotent stromal cells MSCs have been identified to exist and can be isolated from a large number of adult tissues, including bone marrow, adipose tissue, umbilical cord vein or placenta, where they are postulated to carry out the function of replacing and regenerating local cells that are lost to normal tissue turnover, injury, or aging (2). There is no uniformly accepted clear and specific definitive phenotype or surface markers for the prospective isolation of MSCs. The minimal requirements for a population of cells to qualify as MSCs as suggested by the International Society for Cytotherapy include: (a) they must be plastic adherent under standard culture conditions, (b) they should express CD105, CD73, and CD90 and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR surface molecules, and (c) they should possess tripotential mesodermal differentiation capability into osteoblasts, chondrocytes and adipocytes (3). In addition, these cells exhibit immunoregulatory properties (for review, see Ref.4) and secrete a variety of soluble mediators that are crucial for cell proliferation or survival. These key properties make these cells attractive for tissue regeneration or repair as well as anti-inflammatory therapies in the context of various clinical applications in rheumatology.

Biological properties of mesenchymal stem cells. Plasticity and differentiation potential of mesenchymal stem cells

A large body of literature is available on the differentiation process of MSCs from various tissue origins toward chondrocytes, adipocytes, osteoblasts and cells of the musculoskeletal system, namely tendinocytes, ligamentocytes and vascular smooth muscle cells. Although controversial, MSCs have been reported to transdifferentiate into cells from non mesoderm-origin, including cardiomyocytes, hepatocytes or neurons (5,6).

While transdifferentiation of MSCs has been principally shown in vitro, a limited number of MSCs have been shown to transdifferentiate in vivo and participate in the regeneration of specific tissues such as the heart. This raises a point about the range of plasticity of MSCs. It has to be highlighted that a number of signaling pathways seem to be activated in proliferating MSCs suggesting a pre-programming of these cells towards the chondrocytic, osteoblastic, adipocytic and smooth myocytic lineages (7). This study supports the notion of lineage-priming and further argues for the use of MSCs for cell-mediated therapies of skeletal disorders. Differentiation of MSCs towards chondrocytes relies in vitro on the 3D culture and the addition of differentiation factors. Among these growth factors, TGF-β, including TGF-β_1, TGF-β_2, and TGF-β_3, as well as bone morphogenetic proteins (BMP) are the most potent inducers to promote chondrogenesis of MSCs (8). For hMSCs, TGF-β_2 and TGF-β_3 were shown to be more active than TGF-$\beta_1$in promoting chondrogenesis, with a stronger mineralisation effect of TGF-β3 (9). PTHrP plays key regulatory roles in the terminal differentiation of MSCs by suppressing expression of collagen X whereas, the expression of other cartilage-specific matrix proteins was is not affected (10).

The major limitations of cell therapy applications of MSCs for cartilage are however due to the lack of specific differentiation factors and the occurrence of cell hypertrophy after implantation in vivo. A number of studies on the factors involved in chondrocyte biology have been performed on a large scale by our group and several teams. One of the major results we obtained has been the identification of a signature of genes communally

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commonly regulated by the BMP-2 and TGF-β3 signaling pathways as well as a new transcription factor involved in terminal differentiation (11,12). We also focused our attention on new transcription factors involved in early stages of chondrogenic differentiation. Forkhead box protein O1 (FOXO1A) was increased as soon as day 2 and was shown to be sufficient to induce chondrogenesis (pers.comm).

In another work, we studied the cartilaginous microenvironment generated by chondrocytes derived from human bone marrow MSCs. The data obtained through large-scale Taqman Low-Density Array have been assembled into a biological process-oriented database that represented the first molecular profile of a cartilaginous MSC niche (13). Secreted cysteine-rich regulatory proteins (CCNs), matrix metalloproteinases (MMPs), members of the disintegrin and metalloproteinase domain-containing protein family (ADAMs) and cell adhesion molecules (CAMs including cadherins) were highly modulated during chondrogenesis. As an example, CCN3, CCN4 and CCN5 were up-regulated after differentiation whereas CCN1 and CCN6 were down-regulated. MMPs are involved in morphogenesis and remodelling.

Some of them, namely MMP-2 and MMP-9, were expressed by MSCs before and after differentiation. Others, like MMP-3, MMP-7, MMP-28, which were not expressed by MSCs before differentiation, were highly up-regulated during chondrogenic differentiation. Significant progress in the identification of the molecular microenvironment associated with the chondrocytic differentiation of MSCs and the molecular characterization of this process have thus been obtained.

Paracrine activity of mesenchymal stem cells

MSCs produce a number of secreted factors, such as cytokines, chemokines or growth factors, which mediate diverse functions. In the bone marrow, MSCs support haematopoiesis through the production of stem cell factor (SCF), interleukin (IL)-6, lymphocyte inhibitory factor (LIF), granulocyte macrophage-colony stimulating factor (GM-CSF), G-CSF or M-CSF (14). They also exert anti-fibrotic properties as shown in a pre-clinical model of myocardial infarction (15). HGF or adrenomedullin have been reported to play a role in the anti-fibrotic function of MSCs as well as matrix metalloproteinases (MMPs) and tissue inhibitors of MMP (TIMPs) (16,17).

MSCs have been shown to prevent or reduce apoptosis in a variety of in vitro or in vivo models. Production of SDF-1 and Sfrp2 were reported to participate to the anti-apoptotic function of MSCs (18,19). Finally, MSCs are a source of soluble pro-angiogenic factors that act synergistically on endothelial cells to promote vasculogenesis and angiogenesis. These include: angiopoietin-1 (Ang1), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), tumor necrosis factor alpha (TNF-α), plasminogen activator and vascular endothelial growth factor (VEGF) which is one of the most potent angiogenic factors (20-22). In addition, MSCs secrete chemokines such as IL-8 which is involved in the recruitment of endothelial progenitors (23). Indeed, the combination of the different functional roles of secreted factors may be of interest for joint tissue regeneration both by stimulating the proliferation of endogenous progenitor cells and preventing the more differentiated phenotypes from apoptosis or dedifferentiation that may occur in degenerative disorders.

Chemokine-mediated regulation of MSC migration

Chemokines and cytokines play an important role in cell activation, survival and differentiation. The SDF-1 (CXCL12)/ CXCR4 axis is a key pathway in MSC migration process (24,25).

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Recently, it has been demonstrated that this pathway is crucial in the migration of MSCs to injury sites such as bone fractures, with absence of MSC recruitment if SDF-1 signalling was impaired (26). In a rat experimental myocardial infarction model, SDF-1 expression was increased only in the early phase post infarct stimulating the recruitment of MSCs to injured heart as well as enhanced angiogenesis and improved cardiac function (27). There is evidence that MSCs can respond to chemotactic signaling molecules acting on pathways other than the SDF-1/CXCR4 axis. One of those is the Monocyte Chemotactic Protein-3 (MCP-3). When systemically infused, MSCs migrate transiently toward the infracted myocardium in response to MCP-3 signaling (28). Moreover, the previous implantation of MCP-3-over-expressing cardiac fibroblasts in the infarct border zone induced migration of MSCs to the infracted area. Structural and functional improvements were reported, mainly due to remodelling of the cardiac collagen matrix, in the absence of angiogenesis or cardiomyocyte regeneration. A better understanding of mechanisms mediating trafficking and homing of MSCs should lead to the design of new strategies for MSC applications compensating the loss of cells associated with infusion or local implantation.

Interactions between MSC and cancer stroma: safety of MSC-based therapies

The importance of cross-talk between cancer cells and other components of the tumour microenvironment has been increasingly recognized. MSCs enter tumours because cancer cells secrete chemokines that attract MSCs and increase their migratory activity (29,30). In tumours, MSCs may alter the behaviour of cancer cells and may also differentiate to carcinoma-associated fibroblasts (CAF), which are known to be involved in cancer progression (31). A recent report suggests that MSCs enhance the migratory potential of cancer cells by activating E-cadherin, a protease that down-regulates cell-cell adhesion, promoting cancer progression (32).

Interestingly, MSCs exerted little effect on the migration of aggressive breast cancer cells that had lost E-cadherin. Instead, these highly aggressive cancer cells benefited from the interaction with MSCs by acquiring an increased potential to metastasize (32,33). Yet, contradictory information is available to get a clear picture of what the functions of MSCs are in cancer progression. Among the many questions that remain are whether MSCs act primarily on cancer cells as stem cells or as differentiated cells such as CAFs, and whether, MSCs may actually mistake cancers for wounds, and may then influence the proliferative and metastatic activities of the cancer cells (34).

Of importance, in animal models, it has been shown that the timing of MSC injection may be a critical element. The infusion of MSCs into established tumours results in tumour growth inhibition whereas coinjection of MSCs and tumour cells yields to tumour promotion (35). Moreover to date, no evidence of tumour formation has been reported so far in over 1,000 patients treated with MSCs for a variety of indications. The ability of MSCs to migrate to tumour sites has encouraged investigations into the possibility of using these cells as gene delivery mechanisms (36,37). Treatment of glioma xenografts with IFN-γ expressing MSCs significantly increased animal survival compared with controls (38). In a similar model, naïve MSCs as well as MSCs genetically engineered to secrete IL-2 caused significant inhibition of tumour growth and increased survival of rats (39). More recently, innate anti-tumour effects of MSCs were shown for the treatment of pancreatic cancer (40). These effects were enhanced when MSCs were used as delivery vehicles for IFN-β. However, these beneficial effects may be lost in therapies combining MSCs with anti-

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inflammatory agents. Indeed, a better understanding of the interplay between MSCs and the tumour cells will be important in developing strategies for improved treatments that take into account the influence of the microenvironment on tumour survival and growth.

Immunomodulatory effects of MSC

In addition to the properties mentioned above, MSCs are potent immunomodulatory functions, having anti-proliferative and anti-inflammatory capacities. MSC-mediated immunomodulation requires priming by immune cells through secretion of the pro-inflammatory cytokines interferon (IFN)-γ with tumour necrosis factor (TNF)-α or IL-1β (41). After activation, immunosuppressive activity is mainly mediated via the secretion of soluble factors. Proposed mechanisms include indoleamine 2,3-dioxygenase (IDO) or nitric oxide synthase (iNOS) activities, secretion of human leukocyte antigen (HLA)-G, prostaglandin (PGE2) (42,43), tumour necrosis factor-stimulated gene (TSG)-6, (for review, see Ref.4). A recent study also confirmed the role of hemeoxydase(HO-1) in promoting the generation of Th1 and Th3 regulatory T cells and production of IL-10 (44).

These soluble mediators can inhibit both T and B cell proliferation and function. MSCs inhibited antigen-dependent proliferation and differentiation to plasma cells of follicular and marginal zone B cells in vitro. This inhibitory effect was dependent on IFNγ and was mediated by cell-to-cell contact, involving the programmed death 1 (PD-1)/PD ligand pathway (45). MSCs also suppress the generation of dendritic cells (DC) from monocytes or progenitor cells isolated from bone marrow and inhibit their maturation and function (46,47). Finally, it was shown recently that MSCs inhibit Th17 cell differentiation and induce fully differentiated Th17 cells to exert a T cell regulatory phenotype (48). Bone remodelling and inflammation are closely related and the subject of investigations in the field of osteoimmunology. Indeed, receptor activator of NF-kappaB ligand (RANKL), RANK and osteoprotegerin (OPG) play an important role in the development and maturation of the immune system in rodents, including functions of T and/or B cells, whereas, OPG overexpression in mice and rats seems innocuous with regard to immunity (49). RANKL and OPG stimulate osteoclast formation from haematopoietic precursor cells and inhibit bone formation, respectively. MSCs produce RANKL and OPG and are likely participating to inflammation-triggered bone turnover. IL-17 may be one factor regulating hMSC recruitment, proliferation, motility, and differentiation in this process (50).

Moreover, MSCs regulate immunological memory by organizing defined numbers of dedicated survival niches for plasma cells and memory T cells. A distinct subpopulation of MSCs, characterized by the expression of CXCL12 and VCAM1 might provide a survival niche for memory plasma cells in the bone marrow (51). In contrast, another fraction of CXCL12 negative MSCs expresses IL-7. These cells are in close contact with memory $CD4^+$ T cells and keep the T cells quiescent through the effect of IL7. Sub-populations of MSCs, polarized toward pro-inflammatory MSC1 or anti-inflammatory MSC2 subsets, with different immune modulating properties have also been proposed (52). These results suggest heterogeneity of MSCs in terms of immune and hematopoietic functions, but also that MSCs have key role to maintain immune homeostasis.

MSC-based therapies in osteo-articular diseases

MSCs for OA applications

Primary osteoarthritis (OA) is the most common joint disease in adults with a prevalence of 12% in the age group >60 years. Severe knee OA is

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responsible of persistent knee pain, morning stiffness leading to reduced function and loss of quality of life. At that stage, the only efficient available therapy is surgery with knee arthroplasty. The proof of concept of therapeutic benefit of intra-articular injection of adipose tissue- or bone marrow-derived (ASC or MSCs, respectively) has been obtained in pre-clinical OA models in large animals (goats and rabbits) and in murine models) (53, Adipoa consortium, pers. comm.).

ASCs share many properties with MSCs but in contrast to MSCs, which have to be harvested from bone marrow, ASCs may easily be collected through liposuction of subcutaneous abdominal adipose tissue. Moreover, the proportion of ASCs in adipose tissue is several orders of magnitude higher than that of MSCs in bone marrow. ASCs demonstrated several functional properties, including chondrogenic differentiation, protection of various types of cells against oxidative stress or apoptosis, and immunosuppressive effect both in vitro and in vivo leading to a reduction in local inflammation. For chondrogenic differentiation of ASC, BMP6 is required due to the lack of TGFR1. The biological effect of ASCs on OA cartilage explants or chondrocytes in co-culture experiments has been associated with the production of TIMP-1 and TIMP-2, as well as Hepatocyte Growth Factor (HGF) (manuscript in preparation). MSC-based therapies have been proposed in previous clinical trials for treating graft-versus-host disease (GVHD), limb ischemia, myocardial infraction, fistulae in Crohn's disease as well as in OA.

In order to prevent OA, MSCs have been administered locally in 55 patients undergoing meniscectomy, and absence of local side effects was reported (Osiris Therapeutics Inc trial, ECT). Recently, 4 patients with knee OA were selected for a phase I study. They were aged 54 to 65 years and had moderate to severe knee OA. After signed informed consent, 10^7 bone marrow-derived autologous MSCs were injected in the knee joint. The reported results were encouraging with improvement of the walking time, reduction of walking pain in 3 patients. The number of stairs they could climb and the pain on visual analog scale improved for all of them. Most importantly, no side effects were reported after one year follow up (54). However, due to the low number of patients and the absence of control group it is too early to draw any conclusion of clinical benefit.

Immunomodulation of inflammatory arthritis

The potential of MSCs to modulate the host immune response, mainly by inhibiting the proliferation of T lymphocytes, introduced the possibility that they might be effective in inflammatory arthritis where the T cell response is prominent. Studies using the collagen-induced arthritis (CIA) experimental mouse model reported improvement of clinical and biological scores after injection of MSCs derived from bone marrow or adipose tissue (55,56). We and others have however reported contradictory results with absence of therapeutic benefit after MSC infusion and even exacerbation of arthritis (57,58). More recently, our group has shown that IL-6-dependent PGE2 secretion by primary murine MSCs inhibits local inflammation in experimental arthritis in a time-dependent fashion (42). We also showed that therapeutic effect of MSCs was observed during a narrow window of MSC application suggesting that discrepancy between studies may be related to the time of injection and/or the immune status of animals at that time.

Tissue engineering for large defects in late stage arthritis

Because articular cartilage has a poor capacity of repair and in absence of pharmacological agents able to stimulate cartilage regeneration, new approaches of cartilage repair have been developed to provide alternative treatments to the surgical methods currently used.

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The first approaches of cell-based therapies have used autologous chondrocytes isolated from non bearing zones of cartilage, which have been expanded in vitro and reimplanted into the lesions. The first generation of autologous chondrocyte implantation (ACI) relied on the implantation of chondrocytes under a periosteal graft. Now, the third generation of ACI, which consists in preincubated chondrocytes within a scaffold before implantation, was reported to improve clinical symptoms and the quality of the repaired tissue. Moreover, associated to microfracture, ACI was shown to lead to better clinical outcomes compared with osteochondral grafts (59,60).

MSCs have also been used for cartilage repair applications. This can be achieved either using cells embedded in scaffolds combined with growth factors or using beads releasing TGFβ. It should be noticed that dynamic compression on MSCs embedded in scaffolds induces chondrogenesis. Although the number of reports on MSC transplantation for cartilage repair in humans is low, they reported the feasibility of MSC implantation in few patients (61-64). Generally, improvement of clinical symptoms and formation of hyaline cartilage were observed at least in some areas. Recently, MSCs embedded in platelet rich-fribrin glue were transplanted in full-thickness cartilage defects and filled completely large-sized defects (65). Finally, efficacy of MSC implantation by comparison to ACI was recently described in 72 matched patients (66). The authors concluded that MSC implantation is as effective as chondrocytes for cartilage repair with reduced costs and minimized donor-site morbidity. MSC-based cell therapies represent innovative strategies for the treatment of rheumatic diseases for which currently available treatments are limited and rarely restore the full functions of the tissue. New concepts and future therapeutic perspectives based on MSC or ASC are proposed in osteo-articular diseases because these cells shares both anti inflammatory effect and chondroprotective effect through growth factor release. Feasibility and safety of MSC administration are currently being investigated in clinical trials for cartilage defects following degenerative arthritis and the therapeutic potential of these cells for various auto-immune diseases are under evaluation.

In the next future, results on the current trials based on MSC administration should help at elucidating the mechanisms by which MSCs promote tissue repair or regeneration and provide clinical evidence of efficacy of these MSC-based therapies. Stem cells based therapy will be a clinical option if the first trials show safety and efficacy, with a trend to develop allogenic cells available as a vial on the shelf combined with beads releasing specific factors.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the review.

Conflict of Interest: None declared

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