

Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases

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Abstract | Mesenchymal stem cells (MSCs), or multipotent mesenchymal stromal cells as they are also known, have been identified in bone marrow as well as in other tissues of the joint, including adipose, synovium, periosteum, perichondrium, and cartilage. These cells are characterized by their phenotype and their ability to differentiate into three lineages: chondrocytes, osteoblasts and adipocytes. Importantly, MSCs also potently modulate immune responses, exhibit healing capacities, improve angiogenesis and prevent fibrosis. These properties might be explained at least in part by the trophic effects of MSCs through the secretion of a number of cytokines and growth factors. However, the mechanisms involved in the differentiation potential of MSCs, and their immunomodulatory and paracrine properties, are currently being extensively studied. These unique properties of MSCs confer on them the potential to be used for therapeutic applications in rheumatic diseases, including rheumatoid arthritis, osteoarthritis, genetic bone and cartilage disorders as well as bone metastasis.

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Introduction

The use of mesenchymal stem cells (MSCs; also known as multipotent mesenchymal stromal cells) has been proposed as a ‘magic bullet’ approach towards skeletal tissue regeneration. Progenitors of multiple cell lineages, including bone, cartilage, muscle, fat and tendon, MSCs can be easily isolated from bone marrow or adipose tissue and rapidly propagated in culture.¹ These cells have also been shown to have immunosuppressive and healing capacities, improve angiogenesis and prevent fibrosis. These properties open the way for novel therapeutic applications in various disorders, including rheumatoid arthritis (RA), osteoarthritis (OA), genetic bone and cartilage disorders and bone metastasis.

Full tissue healing requires true cellular differentiation through pathways that are involved in embryonic development and integration of the regenerated, differentiated tissue within the surrounding host tissue. This goal can potentially be achieved through MSC-mediated therapy, which involves the use of innovative cell scaffolds and the expression in these cells of selective differentiating factors identified through genomic analysis (Box 1). However, the behavior of MSCs *in vivo* and the safety of their long-term use remain to be determined before these cells can be used in clinical applications. Here, we review current knowledge on the differentiation potential of MSCs, their immunomodulatory and paracrine properties, and thoughts on their optimal use for therapeutic applications in rheumatic diseases.

Competing interests

The authors declare no competing interests.

MSC characteristics

MSCs are defined according to three criteria: their ability to adhere to plastic; their phenotype (CD73⁺, CD90⁺, CD105⁺, CD45⁻, CD14⁻, CD11b⁻, CD34⁻); and their capacity to differentiate into chondrocytes, osteoblasts or adipocytes.² Besides these three lineages, MSCs can differentiate into myocytes, tendinocytes, ligamentocytes,³ cardiomyocytes,⁴ neuronal cells⁵ and other cell types.⁶ Their differentiation potential is largely dependent on environmental factors; growth factors, in particular, are important, but hypoxia and the extra-cellular three-dimensional environment are also pivotal in helping to support the chondrocytic phenotype (reviewed elsewhere⁷). Indeed, for their use in tissue engineering, a combination of fully characterized MSCs, scaffolds and selective differentiating factors should be selected before clinical application.

Sources of MSCs

MSCs are present in various tissues inside the joint, although they show different potentiality. MSCs have been identified in bone marrow, but also in other tissues of the joint including adipose, periosteum, perichondrium, synovium and cartilage.^{8–10} Indeed, adipose tissue is a major source of adipose-derived stromal cells (ADSCs)—multipotent cells with characteristics similar to bone-marrow-derived MSCs, but easier to isolate in high numbers.¹¹ Differences between MSCs derived from bone marrow and adipose have been shown at the genomic and proteomic level, which might reflect the influence of the microenvironment, as well as functional differences in their differentiation programs.¹² ADSCs reportedly show a strong angiogenic potential via transdifferentiation towards the endothelial phenotype,¹³

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can limit scar size through their anti-fibrotic effects, and also protect against apoptosis.^{14,15} However, the plasticity of stem cell differentiation needs to be carefully validated to ascertain whether it is meaningful.¹⁶

MSC-like CD105⁺ and CD166⁺ progenitor cells have also been isolated from cartilage and shown to differentiate, after appropriate induction, into osteoblasts, chondrocytes or adipocytes.⁸ Interestingly, cartilage from OA patients contains ~7% MSCs (relative to the total number of cells), compared with only 3% in patients without OA. Clusters of proliferating normal articular cells express Notch-1, a transmembrane receptor that regulates cell fate and differentiation; the frequency of these cells is increased in OA, suggesting that Notch-1 could serve as a marker of progenitor cells.¹⁷ Another stem cell population, called 'side population cells', has also been identified in cartilage.¹⁸

Within the synovium, CD9⁺, CD44⁺, CD54⁺, CD90⁺ and CD166⁺ stromal cells that show multipotency for chondrogenic, osteogenic and adipogenic lineages have been described.¹⁹ Although MSCs derived from bone marrow and synovium share similar phenotypic and functional properties, their differentiation capacities and transcriptional profiles enable the cell populations to be discriminated, again reflecting the importance of the microenvironment.⁹

Immunomodulatory effects of MSCs

In addition to their potential use in tissue repair, MSCs can potently modulate immune responses, showing anti-proliferative and anti-inflammatory capacities. Although terminally differentiated stromal cells, such as fibroblasts, can also suppress T-cell proliferation *in vitro*,²⁰ they do not exert the immunosuppressive effects mediated by MSCs *in vivo*.²¹ MSC-mediated immunosuppression requires their previous activation by immune cells—in particular, secretion of the proinflammatory cytokine interferon (IFN)- γ with tumor necrosis factor (TNF), interleukin (IL)-1 α or IL-1 β .^{22–24} Notably, MSCs from mice deficient for the IFN- γ receptor lack suppressive capacities.²⁴ The possible mechanisms underlying the immunological effects of MSCs are only partially known. Although cell–cell interactions might be important, the induction of MSC-mediated immunosuppression has been shown to be largely mediated by soluble molecules.

Soluble mediators

On stimulation with IFN- γ , indoleamine 2,3-dioxygenase (IDO) metabolizes tryptophan to kynurenine, causing depletion of local tryptophan and accumulation of toxic breakdown products, both of which reduce lymphocyte proliferation. The role of IDO in MSC-mediated immunosuppression is contentious; whereas the majority of studies indicate a potentially important function for IDO,^{25,26} human MSCs that lack both IFN- γ receptor 1 and IDO still exert important immunomodulatory activity.²⁷ This result is also confirmed by our own results with primary

Key points

- In addition to their differentiation potential, mesenchymal stem cells (MSCs) exhibit immunosuppressive activity, as shown by their ability to inhibit the proliferation and function of immune cells
- The immunosuppressive effect of MSCs is mediated by soluble factors
- Another important feature of MSCs is their capacity to stimulate resident cells or to attract cells via a paracrine mode of action
- The usefulness of MSCs for bone and cartilage repair has been well documented in various experimental models
- The therapeutic benefit of MSCs for osteoarthritis, osteogenesis imperfecta and graft-versus-host disease is under evaluation in humans

Box 1 | Mesenchymal stem cells for tissue engineering

Mesenchymal stem cells (MSCs) represent a suitable source of cells for tissue engineering applications, as they display trilineage differentiation potential and can be rapidly expanded to high numbers after isolation from various tissues. MSCs were first isolated and characterized from the bone marrow, but they are now cultured from various organs and tissues. However, their transcriptomic/proteomic profile and differentiation potential has been shown to depend on the tissue origin.^{9,81} Even among bone-marrow-derived MSCs, subpopulations of stromal cells can be distinguished according to distinct biological properties or commitment stages.

For cartilage repair, it is widely accepted that the three-dimensional environment has a pivotal role that is likely to help support or restore the chondrocytic phenotype. Consequently, there has been much focus on the development of various biomaterials that are now clinically available for autologous chondrocyte implantation (reviewed elsewhere⁷) but that need to be validated for MSC use. Together with an appropriate scaffold, implantation of MSCs requires the use of growth and differentiation factors that will allow the induction of the specific differentiation pathway and the maintenance of the chondrocyte phenotype. Among these factors, the transforming growth factor (TGF)- β family, including TGF- β and bone morphogenetic proteins (BMPs), have been validated in various preclinical animal models^{82–84} and approved for some clinical applications.⁸⁵ In summary, the feasibility of cell-based strategies for tissue engineering, particularly cartilage repair, has not only been proved, but has also provided acceptable clinical results. Tissue engineering is becoming a promising therapeutic modality for the treatment of osteoarticular disorders.

murine MSCs, which lack IDO activity²⁸ (C. Bouffi *et al.*, unpublished data), indicating that different mechanisms might exist in different species.

Secretion of nitric oxide (NO) from MSCs has been shown to inhibit T-cell proliferation.²⁹ NO is considered an important cytotoxic effector molecule, the activity of which is dependent on the presence of IFN- γ .²⁴ MSCs from mice that lack the inducible form of nitric oxide synthase show a reduced ability to suppress T-cell proliferation *in vitro* and *in vivo*.²⁴

Prostaglandin E2 (PGE2) is potentially also involved in the immunosuppressive activity of MSCs. The production of this enzymatic product of arachidonic acid metabolism is enhanced in MSCs following TNF or IFN- γ stimulation.³⁰ PGE2 is a powerful immune suppressant that inhibits T-cell mitogenesis and IL-2 production, and is a cofactor for the induction of T helper lymphocyte (T_H)₂ activity. Specific inhibition of PGE2 synthesis abrogates the antiproliferative effects of MSCs, thereby confirming its critical role in this process.^{28,31}

Transforming growth factor (TGF)- β 1, hepatocyte growth factor (HGF), heme oxygenase-1, IL-6, leukemia inhibitory factor (LIF) and human leukocyte antigen (HLA)-G5 have been proposed as other possible mediators of MSC-mediated immunosuppression.^{28,32–35}

However, as inhibition of any one of these mediators results in only a partial reduction of the immunosuppressive effect of MSCs, several independent mechanisms are clearly involved in mediating the immunosuppressive capacity of MSCs.

Interactions with immune cells

MSCs suppress T-cell proliferation that occurs in response to mitogenic or antigenic stimuli. Similar suppression has been observed using MSCs from autologous or allogeneic sources.^{36–38} Inhibition of proliferation depends on arrest in the G0–G1 phase of the cell cycle.³⁹ This inhibition is not the result of the induction of apoptosis, but instead entails a state of quiescence that can be reversed by stimulation of T cells with IL-2.⁴⁰ MSCs alter other T-cell functions, such as decreasing the production of IFN- γ , IL-2 and TNF and increasing IL-4 secretion.²⁸ They can also suppress the cytotoxic effects of CD8⁺ cytotoxic T lymphocytes (CTLs), although they cannot inhibit activated CTLs.⁴¹ Perhaps MSCs suppress CTL proliferation rather than directly inhibiting cytolytic activity. This possibility is also supported by data demonstrating that MSCs exert little effect on virus-specific T-cell function, which contrasts with their strong suppression of alloreactive T-cell responses.⁴² Finally, MSCs have been reported to promote, both *in vitro* and *in vivo*, the generation of CD4⁺CD25⁺ or CD8⁺ regulatory T cells (T_{REG} cells)^{35,43} with functional properties.^{36,44}

Myeloid dendritic cells (DCs) are essential in the induction of immunity and tolerance, depending on their maturation stage. MSCs interfere with the generation *in vitro* of mature DCs from monocytes or CD34⁺ progenitor cells, and induce an immature DC phenotype characterized by decreased expression of MHC class II and costimulatory molecules (CD40, CD80, CD86) and low secretion of IL-12.^{28,45,46} Consequently, these DCs have an impaired antigen-presenting function and a reduced ability to stimulate lymphocyte proliferation and the production of proinflammatory cytokines, such as IFN- γ , TNF and IL-2. MSCs might, therefore, direct the maturation of DCs towards a suppressor phenotype that is responsible for an attenuated or regulatory T-cell response.

Natural killer (NK) cells are constitutively cytotoxic for cells that lack MHC class I molecules or whose MHC class I molecules are not recognized by NK cells. The presence of IFN- γ decreases the susceptibility of MSCs to NK cell-mediated lysis;⁴⁷ in its absence, other MSC ligands trigger NK alloreactivity and induce lysis. MSCs have been reported to inhibit the proliferation of activated NK cells and their production of IFN- γ .³⁰ Suppression of NK cell activity is at least partially mediated by PGE2 and TGF- β 1 secretion.⁴⁸

It is currently accepted that MSCs inhibit the proliferation and differentiation of activated B lymphocytes,⁴⁹ mainly through the secretion of soluble factors. Conflicting results have been reported,⁵⁰ most of which can be explained by the fact that B-cell responses are mainly T-cell dependent, and the final outcome can be influenced by MSC-mediated inhibition of T-cell functions.

MSCs have been shown to reprogram host macrophages to increase the secretion of the anti-inflammatory cytokine IL-10, preventing neutrophils from migrating into tissues and causing oxidative damage, thus mitigating multi-organ damage.²¹ Neutrophils are important effectors that are activated during bacterial infections to kill micro-organisms through the secretion of reactive oxygen species (respiratory burst).⁵¹ The immunosuppressive effect of MSCs is likely to be caused by the MSC-mediated release of PGE2, which stimulates the secretion of IL-10 by macrophages.

Altogether, the various results demonstrate that MSCs suppress the function of several immune cells; notably the proliferation of T lymphocytes and DC maturation. A schematic representation summarizing the interactions between MSCs and immune cells is shown in Figure 1. Some mechanisms of immunomodulation, in particular the effect of MSCs on IDO and inducible nitric oxide synthase, differ between humans and mice, suggesting that a combination of events, rather than a unique mechanism, mediates the various effects reported to date. These combined effects possibly converge on the generation of T_{REG} cells, as has been suggested *in vitro* and *in vivo*. Thus, CD4⁺CD25⁺Foxp3⁺ or CD4⁺/CD8⁺Foxp3⁺ T_{REG} expansion was detected in animals injected with MSCs in a semi-allogeneic heart transplant mouse model and in a murine model for autoimmune diabetes.^{52,53}

Paracrine effects of MSCs

Besides their capacity to differentiate into multiple cell lineages or to modulate the host immune response, the therapeutic importance of MSCs also relies on their capacity to stimulate resident cells or to attract cells via a paracrine mode of action. MSCs secrete various soluble molecules that reflect both their functionality and the influence of their local environment. The effects of the bioactive factors might be direct, triggering intracellular mechanisms, or indirect, inducing secretion of functionally active mediators by neighboring cells.⁵⁴ MSCs will respond to these signals by themselves participating in tissue regeneration or turnover or by inducing cells in the vicinity to respond to the secreted bioactive molecules and take part in the tissue regeneration process.

MSCs as marrow stromal cells

One of the best examples of an MSC-mediated paracrine effect is their role as marrow stromal cells, supporting hematopoiesis through the secretion of various cytokines and growth factors, such as stem cell factor, IL-6, LIF and granulocyte–macrophage colony-stimulating factor.⁵⁵ Also in the bone marrow niche, MSCs produce

receptor activator of NF κ B ligand (RANKL; also known as TNF ligand superfamily, member 11) and osteoprotegerin, which stimulate the formation of osteoclasts from hematopoietic precursor cells and inhibit bone formation, respectively.⁵⁶

Angiogenesis and tissue repair

Another role of MSCs is to stimulate angiogenesis via the secretion of vascular endothelial growth factor. This function was demonstrated in the ischemic heart after implantation of MSCs, which were able to improve heart function.⁵⁷ Besides neovascularization, MSCs might exert their therapeutic effects in the heart by inhibiting scarring, decreasing apoptosis and by directly differentiating into cardiomyocytes.⁵⁸ Similar mechanisms have been proposed to support the therapeutic effect mediated by implanted MSCs after brain injury.⁵⁹ Although the exact contribution of MSCs has still to be demonstrated, the overall experimental evidence indicates a significant positive effect of these cells on tissue repair through the secretion of bioactive factors.

Anti-fibrosis

The paracrine effect of MSCs is also shown through their anti-fibrotic properties. Following repeated injury, a tissue will undergo remodeling and fibrosis, which is characterized by the excessive accumulation of extracellular matrix, with the formation of scar tissue encapsulating the area of injury. The cells involved in this process are myofibroblasts. They originate from tissue-resident fibroblasts, from epithelial or endothelial cells through epithelial–mesenchymal or endothelial–mesenchymal transition (EMT), or from fibrocytes, which are circulating bone-marrow-derived MSC progenitors that express CD34 and CD45.⁶⁰ Indeed, myofibroblasts are likely to be the progeny of MSCs, but they express different markers, suggesting different functionality. MSCs secrete anti-fibrotic factors, such as HGF and adrenomedullin, which are thought to be involved in the attenuation of fibrosis in a model of experimental heart failure.⁶¹ In this study, MSC implantation significantly decreased the expression of collagens I and III, as well as matrix metalloproteinases 2 and 9. MSC-conditioned medium has been shown to exert anti-fibrotic effects *in vitro*, at least in part through the regulation of cardiac fibroblast proliferation and transcriptional downregulation of type I and III collagen synthesis.⁶²

Applications for rheumatic diseases

The therapeutic applications of MSCs for rheumatic and autoimmune diseases are broad (see Figure 2); their therapeutic potential has been tested in various animal models, and they are currently under evaluation in humans for treatment of osteogenesis imperfecta (see below).

Bone and cartilage repair

The first obvious therapeutic application of MSCs is in bone or cartilage engineering. Percutaneous autologous

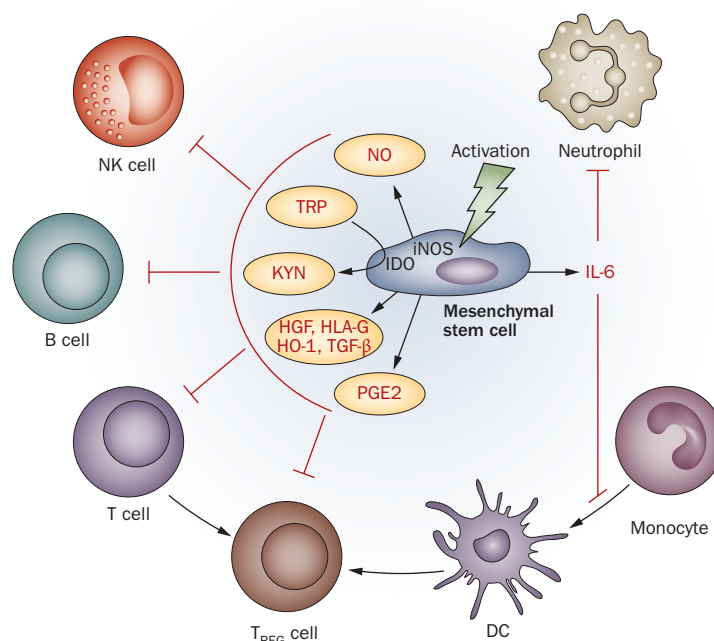


Figure 1 | Schematic illustration of the interactions between MSCs and cells of the immune system. After activation, MSCs inhibit the proliferation of NK cells, B cells and T cells. This effect is mediated through the secretion of various factors, such as PGE2, HGF, HLA-G and TGF- β ; the expression of HO-1; the production of NO by iNOS or the depletion of TRP into KYN by IDO. Secretion of IL-6 might be involved in inhibiting neutrophils or preventing the generation and maturation of DCs from monocytes. Immature DCs could then induce the generation of T_{REG} cells. Abbreviations: DCs, dendritic cells; HGF, hepatocyte growth factor; HLA-G, human leukocyte antigen-G; HO-1, heme oxygenase 1; IDO, indoleamine 2,3-dioxygenase; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; KYN, kynurenin; MSCs, mesenchymal stem cells; NK, natural killer; NO, nitric oxide; PGE2, prostaglandin E2; TGF- β , transforming growth factor β ; T_{REG} cells, regulatory T cells; TRP, tryptophan.

bone marrow grafting is an effective and safe method for treating an atrophic tibial diaphyseal nonunion. The procedure has improved with approaches that involve a combination of bone-marrow-derived MSCs, bone morphogenetic proteins (BMPs) and scaffolds (including ceramics and coral).⁶³ When MSCs were added to BMP2 on a coral scaffold, a significant amount of new bone was formed and incorporated into the endogenous tissue of critical-sized bone defects in rabbits, comparable to autologous bone grafting.⁶⁴ By 12 weeks after the procedure, a union of ~80% with good mechanical properties was achieved, compared with 38% using bone graft or 47% using MSCs alone. This procedure has been validated in clinics using bone marrow, and its efficacy seems to be related to the number of progenitor cells in the graft.⁶⁵ The volume of mineralized callus showed a positive correlation with the number of fibroblast colony-forming units in the graft. Further clinical trials based on the isolation and expansion of fully characterized MSCs are warranted.

Traumatic cartilage injuries could potentially be treated by transplanting allogeneic cartilage MSCs or

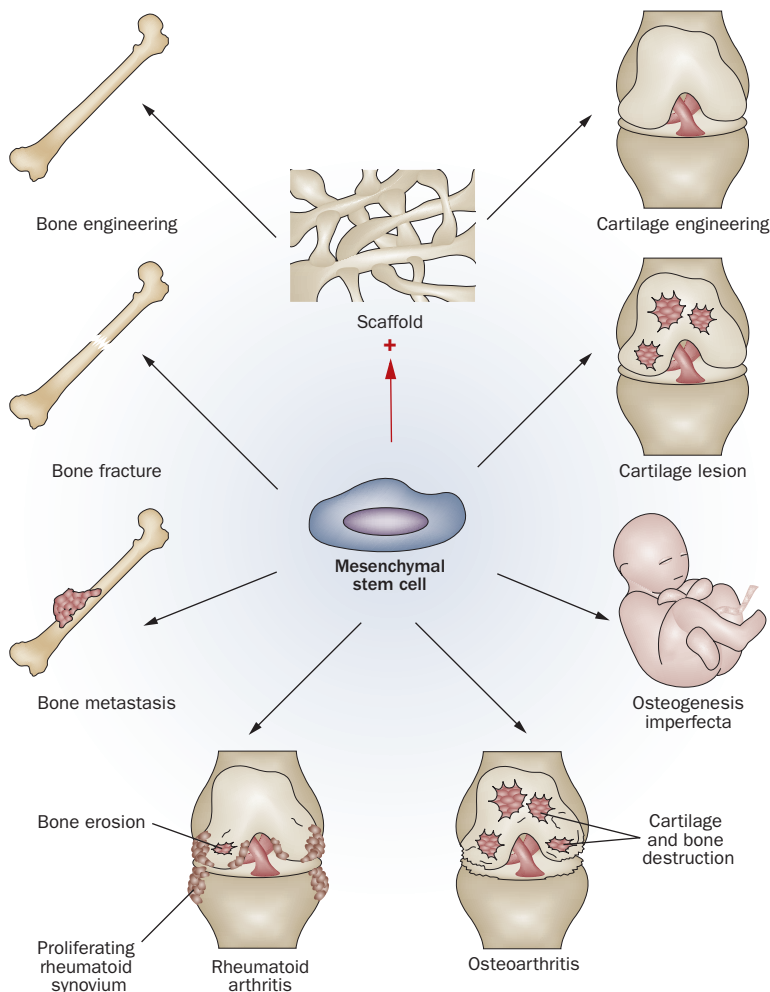


Figure 2 | Principal therapeutic applications of MSCs for rheumatic and autoimmune diseases. MSCs might be directly injected systemically or locally to treat diseases such as rheumatoid arthritis, osteoarthritis or osteogenesis imperfecta. They might be genetically modified to express anti-tumor mediators in bone tumors or metastases. They could also be used in bone and cartilage engineering approaches when injected in combination with scaffolds to repair bone fractures or cartilage lesions. Abbreviation: MSCs, mesenchymal stem cells.

implanting MSCs differentiated into chondrocytes into the defect.^{66,67} Clinical outcomes and data regarding regeneration of OA lesions treated with an articular cartilage paste grafting technique are available for 125 patients. Two thirds of patients showed strong and consistent evidence of replacement of their articular surface, but only 27% showed development of areas of cartilage, suggesting the need to use progenitor cells rather than existing cartilage.⁶⁸ In a preclinical study, we showed that MSCs combined with chitosan-based scaffolds and TGF- β 3 improved cartilage repair in a sheep model of patella defect.⁶⁹

Biodegradable polycaprolactone nanofibrous scaffolds seeded with xenogeneic human MSCs have been implanted in 7 mm full-thickness cartilage defects in a swine model. Six months after implantation, MSC-seeded constructs showed a more complete repair than controls

(chondrocyte-seeded constructs). Macroscopically, the MSC-seeded constructs regenerated hyaline cartilage-like tissue and restored a smooth cartilage surface, whereas the chondrocyte-seeded constructs produced mostly fibrocartilage with a discontinuous superficial cartilage contour.⁷⁰ These data underscore the interest in MSCs for cartilage repair in clinical applications.

MSCs for the treatment of OA

As well as their capacity to differentiate into chondrocytes, MSCs have shown the potential to prevent chondrocyte apoptosis and OA development through a paracrine effect. Adult MSCs were isolated from caprine bone marrow, expanded in culture, and transduced to express green fluorescent protein.⁷¹ When 10 million of these autologous MSCs suspended in hyaluronan were injected intra-articularly into a goat model of OA, the medial meniscus showed evidence of marked regeneration, and implanted cells were detected in the newly formed tissue. Degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis were reduced in cell-treated joints compared with joints treated with vehicle alone. On the basis of these data, a phase II clinical trial is underway in which MSCs (in the form of ChondrogenTM [Osiris Therapeutics, Columbia, MD]) are directly injected into patients' knees to repair the meniscus and prevent OA progression. Fifty patients, randomized into three groups (hyaluronan alone; autologous MSCs diluted in low-dose hyaluronan; or autologous MSCs diluted in high-dose hyaluronan) have participated in this 3-year program. Complete results have yet to be published, but preliminary data suggest that MSCs are well tolerated, with no serious adverse events. Moreover, compared with control patients treated with hyaluronan, patients who received ChondrogenTM showed statistically significant improvement with regard to pain score, and decreased subchondral sclerosis and osteophyte formation, as monitored by MRI. Further clinical evaluation is required, as is more information relating to the factors delivered by MSCs that might account for the beneficial effect.

MSCs for genetic diseases

Theoretically, transplantation of MSCs should attenuate, or even correct, genetic disorders of bone or cartilage. Osteogenesis imperfecta is a rare genetic disorder in which osteoblasts produce defective type I collagen, resulting in osteopenia, multiple fractures, severe bone deformities and considerably shortened stature. A female fetus with multiple intrauterine fractures, diagnosed with severe osteogenesis imperfecta, underwent transplantation with allogeneic HLA-mismatched male fetal MSCs in week 32 of gestation. At 9 months of age, bone biopsy revealed the presence and persistence of 0.3% of XY-positive allogeneic cells.⁷² Histologic analysis showed regularly improved bone formation over time. Three fractures were experienced during the first 2 years of life, but psychomotor development was normal.

In the US, six children have undergone allogeneic bone marrow transplantation for the treatment of severe osteogenesis imperfecta. In five of these patients, the MSCs were engrafted in bone and marrow stroma, and growth velocity increased during the first 6 months post-infusion. The median improvement in growth was close to 70% of the predicted median values for age-matched and sex-matched unaffected children. All patients improved their total body bone mineral content by a median of 28 g (range 21–29 g) compared with predicted values of 0–4 g (median 0 g) for healthy children with similar changes in weight. Failure to detect engraftment of transplanted MSCs expressing the marker gene after 12 months suggested a possible immune response against therapeutic allogeneic cells.⁷³

MSCs for RA and other autoimmune diseases

The immunosuppressive capacities of MSCs have been evaluated in humans, as well as in experimental autoimmune models, to prevent acute graft-versus-host disease (GVHD).⁷⁴ Allogeneic MSCs are not rejected by the host immune system after implantation into immunocompetent mice, and allow the growth of allogeneic tumors.³⁶ Zappia *et al.*⁴⁰ have reported the therapeutic efficacy of MSCs in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis. In this model, MSCs decreased the clinical signs associated with demyelination (ataxia and paralysis of one or more limbs) when injected before or at the onset of the disease, but not after disease stabilization. Similar results were observed in a model of autoimmune diabetes: MSC injection led to a decrease in mesangial thickening and macrophage infiltration, preventing pancreatic injury.⁷⁵

Conflicting results have been reported in RA, using the experimental collagen-induced arthritis (CIA) mouse model. In one study, a single injection of MSCs prevented the occurrence of severe arthritis, and was associated with a decrease in serum levels of proinflammatory cytokines.³⁷ However, our group has shown that the allogeneic C3H10T1/2 MSC line did not exert a beneficial effect on CIA.⁷⁶ As in other autoimmune models, MSCs were not observed in the target organ, suggesting that the immunosuppressive effect might be more systemic than local. The mechanisms underlying the beneficial effect described by Augello *et al.*³⁷ need to be explored, as no convincing increase in the number of regulatory T cells was observed *in vivo*, despite *in vitro* evidence of T-cell inhibition by MSCs.⁷⁷

Using MSCs to target bone metastasis

MSCs have the potential to be used as cellular vehicles to target bone metastases, locally delivering anti-tumor agents and rebuilding osteolytic bone. The hypothesis that circulating MSCs can migrate to tumor stroma led us to engineer MSCs that expressed an anti-tumor factor as an innovative approach to cell-mediated gene therapy to counteract tumor growth. Tumor growth was significantly inhibited when MSCs expressing the urokinase-type

plasminogen antagonist amino-terminal fragment were co-injected with tumor cells into mouse tibiae.¹² MSCs genetically modified to express IFN- γ are already known to inhibit the growth of melanoma or carcinoma cells *in vitro* and *in vivo*.⁷⁸ Furthermore, adenovirally infected MSCs expressing recombinant IL-12 potentially inhibited the growth of melanoma cells, hepatoma cells or lung cancer cells when both cell types were injected into mice.⁷⁹ It should, however, be underlined that MSCs might be a source of carcinoma-associated fibroblasts, which associate with the tumor microenvironment.⁸⁰ Nevertheless, these data indicate that MSCs have the potential to move towards tumor lesions and might, therefore, offer an alternative therapy approach when tumor cells have escaped from conventional treatments.

Conclusions

Stromal cells are no longer second-class citizens but first-line players. They appear as major regulatory cells in skeletal tissues, controlling inflammation, immune response, fibrosis and tissue regeneration. A better understanding of the interactions that occur between stromal cells and specialized cells is required to improve the therapeutic applications and to validate the strong potential of MSCs in the treatment of rheumatologic diseases. However, the unique potential of these cells—their differentiation, immunosuppressive and paracrine functions—and their effect on various pathways that control important physiological processes already make them attractive potential tools for therapy in rheumatology. MSC-based therapies undoubtedly represent a promising approach in the treatment of different rheumatologic diseases to circumvent current treatments, which rarely restore the full functions of the tissue.

Future research should focus on the development of more rapid and reproducible methods to isolate, expand and better characterize progenitors from adipose tissue or bone marrow, as well as on the identification of pathways that activate endogenous stromal cells in the joint. Moreover, the regeneration of a complete, functional cartilage or bone tissue will require an optimal combination of MSCs, chondroinductive and biodegradable scaffolds, and selective differentiating and/or anti-inflammatory factors. Finally, the long-term behavior of MSCs *in vivo* and in the context of pathological situations remains to be further studied before clinical trials can be started.

Review criteria

A literature search for original articles was performed in PubMed using the following keywords, alone or in combination: “mesenchymal stem cells”, “immunosuppression”, “autoimmune diseases”, and “rheumatic diseases”. The search was limited to English-language articles only, and full papers, mostly original articles, were reviewed. No early time limit was placed on any of the search criteria.

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