MicroRNA expression during osteogenic differentiation of human multipotent mesenchymal stromal cells from bone marrow.

Gao J, Yang T, Han J, Yan K, Qiu X, Zhou Y, Fan Q, Ma B. Department of Orthopedic Surgery, Tangdu Hospital, Fourth Military Medical University, Xi’an, Shanxi, 710038, P. R. China.

Abstract
MicroRNAs comprise a group of non-coding small RNAs (17-25 nt) involved in post-transcriptional regulation that have been identified in various plants and animals. Studies have demonstrated that miRNAs are associated with stem cell self-renewal and differentiation and play a key role in controlling stem cell activities. However, the identification of specific miRNAs and their regulatory roles in the differentiation of multipotent mesenchymal stromal cells (MSCs) have so far been poorly defined. We isolated and cultured human MSCs and osteo-differentiated MSCs from four individual donors. miRNA expression in MSCs and osteo-differentiated MSCs was investigated using miRNA microarrays. miRNAs that were commonly expressed in all three MSC preparations and miRNAs that were differentially expressed between MSCs and osteo-differentiated MSCs were identified. Four underexpressed (hsa-miR-31, hsa-miR-106a, hsa-miR-148a, and hsa-miR-424) and three novel overexpressed miRNAs (hsa-miR-30c, hsa-miR-15b and hsa-miR-130b) in osteo-differentiated MSCs were selected and their expression were verified in samples from the fourth individual donors. The putative targets of the miRNAs were predicted using bioinformatic analysis. The four miRNAs that were underexpressed in osteo-differentiated MSCs were predicted to target RUNX2, CBFB and BMPs, which are involved in bone formation; while putative targets for miRNAs overexpressed in osteo-differentiated MSCs were predicted to target RUNX2, CBFB and BMPs, which are involved in bone formation.

Back to the future: moving beyond "mesenchymal stem cells"

Bianco P. Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy. paolo.bianco@uniroma1.it.

Abstract
The last decade was dominated by dissemination of the notion that postnatal "mesenchymal stem cells," found primarily in bone marrow but also in other tissues, can generate multiple skeletal and non-skeletal tissues, and thus can be exploited to regenerate a broad range of tissues and organs. The concept of "mesenchymal stem cells" and its applicative implications represent a significant departure from the solidly proven notion that skeletal stem cells are found in the bone marrow (and not in other tissues). Recent data that sharpen our understanding of the identity, nature, origin and in vivo function of the archetypal "mesenchymal stem cells" (bone marrow skeletal stem cells) point to their microvascular location, mural cell identity, and function as organizers and regulators of the hematopoietic microenvironment/niche. These advances bring back the original concept from which the notion of "mesenchymal stem cells" evolved, and clarify a great deal of experimental data that accumulated in the past decade. As a novel paradigm emerges that accounts for many facets of the biology of skeletal stem cells, a novel paradigm independently emerges for their applicative/translational use. The two paradigms meet each other back in the future.

CD146 expression on primary non-hematopoietic bone marrow stem cells correlates to in situ localization.

Tormin A, Li O, Brune JC, Walsh S, Schütz B, Ehinger M, Ditzel N, Kassem M, Scheding S. Lund Stem Cell Center, University of Lund, Lund, Sweden;
Abstract
Non-hematopoietic bone marrow mesenchymal stem cells (BM-MSC) are of central importance for bone marrow stroma and the hematopoietic environment. However, the exact phenotype and anatomical distribution of specified MSC populations in the marrow are unknown. We have characterized the phenotype of primary human BM-MSC and found that all assayable CFU-F were highly and exclusively enriched not only in the lin(-)/CD271(+)/CD45(-)/CD146(+) stem cell fraction, but also in lin(-)/CD271(+)/CD45(-)/CD146(-)/low cells. Both populations, regardless of CD146 expression, shared a similar phenotype and genotype, gave rise to typical cultured stroma cells, and formed bone and hematopoietic stroma in vivo. Interestingly, CD146 was up-regulated in normoxia, and down-regulated in hypoxia. This correlated to in situ localization differences with CD146 co-expressing reticular cells located in perivascular regions, whereas bone-lining MSC expressed CD271 alone. In both regions, CD34(+)/hematopoietic stem/progenitor cells were located in close proximity to MSC. These novel findings show that the expression of CD146 differentiates between perivascular versus endosteal localization of non-hematopoietic bone marrow stem cell populations, which has apparent implications for the study of the hematopoietic environment.

Purified Mesenchymal Stem Cells Are an Efficient Source for iPS Cell Induction.

Department of Physiology, Keio University School of Medicine, Tokyo, Japan.

Abstract
BACKGROUND: Induced pluripotent stem (iPS) cells are generated from mouse and human somatic cells by the forced expression of defined transcription factors. Although most somatic cells are capable of acquiring pluripotency with minimal gene transduction, the poor efficiency of cell reprogramming and the uneven quality of iPS cells are still important problems. In particular, the choice of cell type most suitable for inducing high-quality iPS cells remains unclear.

METHODOLOGY/PRINCIPAL FINDINGS: Here, we generated iPS cells from PDGFRα(+)/Sca-1(+) (PoS) adult mouse mesenchymal stem cells (MSCs) and PDGFRα(-)/Sca-1(-) osteo-progenitors (OP cells), and compared the induction efficiency and quality of individual iPS clones. MSCs had a higher reprogramming efficiency compared with OP cells and Tail Tip Fibroblasts (TTFs). The iPS cells induced from MSCs by Oct3/4, Sox2, and Klf4 appeared to be the closest equivalent to ES cells by DNA microarray gene profile and germline-transmission efficiency.

CONCLUSIONS/SIGNIFICANCE: Our findings suggest that a purified source of undifferentiated cells from adult tissue can produce high-quality iPS cells. In this context, prospectively enriched MSCs are a promising candidate for the efficient generation of high-quality iPS cells.

Evaluation of senescence in mesenchymal stem cells isolated from equine bone marrow, adipose tissue and umbilical cord tissue.

Vidal M, Walker NJ, Napoli E, Borjesson DL.
University of California, Surgical and Radiological Science, Davis, California, United States; mavidal@ucdavis.edu.

Abstract
Mesenchymal stem cells (MSCs) from adult and neonatal tissues are intensively investigated for their use in regenerative medicine. The purpose of this study was to compare the onset of replicative senescence in MSCs isolated from equine bone marrow (BMSC), adipose tissue (ASC) and umbilical cord tissue (UCMSC). MSC proliferation (cell doubling), senescence associated β-galactosidase staining, telomere length, Sox-2 and lineage-specific marker expression were assessed for MSCs harvested from tissues of 4 different donors. The results show that before senescence ensued, all cell types proliferated at approximately 1 day/cell doubling. BMSCs significantly increased population doubling rate by passage 10 and ceased proliferation after a little more than 30 total population doublings, while UCMSCs and ASCs achieved about 60 to 80 total population doublings. UCMSC and ASCs showed marked β-galactosidase staining after approximately 70 population doublings while BMSCs stained positive by approximately 30 population doublings. The onset of senescence was associated with significant reduction in telomere length averaging 10.2 kbp at passage 3 and 4.5 kbp in senescent cultures. MSCs stained intensely for osteonectin at senescence compared to earlier passages, while vimentin and low levels of smooth muscle actin were consistently expressed. Sox-2 gene expression was consistently noted in all three MSC types. In conclusion, equine BMSCs appear to senesce much earlier than ASCs and UCMSCs. These results demonstrate the limited passage numbers of subcultured BMSCs available for use in research and tissue engineering and suggest that adipose tissue and umbilical cord tissue may be preferable for tissue banking purposes.
The generation of three-dimensional tissue structures with mesenchymal stem cells.

Genever PG.
Department of Biology, University of York, UK. paul.genever@york.ac.uk

Abstract
Mesenchymal stem cells (MSCs) are multipotent stem cells, found in the bone-marrow and other adult tissues, which give rise to various cell lineages. Although MSCs are biologically important, and may have widespread therapeutic potential, they are not well-characterised, particularly in terms of their cell surface receptors and in vivo phenotype. We aimed to develop a three-dimensional (3-D) MSC in vitro model, in order to understand the factors involved in the regulation of lineage specification routes. A suitable model, which replicates the MSC microenvironment as accurately as possible, will allow more detailed investigations into the phenotype of the cells. Our MSC spheroids appear to have an enhanced mesenchymal differentiation compared to two-dimensional MSC monolayers. With this in vitro system, it is possible to perform real-time analysis of cellular differentiation status. MSC spheroids may also be amenable for use in high-throughput assays. A more-recent research project aims to generate knockout micro-tissues, based on human 3-D MSCs, as an alternative to animal studies.

Combined Effects of Surface Morphology and Mechanical Straining Magnitudes on the Differentiation of Mesenchymal Stem Cells without Using Biochemical Reagents.


Abstract
Existing studies examining the control of mesenchymal stem cell (MSC) differentiation into desired cell types have used a variety of biochemical reagents such as growth factors despite possible side effects. Recently, the roles of biomimetic microphysical environments have drawn much attention in this field. We studied MSC differentiation and changes in gene expression in relation to osteoblast-like cell and smooth muscle-like cell type resulting from various microphysical environments, including differing magnitudes of tensile strain and substrate geometries for 8 days. In addition, we also investigated the residual effects of those selected microphysical environment factors on the differentiation by ceasing those factors for 3 days. The results of this study showed the effects of the strain magnitudes and surface geometries. However, the genes which are related to the same cell type showed different responses depending on the changes in strain magnitude and surface geometry. Also, different responses were observed three days after the straining was stopped. These data confirm that controlling microenvironments so that they mimic those in vivo contributes to the differentiation of MSCs into specific cell types. And duration of straining engagement was also found to play important roles along with surface geometry.

Mandibular Alveolar Bony Defect Repair Using Bone Morphogenetic Protein 2-Expressing Autologous Mesenchymal Stem Cells.

Chung VH, Chen AY, Kwan CC, Chen PK, Chang SC.
From the *Department of Applied Chemistry, Providence University, Taichung, †Department of Dentistry, Chang-Gung Memorial Hospital, Taoyuan; ‡Department of Plastic Surgery, Chang Gung Memorial Hospital, Chang Gung University College of Medicine; Taoyuan; and §Department of Plastic Surgery and ¶ School of Medicine, China Medical University, Taichung,Taiwan.

Abstract
BACKGROUND: Mandibular bone regeneration is stepped up by human recombinant bone morphogenetic protein 2 (BMP-2) whose application is also related to limited cementum and periodontal ligament regeneration, local root
resorption, and ankylosis. The alveolar bone grafting without traditional autologous bone grafts remains a challenge for plastic surgeons.

**METHODS:** Bilateral mandibular alveolar and periodontal defects were created over the premolar areas in 9 mature male beagles. The defects were randomly assigned for either the adenovirus BMP-2 (advBMP-2) group with BMP-2-expressing mesenchymal stem cells (MSCs) or the control with MSCs alone. The regenerated periodontal attachment apparatus was evaluated histologically, and the whole regenerated bone volume was scrutinized from three-dimensional computed tomography analysis.

**RESULTS:** Periodontal apparatus regeneration was significantly better in the advBMP-2 group. New cementum and Sharpey fibers were observed on the denuded root surfaces in the advBMP-2 group, whereas incomplete healing with localized root surface resorption was noted in the control group. Eight weeks after implantation, the advBMP-2 group showed significant increase in bone regeneration than the control one.

**CONCLUSIONS:** Thus, the use of ex vivo BMP-2-engineered autologous MSCs boosted bone and periodontal apparatus regeneration in mandibular periodontal defects. This de novo approach might be suitable for clinical mandibular bone repair and periodontal apparatus repair.


The bone marrow stem cell niche grows up: mesenchymal stem cells and macrophages move in.

**Ehninger A, Trumpp A.**
Division of Stem Cells and Cancer, German Cancer Research Center, D-69120 Heidelberg, Germany.

**Abstract**
Stem cell niches are defined as the cellular and molecular microenvironments that regulate stem cell function together with stem cell autonomous mechanisms. This includes control of the balance between quiescence, self-renewal, and differentiation, as well as the engagement of specific programs in response to stress. In mammals, the best understood niche is that harboring bone marrow hematopoietic stem cells (HSCs). Recent studies have expanded the number of cell types contributing to the HSC niche. Perivascular mesenchymal stem cells and macrophages now join the previously identified sinusoidal endothelial cells, sympathetic nerve fibers, and cells of the osteoblastic lineage to form similar, but distinct, niches that harbor dormant and self-renewing HSCs during homeostasis and mediate stem cell mobilization in response to granulocyte colony-stimulating factor.

**Physiol Res.** 2011 Mar 14. [Epub ahead of print]

Osteogenic differentiation of miniature pig mesenchymal stem cells in 2D and 3D environment.

Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic, Liběchov, Czech Republic. juhas@iapg.cas.cz.

**Abstract**
Mesenchymal stem cells (MSCs) have been repeatedly shown to be able to repair bone defects. The aim of this study was to characterize the osteogenic differentiation of miniature pig MSCs and markers of this differentiation in vitro. Flow-cytometrically characterized MSCs were seeded on cultivation plastic (collagen I and vitronectin coated/uncoated) or plasma clot (PC)/plasma-alginate clot (PAC) scaffolds and differentiated in osteogenic medium. During three weeks of differentiation, the formation of nodules and deposition of calcium were visualized by Alizarin Red Staining. In addition, the production of alkaline phosphatase (ALP) activity was quantitatively detected by fluorescence. The expression of osteopontin, osteonectin and osteocalcin were assayed by immunohistochemistry and Western Blot analysis. We revealed a decrease of osteopontin expression in 2D and 3D environment during differentiation. The weak initial osteonectin signal, culminating on 7(th) or 14(th) day of differentiation, depends on collagen I and vitronectin coating in 2D system. The highest activity of ALP was detected on 21(th) day of osteo-differentiation. The PC scaffolds provided better conditions for osteogenic differentiation of MSCs than PAC scaffolds in vitro. We also observed expected effects of collagen I and vitronectin on acceleration of the osteogenic differentiation of miniature pig MSC. Our results indicate similar ability of miniature pig MSC osteo-differentiation in 2D and 3D environment, but the expression of osteogenic markers in scaffolds and ECM coated monolayers started earlier than in the monolayers without ECM.

**Cancer Lett.** 2011 Mar 9. [Epub ahead of print]
Potential implications of mesenchymal stem cells in cancer therapy.

Dai LJ, Moniri MR, Zeng ZR, Zhou JX, Rayat J, Warnock GL.
Department of Surgery, University of British Columbia, Vancouver, Canada.

Abstract
Mesenchymal stem cells (MSCs) are the first type of stem cells to be utilized in clinical regenerative medicine, mainly owing to their capacity for multipotent differentiation and the feasibility of autologous transplantation. More recently, the specific tumor-oriented migration and incorporation of MSCs have been demonstrated in various pre-clinical models, highlighting the potential for MSCs to be used as an ideal carrier for anticancer gene delivery. Engineered with specific anticancer genes, MSCs possess the ability of dual-targeting tumor cells. This contrasts with non-engineered native MSCs which have intrinsic pro- and anti-tumorigenic properties. Engineered MSCs are capable of producing specific anticancer agents locally and constantly. Astute investigation on engineered MSCs may lead to a new avenue toward an efficient therapy for patients with cancer.


Mesenchymal stem cells for treatment of acute and chronic graft-versus-host disease, tissue toxicity and hemorrhages.

Ringden O, Le Blanc K.
Center for Allogeneic Stem Cell Transplantation, Division of Clinical Immunology, and Hematology Center, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, F79, SE-141 86 Stockholm, Sweden.

Abstract
Mesenchymal stem cells (MSCs) have immunomodulatory effects and low immunogenicity. MSCs inhibit T-cell alloreactivity in vitro. Immune inhibition is caused by soluble factors. MSCs affect almost all cells of the immune system. They are safe to infuse in humans with no acute toxicity and no ectopic tissue formation. We treated patients with life-threatening acute graft-versus-host disease (GVHD) not responding to conventional immunosuppressive therapy with MSCs. Approximately half of the patients responded. HLA-identical or third party MSCs were equally effective. Children tended to have a better response compared to adults. MSCs have also been used for chronic GVHD with positive effects. MSCs also reversed tissue toxicity such as hemorrhagic cystitis, pneumomediastinum and colon perforation with peritonitis. A patient with extensive hemorrhages was successfully treated with repeated doses of MSCs pooled from two donors. This may indicate that MSCs apart from wound healing may stimulate clotting and vasoconstriction. To conclude, MSCs is a novel treatment that may be used for GVHD, tissue toxicity and hemorrhages because of its immune inhibitory and anti-inflammatory effects.


Mesenchymal stem cells and autoimmune diseases.

Dazzi F, Krampera M.
Stem Cell Biology, Haematology Centre, Department of Medicine, Imperial College, London, UK.

Abstract
Mesenchymal stem cell (MSC) immunosuppressive properties offer a potentially attractive therapeutic modality for autoimmune diseases. MSC inhibit virtually all types of immune responses in vitro and prevent the induction of disease in several experimental models of autoimmunity. However, the processes involved in the pathogenesis of human diseases are more complicated and treatment cannot be administered before disease induction. In autoimmune diseases persistent antigenic stimulation recruits endogenous MSC to the site of lesion that contribute to the fibrotic evolution. Therefore, administering MSC to a chronic inflammatory disorder may not be desirable. In fact, MSC are not constitutively immunosuppressive but require a ‘licensing’ step provided by molecules of acute phase inflammation, like IFNγ and TNF-α, or toll-like receptor (TLR) ligands. Conversely, different cytokines and/or the stimulation of selective TLR make MSC to become immunostimulatory. Therefore, dissecting the inflammatory environment in autoimmune diseases will identify the best conditions amenable to successful MSC therapy.

Osteoprogenitors and the hematopoietic microenvironment.

Bianco P, Sacchetti B, Riminucci M.
Department of Molecular Medicine, La Sapienza University, 00161 Rome, Italy; Biomedical Science Park San Raffaele, 00128 Rome, Italy.

Abstract
The identification of skeletal progenitor cells in the human bone marrow (so-called mesenchymal stem cells) by anatomy and phenotype (CD146-expressing, adventitial reticular cells) has coincided with the recognition that the ability to transfer the hematopoietic microenvironment is an inherent property of skeletal progenitor cells. Inasmuch as these cells generate osteoblasts, associate with sinusoids (the assembly of which they dynamically direct), and coincide with, and self-renew into, stromal reticular cells, these cells are pivotal organizers of the hematopoietic microenvironment. Their nature as osteogenic cells and sinusoidal location reconcile the dual view of endosteal surfaces and sinusoidal walls as the hematopoietic stem cell "niches", and highlight the dynamic nature of a niche/microenvironment essentially maintained by cells with properties of progenitors/stem cells for skeletal tissues. This view brings the long recognized, and somewhat mysterious, interaction between bone and bone marrow into a new perspective, where two stem cells interact with each other at the same niche.


Prospective isolation of human MSC.

Harichandan A, Bühring HJ.
University Clinic of Tübingen, Department of Internal Medicine II, Division of Haematology, Immunology, Oncology, Rheumatology, and Pulmonology, Laboratory for Stem Cell Research, Otfrid-Müller-Str. 10, 72076 Tübingen, Germany.

Abstract
Conventionally, mesenchymal/stromal stem cells (MSC) are functionally isolated from primary tissue based on their capacity to adhere to the plastic surface. This isolation procedure is hampered by the unpredictable influence of secreted molecules or interactions with co-cultured hematopoietic and other unrelated cells as well as by the arbitrarily selected removal time of non-adherent cells prior to expansion of MSC. Early removal of non-adherent cells may result in the elimination of a late adhering MSC subsets and late removal increases the influence of undesired cells on the growth and differentiation of MSC. Finally, in conventional protocols MSC are co-expanded together with macrophages, endothelial cells and other adherent cells. To circumvent these limitations, several strategies have been developed to facilitate the prospective isolation of MSC based on the selective expression or absence of surface markers. Here we summarize the most frequently used markers and introduce new targets for antibody-based isolation procedures of primary bone marrow-derived MSC.


Mesenchymal stem cells.

Ding DC, Shyu WC, Lin SZ.
Department of Obstetrics and Gynecology, Buddhist Tzu Chi General Hospital, Tzu Chi University, Hualien, Taiwan.

Abstract
Stem cells have two features: the ability to differentiate along different lineages and the ability of self-renewal. Two major types of stem cells have been described, namely, embryonic stem cells and adult stem cells. Embryonic stem cells (ESC) are obtained from the inner cell mass of the blastocyst and are associated with tumorigenesis, and the use of human ESCs involves ethical and legal considerations. The use of adult mesenchymal stem cells is less problematic with regard to these issues. Mesenchymal stem cells (MSCs) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc. This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications. Recently, MSCs have been found in new sources, such as menstrual blood and endometrium. There are likely more sources of MSCs waiting to be discovered, and MSCs may be a good candidate for future experimental or clinical applications. One of the major challenges is to elucidate the mechanisms of differentiation, mobilization, and homing of MSCs, which are highly complex. The multipotent properties of MSCs make them an attractive choice for possible development of clinical
applications. Future studies should explore the role of MSCs in differentiation, transplantation, and immune response in various diseases.


Inhibition of metastasis-associated gene 1 expression affects proliferation and osteogenic differentiation of immortalized human mesenchymal stem cells.

Kumar A, Salimath BP, Schieker M, Stark GB, Finkenzeller G.
Department of Plastic and Hand Surgery, University of Freiburg Medical Center, Freiburg, Germany Department of Studies in Biotechnology, University of Mysore, Manasagangotri, Mysore, Karnataka, India Experimental Surgery and Regenerative Medicine, Department of Surgery, Ludwig-Maximilians-University Munich, Munich, Germany.

Abstract
MTA1 is known to be responsible for independent nucleosome Objectives: remodelling and deacetylase complexes with ability to regulate divergent cellular pathways. However, additional biological functions have, up to now, remained largely unexplored. The present study was initiated to investigate involvement of MTA1 in osteogenic differentiation of immortalized human MSCs were examined for mesenchymal stem cells (MSCs). Materials and methods: expression of MTA1 and stably transfected clones expressing shRNA to MTA1 were generated. Cells were grown under osteogenic and non-osteogenic conditions. Effects of silencing on cell proliferation, calcium deposition and alkaline phosphatase (ALP) activity were studied. mRNA expression of bone sialoprotein (BSP), osteopontin (OSP), runt-related transcription factor 2 (Runx2), osteocalcin (OC), collagen type I (Col1A) and ALP were analysed. Results: Transfected cells showed reduction in proliferation and significant increase in calcium deposition and expression of osteogenic marker genes, BSP, OSP, Runx2, OC and Col1A, when they were grown under osteogenic conditions. Under non-osteogenic conditions, expression of BSP and OSP were also markedly upregulated, whereas expression of osteogenic marker genes, Runx2, OC and Col1A, was almost unaffected. Expression of ALP was slightly suppressed under non-osteogenic conditions but significantly increased under osteogenic differentiation conditions, as assessed by enzyme activity and mRNA expression. Our data collectively suggest that endogenously produced MTA1 constrains osteogenic differentiation of MSCs and that targeting of this molecule may provide a novel strategy for enhancing bone regeneration.


Neuroprotective features of mesenchymal stem cells.

Uccelli A, Benvenuto F, Laroni A, Giunti D.
Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Via De Toni 5, 16132 Genoa, Italy; Center of Excellence for Biomedical Research, University of Genoa, Italy; Advanced Biotechnology Center (ABC), Genoa, Italy.

Abstract
Bone marrow (BM) derived mesenchymal stem cells (MSC) differentiate into cells of the mesodermal lineage but also, under certain experimental circumstances, into cells of the neuronal and glial lineage. Their therapeutic translation has been significantly boosted by the demonstration that MSC display significant also anti-proliferative, anti-inflammatory and anti-apoptotic features. These properties have been exploited in the effective treatment of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis where the inhibition of the autoimmune response resulted in a significant neuroprotection. A significant rescue of neural cells has been achieved also when MSC were administered in experimental brain ischemia and in animals undergoing brain or spinal cord injury. In these experimental conditions BM-MSC therapeutic effects are likely to depend on paracrine mechanisms mediated by the release of growth factors, anti-apoptotic molecules and anti-inflammatory cytokines creating a favorable environment for the regeneration of neurons, remyelination and improvement of cerebral flow. For potential clinical application BM-MSC offer significant practical advantages over other types of stem cells since they can be obtained from the adult BM and can be easily cultured and expanded in vitro under GMP conditions displaying a very low risk of malignant transformation. This review discusses the targets and mechanisms of BM-MSC mediated neuroprotection.