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Mechanisms facilitating regenerative therapies with multipotent marrow stromal cells

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Abstract

Cell therapy has become a promising new treatment approach for a large number of different diseases, and applications are continually being developed. Bone marrow derived stem cells are already being tested in clinical trials and have been shown to be promising new therapeutic vehicles. Multipotent marrow stromal cells (MSCs) are a bone marrow derived cell type that can be easily cultured and expanded in vitro and have a broad range of potential and actual therapeutic applications. The mechanism of action of MSCs in the therapeutic situation depends on the disease, and involves differentiation, immunomodulation, paracrine, and anti-apoptotic mechanisms. These mechanisms are discussed in detail in this manuscript.

Keywords: Cell therapy, bone marrow stem cells, multipotent marrow stromal cells, mechanism of action, differentiation, apoptosis, immunomodulation, treatment, clinical trials, review

Cell therapy in medicine

The idea of utilizing cells for therapeutic purposes is by no means new. The Swiss physician Paul Niehans propagated, as early as 1931, different cell types as tools for rejuvenation and cure against diseases, a therapy he called 'Zellulartherapie', which has also been called 'Frischzelltherapie' (Niehans 1956). Niehans treated a patient with tetany with injections of the parathyroid glands of an ox and the patient recovered. He also successfully treated Pope Pious XII. However, the use of animal cells was hampered by considerable side effects and this form of therapy subsequently was banned in Germany (Wolff 2002).

The best-known and most successful example of cell therapy is bone marrow transplantation. Lorenz showed in 1949 that lethally irradiated mice could be rescued by bone marrow cell infusion (Lorenz 1951). A first patient report of intravenous infusion followed by transient engraftment was published in 1957 (Thomas 1957) and in 1968-9 the first matched sibling transplantations were reported (Gatti 1968). Bone marrow transplantation (BMT) is now established as the first successful cell therapy as a routine procedure for the treatment of formerly incurable leukemias and the pioneer of this therapy, E. Donnall Thomas, received the Nobel Price in Physiology in 1990 (Nathan 1990).

The concept of cell therapy

The initial intention of BMT was to replace the lethally injured and ablated organ with a new one to rescue the patient. However, it was recognized later that the infused bone marrow also has anti-leukemic properties, a phenomenon called graft-versus leukemia effect (Kolb 2004). This represents a fundamental advantage of cell therapy over pharmaceutical approaches. Furthermore, cells are able to react in vivo depending on the different circumstances under normal and pathophysiological conditions, systemically through secretion of growth factors, cytokines or chemokines as well as through paracrine and local actions at the site of injury. Additionally, cells are able to integrate into tissues, either as differentiated parenchymal cells or as undifferentiated stromal cells, thereby affecting the organ of engraftment in the long run. These versatile properties make the development of cellular therapies promising and attractive.

Multipotent marrow stromal cells (MSCs)

Friedenstein showed that fibroblast like cells could be generated and propagated in vitro from bone marrow and called these cells 'marrow stromal cells' (Friedenstein 1968). Due to their differentiation into osteocytes, chondrocytes and adipocytes

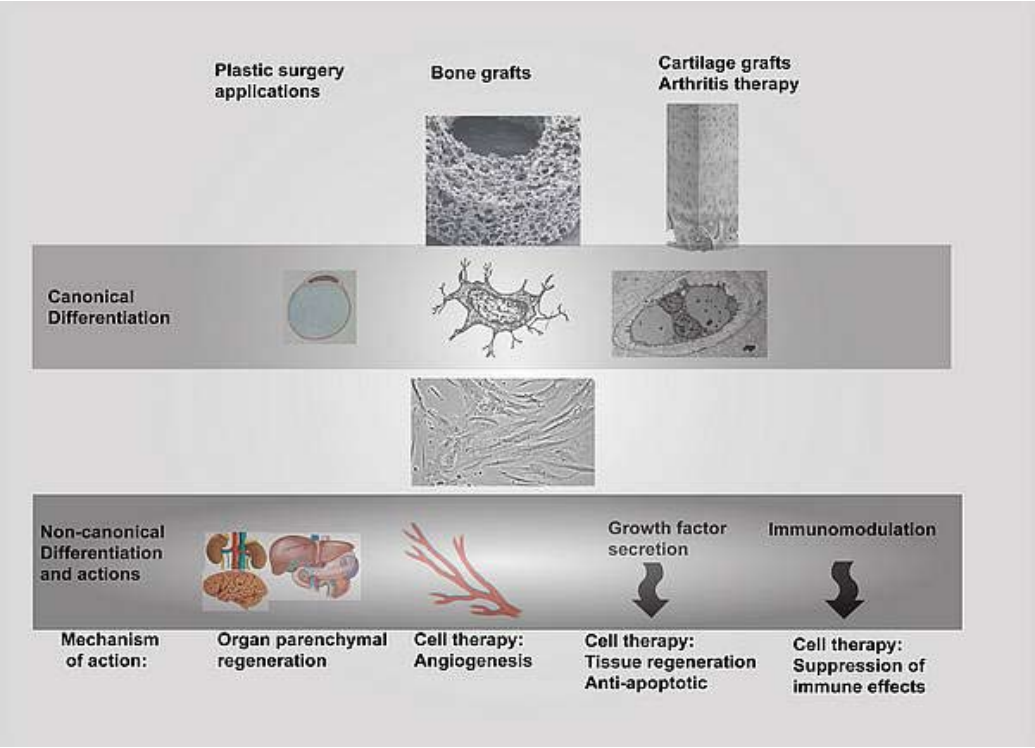
they have also been called 'mesenchymal stem cells'. These cells support hematopoietic stem cells (HSCs) by growth factor and cytokine secretion and differentiate into bone, cartilage and fat. MSCs have now been recognized as the second stem cell population in the bone marrow, next to HSCs, but can also be generated from almost any organ (da Silva Meirelles 2006). They are now defined by plastic adherence, positivity for the surface markers CD73, CD90 and CD105 and absence of CD45, CD34, HLA-DR (Dominici M 2006).

Extensive in vitro and in vivo studies have shown that MSCs exhibit a potential to differentiate into various cell types (Graph 1). Lineage analyses of cloned MSCs showed that their natural differentiation pathway ('default pathway') is the osteogenic lineage and different clones exhibit different lineage potential in vitro (Okamoto 2002). Differentiation of MSCs into different cell types in vitro can be induced through culture conditions and addition of endogenous substances like steroids, growths factors or PPARs or by demethylation agents like 5-azacytidine (Makino 1999). MSCs are not a homogeneous population of cells, in vitro cultures are phenotypically different in size and shape, and can be generated from most organs (Young 1995). MSCs are readily generated from bone marrow aspirations, can be expanded in culture on a large scale without the addition of xenogenic additives like fetal calf serum (Lange 2007) and are susceptible to transduction with viral vectors which makes them ideal vehicles for cell therapy.

MSCs have been originally derived from the bone marrow by a protocol from Friedenstein, however, with subsequent variation in culture conditions different cell populations with similar but not identical properties like MSCs have been described by various groups. It is currently not entirely clear how these different 'brands' of MSCs are related in vivo or if they are derived from a "basic" MSC and how culture conditions, e.g. the addition of growth factors like EGF, a low oxygen environment, low serum conditions and seeding density influence propagation and differentiation potential after several passages in vitro. Verfaillie's group generated multipotent adult progenitor cells (MAPCs) from the bone marrow under low density and low serum conditions and could show that they have embryonic stem cell like properties when injected into blastocysts (Jiang 2002). So-called marrow-isolated adult multilineage inducible cells (MIAMI) were generated under low-oxygen tension on fibronectin from bone marrow cells (D'Ippolito 2004). Lange et al described a population of bone marrow-derived adult stem cells, separated on a Percoll gradient with low density, that showed an extraordinary high proliferative potential and a conserved phenotype characteristic of MSCs (Lange 2005). MSCs not only have been derived from bone marrow but from almost any organ (da Silva Meirelles, 2006).

Unrestricted somatic stem cells (USSCs) have been cultured from human cord blood (Kögler, 2004). The authors state that USSCs have a wider differentiation potential and differ in immunophenotype and in their mRNA expression profile. Not all groups have been successful in generating stem cell like cells from cord blood (Mareschi, 2001). In contrast to Mareschi, Lee et al. found a mesenchymal stem cell like population derived from cord blood cells with classical characteristics of MSCs as well as differentiation into neuroglial- and hepatocyte-like cells under appropriate induction conditions. Adipose tissue contains MSCs that are easy to obtain from lipoaspirates (Zuk, 2002). Because

Graph 1. MSCs exhibit a potential to differentiate into various cell types



they are easy to culture and readily available from different sources, MSCs continue to be a popular research subject with steadily increasing numbers of publications and applications.

Mechanisms of action of MSCs used in cell therapy and regenerative medicine

1. Replacement of injured cells by MSCs through differentiation and integration into organ parenchyma

Cellular differentiation is not an irreversible process. Pathologists know the phenomenon of differentiation of one cell type into another due to prolonged exposure to un-physiological stimuli in epithelia, e.g. gastric reflux causes the squamous epithelium of the esophagus to differentiate into gastric mucosa, and have termed it 'metaplasia'. In the kidney, tubular cells de-differentiate after ischemic injury, re-express embryonic and developmental markers like Pax-2, and start dividing to repopulate the denuded tubular parts, thereby regenerating a sublethally injured tubule (Witzgall 1994; Imgrund 1999).

In the late 1990s researchers described so far unknown and unexpected differentiation of HSCs into a number of cell types, e.g. liver and muscle (Ferrari 1998; Petersen 1999). These results were surprising because a long held dogma stated that adult stem cells are lineage restricted and can only differentiate into tissue from their lineage and that differentiation is terminal (Lemischka 2001). This so called transdifferentiation was immediately recognized as a new and promising way of regeneration of injured tissue and proposed as a mechanism of action for cell therapy. However, initial enthusiasm led researchers to overlook some problems associated with early studies. These studies utilized crude cell preparations, e.g. whole bone marrow, and therefore it was not clear, which cell type was responsible for the observed phenomenon. Furthermore, transdifferentiation was very rare and only some dispersed single cells could be detected after a meticulous search, calling into question the therapeutic value of this approach. Krause et al in a very carefully conducted study showed, that a prospectively isolated HSCs are indeed the cell type responsible for tissue contribution and differentiation into most organ cells, but the contribution was below 0.1% (Krause 2001).

Some time later two groups described fusion of cells in vitro and it was discussed, that this could be a potential explanation for the phenomena described in the early stem cell studies (Terada 2002; Ying 2002). Indeed, some groups attributed cell fusion as the main mechanism for organ regeneration in certain disease models (Medvinsky 2003; Vassilopoulos 2003; Wang 2003).

Meticulous studies by Wagers and Balsam showed that transdifferentiation is an extremely rare event under steady state and ischemic conditions and HSCs do not contribute much to tissue turnover (Wagers 2002; Balsam 2004).

The lessons learned from these studies with HSCs are:

- Transdifferentiation or plasticity is a real phenomenon but exceedingly rare in most disease models.
- Replacement of damaged tissue is therefore not a major mechanism for tissue regeneration.
- Under steady state conditions tissue replacement is rare and in disease conditions it is dependent on the model and kinetics used to study transdifferentiation.

Based on initial observations with whole bone marrow and the fact that MSCs can be differentiated into a large number of differentiated cells in vitro and in vivo, e.g. neurons (Phinney 2007), cardiomyocytes (Makino 1999), myocytes (De Bari 2003), endothelial cells (Oswald 2004; Liu 2007), pulmonary cells (Ortiz 2003) and liver cells (Lange 2005; Lange 2005; Lange 2006), it was hypothesized that differentiation of MSCs into organ parenchymal cells is a major mechanism of tissue protection and regeneration after injury. However, MCSs exhibited tissue repair capacity despite low or transient engraftment in vivo, e.g. in the treatment of osteogenesis imperfecta it was less than 1% (Horwitz 2002), and therefore differentiation into target tissues is most likely only a minor mechanisms of tissue protection and regeneration. The fact that tissue protection is observed without evidence of long-term engraftment also argues against differentiation as a main mechanism of action (Iso 2007).

2. Paracrine mechanisms

MSCs produce a number of cytokines, growth factors and adhesion molecules that have been shown to be involved in tissue homeostasis and regeneration (Deans 2000). Furthermore, transcriptome analysis by serial analysis of gene expression (SAGE) revealed a large number of transcripts for proteins involved in wound repair, immunological regulation, neural factors as well as angiogenesis (Tremain 2001; Phinney 2006) implying a role for these factors in MSC mediated tissue regeneration. These factors stimulate cell proliferation (growth factors like IGF (Imberti 2007)) and are anti-apoptotic (Chen 2003). The advantage of administering MSCs rather than growth factors directly lies in the fact that MSCs act on a local level and are able to interact with damaged tissue, which means they probably respond to cytokines like TNF-a secreted by damaged tissue with more or less secretion of a number of growth factors or modulatory cytokines and thereby influence the local environment directly and better than any systemically administered growth factors (Liu 2005; Segers 2006). In the kidney, MSCs regenerate renal function after acute kidney injury mainly by secreting epidermal growth factor (EGF), insulin-like growth factor (IGF-1), VEGF and by changing the cytokine expression profile of the injured kidney towards a more favorable anti-inflammatory state with higher IL-10 levels (Rabb 2005; Togel 2005). In the heart, MSCs stimulate angiogenesis by secretion of VEGF (Al-Khaldi 2003; Kinnaird 2004). Endogenous cell proliferation in the brain is stimulated by MSCs through paracrine mechanisms after injury mediated by different factors (Mahmood 2004; Crigler 2006).

3. Vasculo- and angiogenesis

Blood supply is the most critical factor for tissue survival and most injury mechanisms involve the vasculature in one way or another. Ischemic injury is the most common mechanism of tissue damage for every organ system and fast restoration of regular blood supply is critical for tissue survival. The microvascular bed can be damaged in many ways, but endothelial dysfunction or apoptosis are major factors. MSCs express a number of angiogenic and vasculogenic factors and proteins that have been shown to increase endothelial cell survival and proliferation (Al-Khaldi 2003; Hung 2007). In vivo studies have shown that vasculo- and angiogenesis by MSCs is either mediated directly by integration into vascular structures or through paracrine mechanisms stimulating angiogenesis, e.g. secretion of VEGF, angiopoietin or other growth factors (Al-Khaldi 2003; Annabi 2004; Tang 2005; Tang 2006; Wu 2007). MSCs can be genetically engineered, using

different strategies like bcl-2, Akt or erythropoietin expression, to enhance endogenous angiogenic activity (Eliopoulos 2006; Gnecchi 2006; Li 2007).

4. Immunomodulation

MSCs exhibit low immunogenity due to low or absent MHC-II expression, low MHC-I expression and negativity for costimulatory molecules CD80, CD86 and CD40. Therefore infusion of MSCs do not trigger a direct rejection reaction, although several groups have shown that MSCs are not neutral towards the immune system and antibodies can be measured as well as T cell activation but not proliferation (Klyushnenkova 2005; Poncelet 2007). A large body of data shows immunomodulatory properties of MSCs in vitro on different cell types such as T-cells, B-cells and NK cells (Fibbe 2007). MSCs suppress T-cell proliferation in vitro, interfere with dendritic cell differentiation, inhibit B-cell proliferation and suppress the proliferation and cytokine production of natural killer cells (Nauta 2007). The in vivo relevance of these in vitro finding has been demonstrated in humans with acute graft versus host (GvHD) and Crohn's disease (Ringden 2006; Taupin 2006). In animal models MSCs have been shown to modify experimental autoimmune encephalitis, a model of multiple sclerosis, and prolonged skin graft survival in baboons (Bartholomew 2002; Uccelli 2006). There are conflicting data about effects of MSCs in organ transplantation models. Inoue reported that MSCs were ineffective at prolonging allograft survival and tended to promote rejection (Inoue 2006). In a different model cardiac allograft survival was prolonged (Zhou 2006). MSCs also favored tumour survival in animal models (Djouad 2003).

While the currently known immunomodulatory effects of MSCs show promise for the treatment of a number of diseases, data have to be interpreted carefully dependent on the animal model or in vitro strategy. Culture conditions and numerous other factors not least the model that is studied play important roles and have to be considered carefully to avoid preliminary conclusions.

5. Other applications for MSCs

MSCs are ideally suited as cellular delivery systems in tumor treatment. They can be engineered to express the interferon-beta (IFN-beta) gene and deliver therapeutic doses of IFN-beta directly into the tumor through infiltration thereby suppressing tumor growth and metastasis (Studeny, 2004). In metabolic diseases and enzyme defects, either allogeneic or genetically engineered MSCs are able to function as enzyme replacement therapy (Muller, 2006) by providing necessary concentrations of an enzyme that is lacking due to a genetic defect. MSCs are rapidly transducable with different viral vectors and are thereby ideal vehicles for therapeutic genes (Prockop 2003). Other important applications include adjunct infusion to enhance hematopoietic engraftment (Ball, 2007) and as a source for engineered tissue such as cartilage and bone in tissue engineering (De Bari, 2007).

Conclusions

In the ongoing story of stem cell treatment for patients MSCs have been so far the most promising development and have rapidly advanced from bench to bedside with several products already in late stage trials. Although little is known about MSCs in vivo, they have been characterized extensively in vitro and clinical studies have been finished and new ones are on their way. The mechanisms of action of MSCs are currently investigated in detail and there is still a large number of questions to be addressed until the full therapeutic benefit of these cells can be utilized but the field is rapidly advancing and is giving a shining example for the whole stem cell community.

References

Al-Khaldi, A., H. Al-Sabti, et al. (2003). "Therapeutic angiogenesis using autologous bone marrow stromal cells: improved blood flow in a chronic limb ischemia model." Ann Thorac Surg 75(1): 204-9

Al-Khaldi, A., N. Eliopoulos, et al. (2003). "Postnatal bone marrow stromal cells elicit a potent VEGF-dependent neoangiogenic response in vivo." Gene Ther 10(8): 621-9.

Annabi, B., E. Naud, et al. (2004). "Vascular progenitors derived from murine bone marrow stromal cells are regulated by fibroblast growth factor and are avidly recruited by vascularizing tumors." J Cell Biochem 91(6): 1146-58.

Ball LM, Bernardo ME, et al. (2007). Cotransplantation of ex vivo expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. Blood. 110(7): 2764-7.

Balsam, L. B., A. J. Wagers, et al. (2004). „Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium." Nature 428(6983): 668-73.

Bartholomew, A., C. Sturgeon, et al. (2002). „Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo." Exp Hematol 30(1): 42-8.

Chen, J., Y. Li, et al. (2003). „Intravenous bone marrow stromal cell therapy reduces apoptosis and promotes endogenous cell proliferation after stroke in female rat." J Neurosci Res 73(6): 778-86.

Crigler, L., R. C. Robey, et al. (2006). „Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis." Exp Neurol 198(1): 54-64.

D'Ippolito, G., S. Diabira, et al. (2004). „Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential." J Cell Sci 117(Pt 14): 2971-81.

Da Silva Meirelles, L., P. C. Chagastelles, et al. (2006). „Mesenchymal stem cells reside in virtually all post-natal organs and tissues." J Cell Sci 119(Pt 11): 2204-13.

De Bari, C., F. Dell'Accio, et al. (2003). „Skeletal muscle repair by adult human mesenchymal stem cells from synovial membrane." J Cell Biol 160(6): 909-18.

De Bari C, Dell'accio F. (2007). Mesenchymal stem cells in rheumatology: a regenerative approach to joint repair. Clin Sci (Lond). 113(8): 339-48.

Deans, R. J. and A. B. Moseley (2000). „Mesenchymal stem cells: biology and potential clinical uses." Exp Hematol 28(8): 875-84.

Djouad, F., P. Plence, et al. (2003). „Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals." Blood 102(10): 3837-44.

Dominici M, Le Blanc K, et al. (2006). „Minimal criteria for defining

multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement.“ Cytotherapy 8(4): 315-7.

Eliopoulos, N., R. F. Gagnon, et al. (2006). „Erythropoietin delivery by genetically engineered bone marrow stromal cells for correction of anemia in mice with chronic renal failure.“ J Am Soc Nephrol 17(6): 1576-84.

Ferrari, G., G. Cusella-De Angelis, et al. (1998). „Muscle regeneration by bone marrow-derived myogenic progenitors.“ Science 279(5356): 1528-30.

Fibbe, W. E., A. J. Nauta, et al. (2007). „Modulation of immune responses by mesenchymal stem cells.“ Ann N Y Acad Sci 1106: 272-8.

Friedenstein, A. J., K. V. Petrakova, et al. (1968). „Heterotopic of bone marrow.Analysis of precursor cells for osteogenic and hematopoietic tissues.“ Transplantation 6(2): 230-47.

Gatti, R. A., H. D. Meuwissen, et al. (1968). „Immunological reconstitution of sex-linked lymphopenic immunological deficiency.“ Lancet 2(7583): 1366-9.

Gnecchi, M., H. He, et al. (2006). „Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement.“ Faseb J 20(6): 661-9.

Horwitz, E. M., P. L. Gordon, et al. (2002). „Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone.“ Proc Natl Acad Sci U S A 99(13): 8932-7.

Hung, S. C., R. R. Pochampally, et al. (2007). „Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis.“ Stem Cells 25(9): 2363-70.

Imberti, B., M. Morigi, et al. (2007). „Insulin-like growth factor-1 sustains stem cell mediated renal repair.“ J Am Soc Nephrol 18(11): 2921-8.

Imgrund, M., E. Grone, et al. (1999). „Re-expression of the developmental gene Pax-2 during experimental acute tubular necrosis in mice 1.“ Kidney Int 56(4): 1423-31.

Inoue, S., F. C. Popp, et al. (2006). „Immunomodulatory effects of mesenchymal stem cells in a rat organ transplant model.“ Transplantation 81(11): 1589-95.

Iso, Y., J. L. Spees, et al. (2007). „Multipotent human stromal cells improve cardiac function after myocardial infarction in mice without long-term engraftment.“ Biochem Biophys Res Commun 354(3): 700-6.

Jiang, Y., B. N. Jahagirdar, et al. (2002). „Pluripotency of mesenchymal stem cells derived from adult marrow.“ Nature 418(6893): 41-9.

Kinnaird, T., E. Stabile, et al. (2004). „Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms.“ Circ Res 94(5): 678-85.

Klyushnenkova, E., J. D. Mosca, et al. (2005). „T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression.“ J Biomed Sci 12(1): 47-57.

Kögler G, Sensken S, Airey JA et al. (2004). A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med. 200(2): 123-35.

Kolb, H. J., C. Schmid, et al. (2004). „Graft-versus-leukemia reactions in allogeneic chimeras.“ Blood 103(3): 767-76.

Krause, D. S., N. D. Theise, et al. (2001). „Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell.“ Cell 105(3): 369-77.

Lange, C., P. Bassler, et al. (2005). „Hepatocytic gene expression in cultured rat mesenchymal stem cells.“ Transplant Proc 37(1): 276-9.

Lange, C., P. Bassler, et al. (2005). „Liver-specific gene expression in mesenchymal stem cells is induced by liver cells.“ World J Gastroenterol 11(29): 4497-504.

Lange, C., H. Bruns, et al. (2006). „Hepatocytic differentiation of mesenchymal stem cells in cocultures with fetal liver cells.“ World J Gastroenterol 12(15): 2394-7.

Lange, C., F. Cakiroglu, et al. (2007). „Accelerated and safe expansion of human mesenchymal stromal cells in animal serum-free medium for transplantation and regenerative medicine.“ J Cell Physiol 213(1): 18-26.

Lange, C., J. Schroeder, et al. (2005). „High-potential human mesenchymal stem cells.“ Stem Cells Dev 14(1): 70-80.

Lemischka, I. (2001). „Stem cell dogmas in the genomics era.“ Rev Clin Exp Hematol 5(1): 15-25.

Li, W., N. Ma, et al. (2007). „Bcl-2 engineered MSCs inhibited apoptosis and improved heart function.“ Stem Cells 25(8): 2118-27.

Liu, C. H. and S. M. Hwang (2005). „Cytokine interactions in mesenchymal stem cells from cord blood.“ Cytokine 32(6): 270-9.

Liu, J. W., S. Dunoyer-Geindre, et al. (2007). „Characterization of endothelial-like cells derived from human mesenchymal stem cells.“ J Thromb Haemost 5(4): 826-34.

Lorenz, E., D. Uphoff, et al. (1951). „Modification of irradiation injury in mice and guinea pigs by bone marrow injections.“ J Natl Cancer Inst 12(1): 197-201.

Mahmood, A., D. Lu, et al. (2004). „Marrow stromal cell transplantation after traumatic brain injury promotes cellular proliferation within the brain.“ Neurosurgery 55(5): 1185-93.

Makino, S., K. Fukuda, et al. (1999). „Cardiomyocytes can be generated from marrow stromal cells in vitro.“ J Clin Invest 103(5): 697-705.

Mareschi K, Biasin E, Piacibello W, Aglietta M, Madon E, Fagioli F. (2001). Isolation of human mesenchymal stem cells: bone marrow versus umbilical cord blood. Haematologica;86: 1099-1100.

Medvinsky, A. and A. Smith (2003). „Stem cells: Fusion brings down barriers.“ Nature 422(6934): 823-5.

Müller I, Kustermann-Kuhn B, et al. (2006). In vitro analysis of multipotent mesenchymal stromal cells as potential cellular therapeutics in neurometabolic diseases in pediatric patients. Exp Hematol. 34(10):1413-9.

Nathan, D. G. (1990). „Nobel Prize for Clinical Investigation.“ New Biol 2(12): 1047-8.

Nauta, A. J. and W. E. Fibbe (2007). „Immunomodulatory properties of mesenchymal stromal cells.“ Blood 110(10): 3499-506.

Niehans, P. (1956). „[History of fresh cell therapy with correction of an error.].“ Hippokrates 27(16): 519-23.

Okamoto, T., T. Aoyama, et al. (2002). „Clonal heterogeneity in differentiation potential of immortalized human mesenchymal stem cells.“ Biochem Biophys Res Commun 295(2): 354-61.

Ortiz, L. A., F. Gambelli, et al. (2003). „Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects.“ Proc Natl Acad Sci U S A 100(14): 8407-11.

Oswald, J., S. Boxberger, et al. (2004). „Mesenchymal stem cells can be differentiated into endothelial cells in vitro.“ Stem Cells 22(3): 377-84.

Petersen, B. E., W. C. Bowen, et al. (1999). „Bone marrow as a potential source of hepatic oval cells.“ Science 284(5417): 1168-70.

Phinney, D. G., K. Hill, et al. (2006). „Biological activities encoded by the murine mesenchymal stem cell transcriptome provide a basis for their developmental potential and broad therapeutic efficacy.“ Stem Cells 24(1): 186-98.

Phinney, D. G. and D. J. Prockop (2007). „Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair--current views.“ Stem Cells 25(11): 2896-902.

Poncelet, A. J., J. Vercruysse, et al. (2007). „Although pig allogeneic mesenchymal stem cells are not immunogenic in vitro, intracardiac injection elicits an immune response in vivo.“ Transplantation 83(6): 783-90.

Prockop DJ, Gregory CA, and Spees JL. (2003). One strategy for cell and gene therapy: Harnessing the power of adult stem cells to repair tissues. PNAS 100: 11917-11923.

Rabb, H. (2005). „Paracrine and differentiation mechanisms underlying stem cell therapy for the damaged kidney.“ Am J Physiol Renal Physiol 289(1): F29-30.

Ringden, O., M. Uzunel, et al. (2006). „Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease.“ Transplantation 81(10): 1390-7.

Segers, V. F., I. Van Riet, et al. (2006). „Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms.“ Am J Physiol Heart Circ Physiol 290(4): H1370-7.

Studeny M, Marini FC et al. (2004). Mesenchymal stem cells: potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents. J Natl Cancer Inst. 96(21): 1593-603.

Tang, J., Q. Xie, et al. (2006). „Mesenchymal stem cells participate in angiogenesis and improve heart function in rat model of myocardial ischemia with reperfusion.“ Eur J Cardiothorac Surg 30(2): 353-61.

Tang, Y. L., Q. Zhao, et al. (2005). „Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction.“ Ann Thorac Surg 80(1): 229-36; discussion 236-7.

Taupin, P. (2006). „OTI-010 Osiris Therapeutics/JCR Pharmaceuticals.“ Curr Opin Investig Drugs 7(5): 473-81.

Terada, N., T. Hamazaki, et al. (2002). „Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion.“ Nature 416(6880): 542-5.

Thomas, E. D., H. L. Lochte, Jr., et al. (1957). „Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy.“ N Engl J Med 257: 4-91-6.

Togel, F., Z. Hu, et al. (2005). „Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms.“ Am J Physiol Renal Physiol 289(1): F31-42.

Tremain, N., J. Korkko, et al. (2001). „MicroSAGE analysis of 2,353 expressed genes in a single cell-derived colony of undifferentiated human mesenchymal stem cells reveals mRNAs of multiple cell lineages.“ Stem Cells 19(5): 408-18.

Uccelli, A., E. Zappia, et al. (2006). „Stem cells in inflammatory demyelinating disorders: a dual role for immunosuppression and neuroprotection.“ Expert Opin Biol Ther 6(1): 17-22.

Vassilopoulos, G., P. R. Wang, et al. (2003). „Transplanted bone marrow regenerates liver by cell fusion.“ Nature 422(6934): 901-4.

Wagers, A. J., R. I. Sherwood, et al. (2002). „Little evidence for developmental plasticity of adult hematopoietic stem cells.“ Science 297(5590): 2256-9.

Wang, X., H. Willenbring, et al. (2003). „Cell fusion is the principal source of bone-marrow-derived hepatocytes.“ Nature 422(6934): 897-901.

Witzgall, R., D. Brown, et al. (1994). „Localization of proliferating cell nuclear antigen, vimentin, c-Fos, and clusterin in the postischemic kidney. Evidence for a heterogenous genetic response among nephron segments, and a large pool of mitotically active and dedifferentiated cells.“ J Clin Invest 93(5): 2175-88.

Wolff, E. (2002). „Vor 50 Jahren: Paul Niehans bringt den Begriff ‚Zellulartherapie‘ in die Öffentlichkeit.“ Schweizerische Ärztezeitung 83: 1726-1727.

Wu, Y., L. Chen, et al. (2007). „Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis.“ Stem Cells 25(10): 2648-59.

Ying, Q. L., J. Nichols, et al. (2002). “Changing potency by spontaneous fusion.” Nature 416(6880): 545-8.

Young, H. E., M. L. Mancini, et al. (1995). „Mesenchymal stem cells reside within the connective tissues of many organs.“ Dev Dyn 202(2): 137-44.

Zhou, H. P., D. H. Yi, et al. (2006). «Administration of donor-derived mesenchymal stem cells can prolong the survival of rat cardiac allograft.» Transplant Proc 38(9): 3046-51.

Zuk PA, Zhu M et al. (2002). Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 13(12): 4279-95.

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Концепции и перспективы регенеративной терапии мультипотентными стромальными стволовыми клетками костного мозга

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Резюме

Обзорная статья содержит сведения об историческом развити и общей концепции клеточной терапии в медицине. Помимо заместительной функции трансплантата при трансплантации костного мозга (ТКМ), рассматриваются другие лечебные эффекты трансплантата (противоопухолевое действие, стимуляция иммунного ответа и др.). Основной материал работы касается мультипотентных стромальных клеток костного мозга (МСК), описаны их фенотипические признаки (CD73+, CD90+, CD105+, CD45-, CD34-, HLA-DR-). Обсуждаются возможности МСК к дифференцировке in vitro и роль различных условий культивирования на их мультипотентность и направленность дифференцировки. Пластичность МСК взрослого организма в плане трансдифференцировки (например, в ткани мышц или печени) может быть в редких случаях одним из источников регенерации. Более вероятны паракринные механизмы действия МСК, а именно выработка ими множества цитокинов, факторов роста и адгезии, что иллюстрируется экспериментальными данными о регенерации почек, сердца и головного мозга. В качестве отдельных механизмов рассматривается инлукция ангиогенеза и модуляция Т- и В-лимфоцитов под влиянием МСК. Делается заключение о необходимости дальнейших исследований клинически актуальных эффектов МСК.

Ключевые слова: мезенхимальные стволовые клетки, паракринная секреция, цитокины, ангиогенез, иммуномодуляция, клинические эффекты, обзор