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Concise Review: Mesenchymal Stem/Multipotent Stromal Cells: The State of Transdifferentiation and Modes of Tissue Repair—Current Views

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ABSTRACT

Mesenchymal stem cells or multipotent stromal cells (MSCs) isolated from the bone marrow of adult organisms were initially characterized as plastic adherent, fibroblastoid cells with the capacity to generate heterotopic osseous tissue when transplanted in vivo. In recent years, MSCs or MSC-like cells have been shown to reside within the connective tissue of most organs, and their surface phenotype has been well described. A large number of reports have also indicated that the cells possess the capacity to transdifferentiate into epithelial cells and lineages derived from the neuroectoderm. The broad developmental plasticity of MSCs was originally thought to contribute to their demonstrated efficacy in a wide variety of experimental animal models of disease as well as in human clinical trials. However, new findings suggest that the ability of MSCs to alter the tissue microenvironment via secretion of soluble factors may contribute more significantly than their capacity for transdifferentiation in tissue repair. Herein, we critically evaluate the literature describing the plasticity of MSCs and offer insight into how the molecular and functional heterogeneity of this cell population, which reflects the complexity of marrow stroma as an organ system, may confound interpretation of their transdifferentiation potential. Additionally, we argue that this heterogeneity also provides a basis for the broad therapeutic efficacy of MSCs. STEM CELLS *2007;25:2896–2902*

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

In the past decade, the field of stem cell biology has undergone a remarkable evolution sparked by reports demonstrating that adult stem cells possess greater plasticity than dictated by established paradigms of embryonic development. Subsequently, much effort has been devoted to deciphering the molecular mechanisms that regulate adult stem cell plasticity and developing ways to exploit it for a therapeutic intent. These efforts have led to the publication of many protocols for inducing adult stem cells to differentiate in vitro across germinal boundaries, a process referred to as transdifferentiation. Additionally, a large number of studies have assessed the fate of adult stem cells administered in vivo and their effect on disease progression in experimental animal models and human clinical trials. Despite some initial encouraging results, these in vivo studies have shown that adult stem cells typically exhibit low levels of engraftment and transdifferentiation within diseased or injured tissue and therefore do not contribute physically to tissue regeneration to a significant extent. These findings initially cast doubt on the prospect of harnessing adult stem cell plasticity to treat disease. However, more recent reports have revealed that stem/progenitor cells, particularly those derived from bone marrow, promote tissue repair by secretion of factors that enhance regeneration of injured cells, stimulate proliferation and differentiation of endogenous stem-like progenitors found in most tissues, decrease inflammatory and immune reactions, and, perhaps, by transfer of mitochondria. Therefore, the ability of such cells to alter the tissue microenvironment may contribute more significantly than their capacity for transdifferentiation in effecting tissue repair.

In this article, we describe recent data pertaining to the plasticity and therapeutic potential of stem/progenitor cells derived from adult bone marrow that were initially referred to as colony forming unit-fibroblasts, then as marrow stromal cells in the hematological literature, and more recently as either mesenchymal stem cells or multipotent mesenchymal stromal cells (MSCs). Our intention is not to provide a comprehensive review of this large and rapidly expanding literature. Rather, our focus is to critically evaluate the evidence in favor of MSC plasticity and provide insight into how the unique biology of MSCs provides a basis for their broad therapeutic efficacy.

MULTIPOTENT MESENCHYMAL STROMAL CELLS

Friedenstein and coworkers were the first to report that fibroblast-like cells elaborated from bone marrow via attachment to tissue culture plastic were inherently osteogenic (reviewed in [1–3]). Thereafter, contributions from many laboratories led to the realization that these osteogenic cells were actually capable of differentiating into multiple connective tissue cell types at a clonal level [4, 5], which validated the concept of a mesenchymal stem cell first proposed by Caplan [6]. Consequently, MSCs

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are typically defined as adherent, fibroblastoid-like cells that differentiate to osteoblasts, adipocytes, and chondrocytes in vitro [7].

In addition to bone marrow, MSCs or MSC-like cells have also been elaborated from skeletal muscle [8], adipose tissue [9], umbilical cord [10], synovium [11], the circulatory system [12], dental pulp [13], and amniotic fluid [14] as well as fetal blood, liver, bone marrow, and lung [15–17]. Therefore, it appears that MSCs reside within the connective tissue of most organs as predicted by early studies with chick embryos [18]. However, it should be noted that these populations are not functionally equivalent with respect to their differentiation potential, particularly when assayed using more stringent in vivo assays [19]. Also, clonal studies have shown that plastic adherent populations isolated from bone marrow are functionally heterogeneous and contain undifferentiated stem/progenitors and lineage-restricted precursors with varying capacities to differentiate into connective tissue cell types [19–21]. Therefore, characterizing populations as MSC or MSC-like also depends, in part, on the methods used to evaluate their differentiation potential. Finally, because MSCs also generate the stromal component of bone marrow, adherent populations contain cells that express adhesion molecules [22] and cytokines [23] that regulate aspects of hematopoiesis [24, 25].

Despite their functional heterogeneity, MSC populations obtained from most tissues commonly express a number of surface receptors including CD29, CD44, CD49a-f, CD51, CD73, CD105, CD106, CD166, and Stro1 and lack expression of definitive hematopoietic lineage markers including CD11b, CD14, and CD45. Recent studies have shown cells that express the aforementioned surface markers and are capable of differentiating into connective tissue cell types can be enriched from peripheral and umbilical cord blood by selection for CD133 [26] and from bone marrow by selection for stage-specific embryonic antigen (SSEA)-1 [27], SSEA-4 [28], or the nerve growth factor receptor CD271 [29]. Moreover, CD271-expressing populations have been shown to coexpress CD140b (platelet-derived growth factor receptor β), CD340 (HER-2/erbB2), and CD349 (frizzled-9) [30]. Other studies have shown that bone marrow-derived MSCs express the pericyte-specific markers CD146 and 3G5 [31], consistent with the fact that specialized vascular pericytes in bone marrow are thought to represent the closest in vivo approximation to MSCs [2, 32]. However, it is important to realize that no single isolation method is regarded as a standard in the field. Therefore, the varied approaches used to culture-expand and select for MSCs make it difficult to directly compare experimental results. Moreover, some isolation schemes introduce epigenetic and genetic changes in cells that may dramatically affect their plasticity and therapeutic utility. Finally, human MSCs exhibit some variation in their pattern of expressed genes among different donor preparations using the same isolation protocols, and larger variations as sparse cultures become confluent and are expanded by serial passage and approach senescence [33]. These subtleties have been overlooked in several publications in which high density and confluent human MSC cultures were assumed to consist of homogeneous cell populations.

Differentiation to Neuroectoderm

Our laboratory was the first to demonstrate that MSCs injected into the central nervous systems of newborn mice migrate throughout the brain and adopt morphological and phenotypic characteristics of astrocytes and neurons [34]. These findings were confirmed by other laboratories [35–37], which prompted efforts to identify conditions that induced neural differentiation of MSCs in vitro as a means to investigate their observed plasticity in vivo. Review of these in vitro studies indicates that the methods used to promote neural cell differentiation and assess the biology of the differentiated cells are fragmented and inconsistent. Furthermore, we argue that ascribing a neural fate to MSCs is further confounded by the lack of specificity of neural markers employed, the heterogeneous nature of the MSC populations under examination, and artifacts associated with methods used to culture-expand cells in vitro.

Several groups first reported that exposure to reducing agents and antioxidants or chemicals that increase intracellular cyclic AMP levels induced MSCs to adopt a neuron-like morphology and express various neural specific proteins including nestin, glial fibrillary acidic protein (GFAP), neurofilament heavy chain (NF-H), and β-III tubulin (reviewed in [38–41]). However, the rapid action of these agents and the reversible nature of the process questioned whether it represented actual cellular differentiation or a culture artifact. Studies by Neuhuber et al. [42] subsequently showed that these agents promoted retraction of the cell cytoplasm due to disruption of the actin network in MSCs and not neurite outgrowth as seen in neurons. This finding was substantiated by Lu et al. [43], who showed that exposure to stressors such as detergents, high pH, and high molarity sodium chloride also induced a neuron-like phenotype in MSCs as well as fibroblasts and keratinocytes. Microarray [44] and proteomic studies [45] further demonstrated that the set of genes modulated in MSCs after neural differentiation was distinct from the set differentially expressed between untreated MSCs and neural tissue. Therefore, cytoskeletal alterations induced by these agents rather then transdifferentiation accounted for the neuron-like morphology of MSCs. Moreover, studies showing that alterations to the biochemical properties of microtubules perturb the network of intermediate filaments in cells [46] explained how these agents altered nestin, GFAP, and NF-H expression levels in MSCs. The latter is consistent with other studies claiming that culture of MSCs on different plating surfaces enhanced their capacity for neural differentiation [47, 48].

Efforts to evaluate the capacity of MSCs to adopt neural cell fates were further confounded by reports that undifferentiated cells constitutively express neural specific proteins [49–52]. In one such study, upregulation of microtubule-associated protein-2, GFAP, and tyrosine hydroxylase in MSCs after five passages in vitro without any specific induction was cited as evidence for their differentiation into neurons and astrocytes [51]. Furthermore, expression by MSCs of nestin, a neural stem cell marker [53], was cited as evidence for the existence of a unique pool of neural progenitors within bone marrow [54]. Several studies have attempted to validate this concept experimentally, but the results are inconclusive. For example, one study reported that nestin-positive murine MSCs differentiated into neurons following exposure to $CoCl_2$, but its effect on cells that did not express nestin was not evaluated [55]. Another study reported that only nestin-expressing rat MSCs were capable of forming neurosphere-like aggregates in vitro [49] or differentiating into neurons after coculture with mouse cerebellar granular neurons [56]. However, comparative studies failed to reveal any significant differences in expressed levels of genes important for neural development between nestin-positive versus nestin-negative MSCs [56].

One difficulty in assessing the significance of nestin expression in MSCs is the fact that this intermediate filament protein is not restricted to neural tissue but also expressed in a variety of mesodermal cell types. For example, nestin is an integral component of the intermediate filament network formed during muscle development and copolymerizes with both vimentin and

desmin [57]. Nestin is also expressed in developing limb buds [58, 59], skeletal myoblasts during muscle regeneration [60], endothelial cells during development [61], and adults [62]. Similarly, GFAP and neurofilaments are also expressed in various connective tissues including chondrocytes of elastic and fibrous cartilage and some fibroblasts [63–65]. The findings reflect the fact that intermediate filaments form dynamic networks whose composition changes in a stage-specific manner during cellular differentiation. Therefore, a more pertinent question is whether nestin-positive MSCs represent a special subset of mesodermal or neural progenitors in bone marrow. One study has shown that nestin-positive MSCs differentiate into skeletal and cardiac muscle cells in vitro and improve cardiac function in an infarction model in vivo [66]. However, further research is needed to resolve the true nature of nestin expressing MSCs.

Other studies have described methods to direct MSCs to differentiate into specific neuronal subtypes as evidenced by their expression of tyrosine hydroxylase [67–69], glutamate receptors [70], Schwann cell markers [71], glutamate transporters [72], inward rectifying potassium channels [73], synaptic vesicle proteins [74, 75], and neurotrophic receptors [76]. However, the capacity of so many different agents to induce neural differentiation is unusual in that transcriptional regulatory networks that control fate decisions in mammalian cells are typically regulated by a single master gene [77]. Therefore, does induction of a few neural proteins in MSCs constitute evidence that cells have entered a program of neural lineage commitment and differentiation? We suggest that the molecular and functional heterogeneity of MSC populations, which express a broad array of regulatory proteins found in neurons, is a confounding variable in efforts to ascertain their transdifferentiation potential. For example, it is well established that bone cells express glutamate receptors including the ionotrophic *N*-methyl-D-aspartate receptor and that pharmacological antagonists of these receptors inhibit bone resorption [78]. Bone cells have also been shown to express the glutamate transporters GLAST and GLT-1, indicating that excitatory amino acids are involved in paracrine intercellular communication in bone [79] and can alter the membrane potential of bone cells [80]. Similarly, catecholamines and neuropeptides including substance P have been shown to be expressed by both nerve fibers and stromal cells in marrow [81, 82]. Stromal cells have also been shown to express all three neurotrophic receptor proteins [83] as well as low- and high-voltage-activated calcium currents, which closely resemble those found in neurons [84]. Finally, bone and marrow are innervated by nervous tissue, and efferent fibers that track into the hematopoietic cords are known to terminate onto adventitial reticular cells at nerve terminals [85], which contain many of the same proteins found in synapses. Therefore, conditions used to induce neural differentiation of MSCs may select for survival of specific stromal subtypes and/or induce in these cells expression of neural regulatory proteins that have well-described functions in bone marrow.

This interpretation is consistent with studies showing that MSC-derived neurons express an unbalanced repertoire of neuronal proteins and/or lack functional properties characteristic of bona fide neurons. For example, although neurofilaments are obligate heteropolymers that accumulate in neurons after synapse formation and myelination, no studies have shown that MSC-derived neurons express the correct repertoire of subunits to form functional filaments. Additionally, Cho et al. [74] reported that MSC-derived neurons exhibit synaptic transmission, but no evidence was provided that currents measured in cells were modulated by neurotransmitters. Similarly, Wislet-Gendebien et al. [56] reported that MSC-derived neurons exhibit an evoked action potential, but a voltage spike induced only modest membrane depolarization that showed no sign of recovery and the capacity for repeated firing. Therefore, definitive evidence for the transdifferentiation of MSCs into neurons is still lacking.

In contrast, mesenchymal adult progenitor cells (MAPCs) isolated form bone marrow have been shown to undergo a molecular program of neural differentiation similar to that described for neural stem cells [86]. However, MAPCs are unique in that they cannot be isolated prospectively from marrow but rather are obtained by long-term propagation of marrow cells under selective conditions. Importantly, a large percentage of MAPCs has been reported to harbor abnormal karyotypes, suggesting that their unique plasticity is attributed to epigenetic and genetic alterations [87]. This is consistent with other reports showing that prolonged exposure to 5-bromo-2′-deoxyuridine, a chemical mutagen, increases the multipotency of human MSCs [88] and that rodent MSCs acquire the capacity to form neurosphere-like aggregates [66] or express nestin [49] only after prolonged culture expansion in vivo. It is also consistent with the fact that, after prolonged culture, cells undergo a process termed crisis, where proliferation ceases and many cells die but a few acquire genetic alterations and become immortalized. Acquisition of further genetic changes may then lead to malignant transformation. This sequence of events has been reported to occur in mouse embryonic fibroblasts [89] and more recently in murine MSCs [90]. Human MSCs are more resistant to malignant transformation but may still occur after prolonged culture under stressful conditions [91]. Therefore, although MAPCs and other MSC-derived cells that were cultured for prolonged periods may exhibit broad plasticity, it remains unclear whether their unique properties reflect that of stem/progenitor cells resident in vivo. Moreover, cells that acquire enhanced plasticity due to genetic alterations would be excluded from human clinical applications.

DIFFERENTIATION TO EPITHELIUM

MSCs have also been reported to differentiate into various epithelial cell types after systemic administration in vivo. For example, we showed that MSC engraftment in lung was enhanced in response to bleomycin exposure in mice and that a small percentage of MSCs localized to areas of lung injury resembled epithelial cells and copurified with type II pneumocytes [92]. Other studies employing the same animal model of lung injury reported that MSCs engrafted in lung differentiated into type I pneumocytes [93] or assumed phenotypic characteristics of all major cell types in lung including fibroblasts, type I and type II epithelial cells, and myofibroblasts [94]. MSCs have also been shown to differentiate into retinal pigment epithelial cells [95, 96], skin epithelial cells [97], sebaceous duct cells [98], and tubular epithelial cells in kidney [99, 100]. In the latter case, epithelial differentiation of MSCs was assessed based on their distribution within tubuli, alignment within epithelial areas showing well-defined brush borders, and expression of epithelial-specific genes.

Consistent with these in vivo studies, Spees et al. [101] reported that coculture with heat-shocked small airway epithelial cells induced human MSCs to differentiate into epithelial-like cells as evidenced by their expression of keratin 17, 18, and 19, the Clara cell marker CC26, and formation of adherens junctions with neighboring epithelial cells. Importantly, in this study, some MSCs were shown to differentiate directly into epithelial cells, whereas a significant number of others were shown to have fused with neighboring epithelial cells. Human MSCs were also shown to differentiate into epithelial cells in vitro following coculture with airway epithelial cells in an air-liquid interface as evidenced by their columnar shape and

expression of keratin 18, occludin, and cystic fibrosis transmembrane regulator [102].

In contrast, several groups have reported that MSCs do not contribute significantly to the structural regeneration of epithelial cells in the postischemic kidney [103] or injured cornea [104]. Accordingly, it is difficult to develop a consensus opinion about MSC plasticity. A large number of variables is likely to contribute to the inconsistencies in these observations. One is the differences in the properties of MSCs prepared in different laboratories, frequently with the investigators being unaware of the differences. There are marked differences between human and rodent MSCs and even among MSCs prepared from different inbred strains of mice [20, 105–108]. In the latter case, plastic adherent populations elaborated from murine bone marrow are known to contain large numbers of contaminating hematopoietic cells that persist in the cultures even after serial passage [105, 109]. Because these contaminating hematopoietic cells retain the potential to engraft in vivo, their presence may confound the outcome of studies that employ unfractionated murine MSCs. In addition, the differentiation of MSCs is largely driven by signals from culture conditions or the microenvironment in vivo, particularly the microenvironment of rapidly developing or injured tissues. In most cases the signals that drive differentiation in vivo remain indeterminate and therefore cannot be replicated in vitro. Under such circumstances it is difficult to design experiments that define the limits of MSC plasticity, and negative outcomes can have multiple explanations. Finally, the definition and as such nature of the bona fide MSC and its niches in vivo remain controversial, making it difficult to assess the number of actual self-renewing stem cells employed in any given experimental system. The balance of evidence indicates that MSCs possess an inherent plasticity that exceeds their ability to form connective tissues. The latter may be attributed to the unique ontogeny of mesenchyme (see below). However, revealing the full differentiation potential of MSCs will not likely occur until the biology of the bona fide mesenchymal stem cell is fully described.

Evolutionary Mechanisms Confer Plasticity to Adult Mesenchyme

A fundamental difference in the development of fungi and plants compared with metazoans is the existence of mesenchymal cells. For example, plants undergo conservative shape changes by differential growth via localized cell proliferation and cell hypertrophy. In contrast, mesenchymal cells are equipped with motor proteins and a proteolytic arsenal that enables them to migrate throughout embryonic regions, interact with and respond to signals from the extracellular matrix, and differentiate into unique structures such as muscle, bone, cartilage, or other connective tissues. Furthermore, it can be inferred that epithelia precede the mesenchyme both evolutionarily and ontogenetically and, as such, all mesenchyme is derived from epithelia [110]. The primitive embryonic mesenchyme that appears after gastrulation in vertebrate development forms from epiblastic cells in a process referred to as an epithelial-to-mesenchymal transition (EMT). Immediately thereafter, primitive mesenchymal cells reorganize via mesenchymal-to-epithelial transitions to form secondary epithelial structures such as paraxial and lateral plate mesoderm [111, 112]. Continued transitions from epithelium to mesenchyme drive the development of various organs including the kidney and heart [113, 114].

As noted earlier, recent experimental evidence suggests that MSCs exist in vivo as specialized marrow pericytes that line the endothelium of the marrow sinuses [2]. Moreover, lineage-tracing experiments revealed that annexin A5 positive cells that arise as angioblasts in the primary vascular plexus generate perivascular cells in most blood vessels [32]. These data are consistent with independent studies showing that pericytes, smooth muscle, and endothelial cells are derived from a common vascular stem cell [115]. Other studies indicate that epithelial cells within the splanchnic mesothelium, an epithelial lining of the coelom, undergo an EMT and invade the adjacent splanchnopleura to give rise to the hemangioblast [116], a common precursor to endothelial and hematopoietic cell lineages. Therefore, there is strong evidence in favor of the fact that MSCs are initially derived from mesothelial cells via an EMT. This developmental program is consistent with other studies showing that stromal cells in the fetal liver undergo an EMT [117] and that cells from bone marrow also contribute to the formation of epithelial tumors of intestinal track [118]. Therefore, the question may not be whether MSCs possess broad developmental plasticity (e.g., the ability to differentiate into epithelial cell types) but rather which cells within adherent populations represent bona fide stem cells and retain the capacity to undergo mesenchymal-to-epithelial transitions in vivo.

Tissue Repair

MSCs have also shown a strong propensity to ameliorate tissue damage in response to injury and disease. As anticipated, MSCs were originally evaluated for their capacity to repair skeletal defects first in experimental animal models and subsequently in human patients afflicted with osteogenesis imperfecta (OI), a genetic defect in bone and other tissues caused by mutations in the genes for type 1 collagen [119]. Subsequently, MSCs have demonstrated efficacy as therapeutic vectors in animal models of lung injury [92, 120], kidney disease [121], diabetes [122], graft versus host disease [123], myocardial infarction [124], and various neurological disorders [39]. However, in a number of such reports, MSCs have affected tissue repair despite exhibiting low and/or transient levels of engraftment in vivo. For example, in the OI trials, children who received therapy showed measurable improvements in growth velocity, bone mineral density, and ambulation despite the fact that the levels of engrafted donor MSCs in bone, skin, and other tissues were less than 1%. Additionally, we observed improvement in cardiac function after infusion of human MSCs into immunodeficient mice with acute myocardial infarction despite the fact that no engrafted donor cells could be detected after 3 weeks postinjection [125]. These and other studies suggest that capacity of MSCs to secrete soluble factors that alter the tissue microenvironment may play a more prominent role than their transdifferentiation in effecting tissue repair [126].

It is well established that MSCs produce a variety of cytokines and adhesion molecules that regulate aspects of hematopoiesis. Additionally, our recent analysis of the human and murine MSC transcriptome further revealed that the cells express transcripts encoding proteins that regulate a broad range of biological activities including angiogenesis, wound repair, immunity, and defense, as well as neural activities [127, 128]. Our analysis also showed that many of these regulatory proteins are expressed by specific subpopulations of cells. These findings indicate that the composition of marrow stroma and its related functions are more complex than initially envisioned. We believe the functional complexity of MSC populations explains, in part, their broad therapeutic efficacy exhibited in vivo.

Our analyses revealed that MSCs express a number of proangiogenic factors as well as proteins that modulate endothelial cell migration. Cooperatively, these factors induce cap-

illary proliferation and expansion of the sinusoidal space as well as vessel remodeling, a process essential for bone growth. Several of these factors have also been shown to mobilize hematopoietic stem cells from marrow and induce their proliferation [129]. Bone and marrow are also innervated by nervous tissue, which explains our finding that MSCs also express various neuroregulatory proteins including neurotrophins, neurite-inducing factors, and neuropeptides. These factors likely participate in the maintenance of nervous tissue as well as guide the innervation of nerve fibers into bone and marrow during growth, remodeling, and reparation after injury. Some neuron-regulatory proteins are also known to effect the growth and differentiation of hematopoietic and osteogenic cells, as well [130, 131]. We have also identified MSC subpopulations that express high levels of interleukin (IL)-1 receptor antagonist [120]. This finding is consistent with the fact that IL-1 functions as a potent bone-resorbing factor [132]. We believe that expression of these and other unidentified factors by MSCs explains their capacity to effect tissue repair by a variety of mechanisms including promoting the survival and proliferation of endogenous cells [122, 133–135], inducing angiogenesis [136–138], inhibiting inflammatory and immune responses [120, 139], reducing apoptosis [140, 141], and perhaps by transfer of mitochondria [142]. Moreover, we anticipate that as different MSC subpopulations are identified and better characterized, their selective application to specific diseases may result in an enhanced therapeutic effect.

CONCLUSION

MSC populations express a diverse array of regulatory proteins that reflect the complexity of bone and marrow as an organ system. These proteins contribute to the broad therapeutic efficacy of MSCs but may also confound evaluation of their transdifferentiation potential.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

REFERENCES

1 Prockop DJ. Marrow stromal cells as stem cells for non-hematopoietic tissues. Science 1997;276:71–74.
2 Bianco P, Riminucci M, Gronthos S et al. Bone marrow stromal stem cells: Nature, biology, and potential applications. STEM CELLS 2001; 19:180–192.
3 Phinney DG. Building a consensus regarding the nature and origin of mesenchymal stem cells. J Cell Biochem Suppl 2002;38:7–12.
4 Dennis JE, Merriam A, Awadallah A et al. A quadri-potential mesenchymal progenitor cell isolated from the marrow of an adult mouse. J Bone Miner Res 1999;14:700–709.
5 Pittenger MF, MacKay AM, Beck SC et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–147.
6 Caplan AI. The mesengenic process. Clin Plast Surg 1994;21:429–435.
7 Dominici M, Le Blank K, Mueller I et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315–317.
8 Williams JT, Southerland SS, Souza J et al. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. Am Surg 1999;65:22–26.
9 Zuk PA, Zhu M, Mizuno H et al. Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Eng 2001;7:211–228.
10 Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol 2000;109:235–242.
11 De Bari C, Dell'Accio F, Tylzanowski P et al. Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 2001;44:1928–1942.
12 Kuznetsov SA, Mankani MH, Gronthos S et al. Circulating skeletal stem cells. J Cell Biol 2001;153:1133–1140.
13 Gronthos S, Mankani M, Brahim J et al. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A 2000;97:13625–13630.
14 In't Anker PS, Scherion SA, Kleijburg-van der Keur C et al. Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation. Blood 2003;102:1548–1549.
15 Noort WA, Kruisselbrink AB, in't Anker PS et al. Mesenchymal stem cells promote engraftment of human umbilical cord blood-derived CD34(+) cells in NOD/SCID mice. Exp Hematol 2002;30:870–878.
16 Campagnoli C, Roberts IA, Kumar S et al. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood 2001;98:2396–3402.
17 Fan CG, Tang FW, Zhang QJ et al. Characterization and neural differentiation of fetal lung mesenchymal stem cells. Cell Transplant 2005; 14:311–321.
18 Young HE, Mancini ML, Wright RP et al. Mesenchymal stem cells reside within the connective tissues of many organs. Dev Dyn 1995; 202:137–144.
19 Kuznetsov SA, Krebsbach PH, Satomura K et al. Single-colony derived strains of human marrow stromal fibroblasts form bone after transplantation in vivo. J Bone Miner Res 1997;12:1335–13457.
20 Phinney DG, Kopen G, Righter W et al. Donor variation in the growth properties and osteogenic potential of human marrow stromal cells. J Cell Biochem 1999;75:424–436.
21 Muraglia A, Cancedda R, Quarto R. Clonal mesenchymal progenitors from human bone marrow differentiate in vitro according to a hierarchical model. J Cell Sci 2000;113:1161–1166.
22 Simmons PJ, Levesque JP, Zannettino AC. Adhesion molecules in haemopoiesis. Baillieres Clin Heamatol 1997;10:485–505.
23 Majumdar MK, Theide MA, Haynesworth SE et al. Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages. J Hematother Stem Cell Res 2000;9: 841–848.
24 Johnson A, Dorshkind K. Stromal cells in myeloid and lymphoid long-term bone marrow cultures can support multiple hemopoietic lineages and modulate their production of hemopoietic growth factors. Blood 1986;68:1348–1354.
25 Deryugina EI, Muller-Sieburg CE. Stromal cells in long-term cultures: Keys to the elucidation of hematopoietic development? Crit Rev Immunol 1993;13:115–150.
26 Tondreau T, Meuleman N, Delforge A et al. Mesenchymal stem cells derived from CD133-positive cells in mobilized peripheral blood and cord blood: Proliferation, Oct4 expression, and plasticity. STEM CELLS 2005;23:1105–1112.
27 Anjos-Afonso F, Bonnet D. Nonhematopoietic/endothelial SSEA-1+ cells define the most primitive progenitors in the adult murine bone marrow mesenchymal compartment. Blood 2007;109:1298–1306.
28 Gang EJ, Bosnakovski D, Figueiredo CA et al. SSEA-4 identified mesenchymal stem cells from bone marrow. Blood 2007;109: 1743–1751.
29 Quirici N, Soligo D, Bossolasco P et al. Isolation of bone marrow mesenchymal stem cells by anti-nerve growth factor receptor antibodies. Exp Hematol 2002;30:783–791.
30 Buhring H-J, Battula VL, Treml S et al. Novel markers for the prospective isolation of human MSC. Ann N Y Acad Sci 2007;1106:262–271.
31 Shi S, Gronthos S. Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. J Bone Miner Res 2003;18:696–704.
32 Brachvogel B, Moch H, Pausch F et al. Perivascular cells expressing annexin A5 define a novel mesenchymal stem cell-like population with the capacity to differentiate into multiple mesenchymal lineages. Development 2005;132:2657–2668.
33 Gregory CA, Ylostalo J, Prockop DJ. Adult bone marrow stem/progenitor cells (MSCs) are preconditioned by microenvironmental "niches" in culture: A two-stage hypothesis for regulation of MSC fate. Sci STKE 2005;2005:pe37.
34 Kopen GC, Prockop DJ, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Acad Sci U S A 1999;96:10711–10716.
35 Chen J, Li Y, Wang L et al. Therapeutic benefit of intracerebral transplantation of bone marrow stromal cells after cerebral ischemia in rats. J Neurol Sci 2001;189:49–57.
36 Zhao LR, Duan WM, Reyes M et al. Human bone marrow stem cells

exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brains of rats. Exp Neurol 2002;174:11–20.
37 Munoz-Elias G, Marcus AJ, Coyne TM et al. Adult bone marrow stromal cells in the embryonic brain: Engraftment, migration, differentiation, and long-term survival. J Neurosci 2004;24:4585–4595.
38 Sanchez-Ramos JR. Neural cells derived from adult bone marrow and umbilical cord blood. J Neurosci Res 2002;69:880–893.
39 Phinney DG, Isakova I. Plasticity and therapeutic potential of mesenchymal stem cells in the nervous system. Curr Pharm Des 2005; 11:1255–1265.
40 Krabbe C, Zimmer J, Meyer M. Neural transdifferentiation of mesenchymal stem cells—a critical review. APMIS 2005;113:831–844.
41 Chen Y, Teng FYH, Tang BL. Coaxing bone marrow stromal mesenchymal stem cells towards neuronal differentiation: Progress and uncertainties. Cell Mol Life Sci 2006;63:1649–1657.
42 Neuhuber B, Gallo G, Howard L et al. Reevaluation of in vitro differentiation protocols for bone marrow stromal cells: Disruption of actin cytoskeleton induces rapid morphological changes and mimics neuronal phenotype. J Neurosci Res 2004;77:192–204.
43 Lu P, Blesch A, Tuszynski MH. Induction of bone marrow stromal cells to neurons: Differentiation, transdifferentiation, or artifact. J Neurosci Res 2004;77:174–191.
44 Bertani N, Malatesta P, Volpi G et al. Neurogenic potential of human mesenchymal stem cells revisited: Analysis by immunostaining, time-lapse video and microarray. J Cell Sci 2005;118:3925–3936.
45 Choi CB, Cho YK, Prakash KV et al. Analysis of neuron-like differentiation of human bone marrow mesenchymal stem cells. Biochem Biophys Res Commun 2006;350:138–146.
46 Chou YH, Goldman RD. Intermediate filaments on the move. J Cell Biol 2000;150:F101–F106.
47 Kim BJ, Seo JH, Bubien JK et al. Differentiation of adult bone marrow stem cells into neuroprogenitor cells in vitro. Neuroreport 2002;13:1185–1188.
48 Qian L, Saltzman WM. Improving the expansion and neural differentiation of mesenchymal stem cells through culture surface modification. Biomaterials 2004;25:1331–1337.
49 Wislet-Gendebien S, Leprince P, Moonen G et al. Regulation of neural markers nestin and GAP expression by cultivated bone marrow stromal cells. J Cell Sci 2003;116:3295–3302.
50 Vogel W, Grunebach F, Messam CA et al. Heterogeneity among human bone marrow-derived mesenchymal stem cells and neural progenitor cells. Haematologica 2003;88:126–133.
51 Tondreau T, Lagneaux L, Dejeneffe M et al. Bone marrow-derived mesenchymal stem cells already express specific neural proteins before any differentiation. Differentiation 2004;72:319–326.
52 Deng J, Petersen BE, Steindler DA et al. Mesenchymal stem cells spontaneously express neural proteins in culture and are neurogenic after transplantation. STEM CELLS 2006;24:1054–1064.
53 Lendahl U, Zimmerman LB, MacKay RD. CNS stem cells express a new class of intermediate filament protein. Cell 1990;60:585–595.
54 Ratajczak MZ, Kucia M, Reca R et al. Stem cell plasticity revisited: CXCR4-positive cells expressing mRNA for early muscle, liver and neural cells "hide out" in the bone marrow. Leukemia 2004;18:29–40.
55 Pacary E, Legros H, Valable S et al. Synergistic effects of $CoCl_2$ and ROCK inhibition on mesenchymal stem cell differentiation into neuron-like cells. J Cell Sci 2006;119:2667–2678.
56 Wislet-Gendebien S, Hans G, Leprince P et al. Plasticity of cultured mesenchymal stem cells: Switch from nestin-positive to excitable neuron-like phenotype. STEM CELLS 2005;23:392–402.
57 Sejersen T, Lenhahl U. Transient expression of the intermediate filament nestin during skeletal muscle development. J Cell Sci 1993;106:1291–1300.
58 Kachinsky AM, Dominov JA, Miller JB. Myogenesis and the intermediate filament protein, nestin. Dev Biol 1994;165:216–228.
59 Wroblewski J, Engstrom M, Edwall-Arvidsson C et al. Distribution of nestin in the developing mouse limb bud in vivo and in micromass cultures of cells isolated from limb buds. Differentiation 1997; 61:151–159.
60 Vaittinen S, Lukka R, Sahlgren C et al. The expression of intermediate filament protein nestin as related to vimentin and desmin in regenerating skeletal muscle. J Neuropathol Exp Neurol 2001;60:588–597.
61 Mokry J, Nemecek S. Angiogenesis of extra- and intraembryonic blood vessels is associated with expression of nestin in endothelial cells. Folia Biol 1998;44:155–161.
62 Klein T, Ling Z, Heimberg H et al. Nestin is expressed in vascular endothelial cells in the adult human pancrease. J Histochem Cytochem 2003;51:697–706.
63 Egerbacher M, Krestan R, Bock P. Morphology, histochemistry, and differentiation of the cat's epiglottic cartilage: A supporting organ composed of elastic cartilage, fibrous cartilage, myxoid tissue, and fat tissue. Anat Rec 1995;242:471–482.
64 Hainfellner JA, Voigtlander T, Strobel T et al. Fibroblasts can express glial fibrillary acidic protein (GFAP) in vivo. J Neuropathol Exp Neurol 2001;60:449–461.
65 Sainio K, Nonclercq D, Saarma M et al. Neuronal characteristics of embryonic renal stroma. Int J Dev Biol 1994;38:77–84.
66 Shiota M, Heike T, Haruyama M et al. Isolation and characterization of bone marrow-derived mesenchymal progenitor cells with myogenic and neuronal properties. Exp Cell Res 2007;313:1008–1023.
67 Fu YS, Cheng YC, Lin MY et al. Conversion of human umbilical cord mesenchymal stem cells in Wharton's jelly to dopaminergic neurons in vitro: Potential therapeutic application for Parkinsonism. STEM CELLS 2006;24:115–124.
68 Guo L, Yin F, Meng HQ et al. Differentiation of mesenchymal stem cells into dopaminergic neuron-like cells in vitro. Biomed Environ Sci 2005;18:36–42.
69 Tao H, Rao R, Ma DD. Cytokine-induced stable neuronal differentiation of human bone marrow mesenchymal stem cells in a serum/free cell-free condition. Dev Growth Differ 2005;47:423–433.
70 Kondo T, Johson SA, Yoder MC et al. Sonic hedgehog and retinoic acid synergistically promote sensory fate specification from bone marrow-derived pluripotent stem cells. Proc Natl Acad Sci USA 2005;102:4789–4794.
71 Caddick J, Kingham PJ, Gardiner NJ et al. Phenotypic and functional characteristics of mesenchymal stem cells along a Schwann cell lineage. Glia 2006;54:840–849.
72 de Hemptinne I, Vermeiren C, Maloteaux JM et al. Induction of glial glutamate transporters in adult mesenchymal stem cells. J Neurochem 2004;91:155–166.
73 Mareschi K, Novara M, Rustichelli D et al. Neural differentiation of human mesenchymal stem cells: Evidence for expression of neural markers and eag K+ channel types. Exp Hematol 2006;34:1563–1572.
74 Cho KJ, Trzaska KA, Greco SJ et al. Neurons derived from human mesenchymal stem cells show synaptic transmission and can be induced to produce the neurotransmitter substance P by interleukin-1α. STEM CELLS 2005;23:383–391.
75 Woodbury D, Reynolds K, Black IB. Adult bone marrow stromal stem cells express germline, ectodermal, endodermal, and mesodermal genes prior to neurogenesis. J Neurosci Res 2002;69:908–917.
76 Jeong JA, Gang EJ, Hong SH et al. Rapid neurodifferentiation of human cord blood-derived mesenchymal stem cells. Neuroreport 2004;15:1731–1734.
77 Odom DT, Zizlsperger N, Gordon DB et al. Control of pancreas and liver gene expression by HNF transcription factors. Science 2004; 303:1378–1381.
78 Chenu C, Serre CM, Raynal C et al. Glutamate receptors are expressed by bone cells and are involved in bone resorption. Bone 1998;22:295–299.
79 Mason DJ, Suva LJ, Genever PG et al. Mechanically regulated expression of a neural glutamate transporter in bone: A role for excitatory amino acids as osteotropic agents. Bone 1997;20:199–205.
80 Laketic-Ljubojevic I, Suva LJ, Maathuis FJM et al. Functional characterization of N-methyl-D-aspartic acid-gated channels in bone cells. Bone 1999;25:631–637.
81 Rameshwar P, Gascon P. Hematopoietic modulation by tachykinins. Acta Haematol 1997;98:59–64.
82 Maestroni GJ. Neurohormones and catecholamines as functional components of the bone marrow microenvironment. Ann N Y Acad Sci 2000;917:29–37.
83 Labouyrie E, Dubus P, Groppi A et al. Expression of neurotrophins and their receptors in human bone marrow. Am J Pathol 1999;154:405–415.
84 Preston MR, el Haj AJ, Publicover SJ. Expression of voltage-operated Ca^{2+} channels in rat bone marrow stromal cells. Bone 1996;19:101–106.
85 Yamazaki K, Allen TD. Ultrastructural morphometric study of efferent nerve terminals on murine bone marrow stromal cells, and the recognition of a novel anatomical unit: The "neuro-reticular complex." Am J Anat 1990;187:261–276.
86 Jiang Y, Henderson D, Blackstad M et al. Neuroectodermal differentiation from mouse multipotent adult progenitor cells. Proc Natl Acad Sci USA 2003;100:11854–11860.
87 Jiang Y, Jahagirdar BN, Reinhardt RL et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418:41–49.
88 Qu Y, Dong XJ, Sugaya I et al. Bromodeoxyuridine increases multipotency of human bone marrow-derived stem cells. Restor Neurol Neurosci 2004;22:459–468.
89 Rubin H. Multistage carcinogenesis in cell culture. Dev Biol (Basel) 2001;106:61–66.
90 Tolar J, Nauta AJ, Osbom MJ et al. Sarcoma derived from cultured mesenchymal stem cells. STEM CELLS 2007;25:371–379.
91 Rubio D, Garcia-Castro J, Martin MC et al. Spontaneous human adult stem cell transformation. Cancer Res 2005;65:3035–3039.
92 Ortiz LA, Gambelli F, McBride C et al. 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 2003;100:8407–8411.
93 Kotton DN, Ma By, Cardoso WV et al. Bone marrow-derived cells as progenitors of lung alveolar epithelium. Development 2001;128: 5181–5188.
94 Rojas M, Xu J, Woods CR et al. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol 2005;33:145–152.
95 Arnhold S, Heiduschka P, Klein H et al. Adenovirally transduced bone marrow stromal cells differentiate into pigment epithelial cells and induce rescue effects in RCS rats. Invest Ophthalmol Vis Sci 2006;47: 4121–4129.
96 Arnhold S, Absenger Y, Klein H et al. Transplantation of bone marrow-derived mesenchymal stem cells rescue photoreceptor cells in the dystrophic retina of the rhodopsin knockout mouse. Graefes Arch Clin Exp Ophthalmol 2007;245:414–422.
97 Nakagawa H, Akita S, Fukui M et al. Human mesenchymal stem cells successfully improve skin-substitute wound healing. Br J Dermatol 2005;153:29–36.
98 Fu X, Fang L, Li X et al. Enhanced wound-healing quality with bone marrow mesenchymal stem cells autografting after skin injury. Wound Repair Regen 2006;14:325–335.
99 Morigi M, Imberti B, Zoja C et al. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol 2004;15:1794–1804.
100 Herrera MB, Bussolati B, Bruno S et al. Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. Int J Mol Med 2004;14:1035–1041.
101 Spees JL, Olson SD, Ylostalo J et al. Differentiation, cell fusion, and nuclear fusion during ex vivo repair of epithelium by human adult stem cells from bone marrow. Proc Natl Acad Sci USA 2003;100: 2397–2402.
102 Wang G, Bunnell BA, Painter RG et al. Adult stem cells from bone marrow stroma differentiate into airway epithelial cells: Potential therapy for cystic fibrosis. Proc Natl Acad Sci U S A 2005;102:186–191.
103 Duffield JS, Park KM, Hsiao LL et al. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. J Clin Invest 2005;115:1743–1755.
104 Ma Y, Xu Y, Xiao Z et al. Reconstruction of chemically burned rat corneal surface by bone marrow-derived human mesenchymal stem cells. STEM CELLS 2006;24:315–321.
105 Phinney DG, Kopen G, Isaacson RL et al. Plastic adherent stromal cells from the bone marrow of commonly used strains of inbred mice: Variations in yield, growth, and differentiation. J Cell Biochem 1999; 72:570–585.
106 Baddoo M, Hill K, Wilkinson R et al. Characterization of mesenchymal stem cells isolated from murine bone marrow by negative selection. J Cell Biochem 2003;89:1235–1249.
107 Javazon EH, Colter DC, Schwarz EJ et al. Rat marrow stromal cells are more sensitive to plating density and expand more rapidly from single-cell-derived colonies than human marrow stromal cells. STEM CELLS 2001;19:219–225.
108 Sekiya I, Larson BL, Smith JR et al. Expansion of human adult stem cells from bone marrow stroma: Conditions that maximize the yields of early progenitors and evaluate their quality. STEM CELLS 2002;20: 530–541.
109 Witte PL, Robinson M, Henley A et al. Relationships between B-lineage lymphocytes and stromal cells in long-term bone marrow cultures. Eur J Immunol 1987;17:1473–1484.
110 Perez-Pomares JM, Munoz-Chapuli R. Epithelial-mesenchymal transitions: A mesodermal cell strategy for evolutive innovation in Metazoans. Anat Rec 2002;268:343–351.
111 Hay ED. Epithelial-mesenchymal transitions. Semin Dev Biol 1990;1: 347–356.
112 Hay ED. An overview of epithelio-mesenchymal transformation. Acta Anat 1995;154:8–20.
113 Davies JA. Mesenchyme to epithelium transition during development of the mammalian kidney tubule. Acta Anat 1996;156:187–201.
114 Timmerman LA, Grego-Bessa J, Raya A et al. Notch promotes epithelial-mesenchymal transition during cardiac development and oncogenic transformation. Genes Dev 2004;18:99–115.
115 Yamashita J, Itoh H, Hirashima M et al. Flk1-positive cells derived from embryonic stem cells serve as vascular progenitors. Nature 2000;408: 92–96.
116 Munoz-Chapuli R, Perez-Pomares JM, Macias D et al. Differentiation of hemangioblasts from embryonic mesothelial cells? A model on the origin of the vertebrate cardiovascular system. Differentiation 1999;64:133–141.
117 Chagraoui J, Lepage-Noll A, Anjo A et al. Fetal liver stroma consists of cells in epithelial-to-mesenchymal transition. Blood 2003;101: 2973–2982.
118 Houghton J, Stoicov C, Nomura S et al. Gastric cancer originating from bone marrow-derived cells. Science 2004;306:1568–1571.
119 Horwitz EM, Gordon PL, Koo WK et al. 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 2002;99:8932–8937.
120 Ortiz LA, DuTreil M, Fattman C et al. Interleukin 1 receptor antagonist mediates the anti-inflammatory and anti-fibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci U S A 2007;104: 11002–11007.
121 Kunter U, Rong S, Djuric Z et al. Transplanted mesenchymal stem cells accelerate glomerular healing in experimental glomerulonephritis. J Am Soc Nephrol 2006;17:2202–2212.
122 Lee RH, Seo MJ, Reger RL et al. Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proc Natl Acad Sci U S A 2006;103:17438–17443.
123 Ringden O, Uzunel M, Rasmusson L et al. Mesenchymal stem cells for the treatment of therapy-resistant graft-versus-host disease. Transplantation 2006;81:1390–1397.
124 Minguell JJ, Erices A. Mesenchymal stem cells and the treatment of cardiac disease. Exp Biol Med (Maywood) 2006;231:39–49.
125 Iso Y, Spees JL, Serrano C et al. Multipotent human stromal cells improve cardiac function after myocardial infarction in mice without long-term engraftment. Biochem Biophys Res Commun 2007;354:700–706.
126 Prockop DJ. "Stemness" does not explain the repair of many tissues by mesenchymal stem/multipotent stromal cells (MSCs). Clin Pharmacol Ther 2007;82:241–243.
127 Tremain N, Korrko J, Kopen GC et al. MicroSAGE analysis of 2353 expressed genes in a single cell-derived colony of undifferentiated human mesenchymal stem cells reveals mRNAs of multiple cell lineages. STEM CELLS 2001;19:408–418.
128 Phinney DG, Hill K, Michelson C et al. Biological activities encoded by the murine mesenchymal stem cell transcriptome provide a basis for their developmental plasticity and broad clinical efficacy. STEM CELLS 2006;24:186–198.
129 Hattori K, Dias S, Heissig B et al. Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. J Exp Med 2001;193: 1005–1014.
130 Matsuda H, Coughlin MD, Bienestock J et al. Nerve growth factor promotes human hematopoietic colony growth and differentiation. Proc Natl Acad Sci U S A 1988;85:6508–6512.
131 Yang X, Tare RS, Partridge KA et al. Induction of human osteoprogenitor chemotaxis, proliferation, differentiation and bone formation by osteoblast stimulating factor-1/pleiotrophin: Osteoconductive biomimetic scaffolds for tissue engineering. J Bone Miner Res 2003;18:47–57.
132 Lorenzo JA, Naprta A, Rao Y et al. Mice lacking the type I interleukin-1 receptor do not lose bone mass after ovariectomy. Endocrinology 1998; 139:3022–3025.
133 Mahmood A, Lu D, Chopp M. Marrow stromal cell transplantation after traumatic brain injury promotes cellular proliferation within the brain. Neurosurgery 2004;55:1185–1193.
134 Crigler L, Robey RC, Asawachaicham A et al. Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis. Exp Neurol 2006;198:54–64.
135 Munoz JR, Stoutenger BR, Robinson AP et al. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. Proc Natl Acad Sci U S A 2005;102:18171–18176.
136 Shyu KG, Wang BW, Hung HF et al. Mesenchymal stem cells are superior to angiogenic growth factor genes for improving myocardial performance in the mouse model of acute myocardial infarction. J Biomed Sci 2006;13:47–58.
137 Tang J, Xie Q, Pan G et al. Mesenchymal stem cells participate in angiogenesis and improve heart function in rat model of myocardial ischemia with reperfusion. Eur J Cardiothorac Surg 2006;30:353–361.
138 Zwezdaryk KJ, Coffelt SB, Figueroa YG et al. Erythropoietin, a hypoxia-regulated factor, elicits a pro-angiogenic program in human mesenchymal stem cells. Exp Hematol 2007;35:640–652.
139 Zappia E, Casazza S, Pedemonte E et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 2005;106:1755–1761.
140 Inoue Y, Iriyama A, Ueno S et al. Subretinal transplantation of bone marrow mesenchymal stem cells delays retinal degeneration in the RCS rat model of retinal degeneration. Exp Eye Res 2007;85:234–241.
141 Hung SC, Pochampally RR, Chen SC et al. Angiogenic effects of human multipotent stromal cells (MSCs). Conditioned medium activates the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. STEM CELLS 2007;25:2363–2370.
142 Spees JL, Olson SD, Whitney MJ et al. Mitochondrial transfer between cells can rescue aerobic respiration. Proc Natl Acad Sci U S A 2006; 103:1283–1288.