

## Concise Review: Mesenchymal Stem/Multi-Potent Stromal Cells (MSCs): The State of Transdifferentiation and Modes of Tissue Repair - Current Views

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### ABSTRACT

Mesenchymal stem cells or multi-potent 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 neuro-ectoderm. 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.

### 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.

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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 multi-potent 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.

### **Multi-Potential Mesenchymal Stromal Cells (MSCs).**

Friedenstein and co-workers 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 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], 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 SSEA-1 [27], SSEA-4 [28], or the nerve growth factor receptor (CD271) [29]. Moreover, CD271-expressing populations have been shown to co-express CD140b (platelet-derived growth factor

receptor  $\beta$ ), CD340 (HER-2/erbB2), and CD349 (frizzled-9) [30]. Other studies have shown that bone marrow-derived MSCs express the pericytes-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 over-looked in several publications in which high density and confluent human MSC cultures were assumed to consist of homogeneous cell populations.

### **Differentiation to Neuro-ectoderm.**

Our laboratory was the first to demonstrate that MSCs injected into the CNS 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 anti-oxidants 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  $\beta$ -III tubulin [reviewed in 38-41]. However, the rapid action of these agents and the reversible nature of the process questioned if 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 than 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, up regulation of MAP-2, GFAP and tyrosine hydroxylase (TH) in MSCs after 5 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  $\text{CoCl}_2$  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 neurospheres-like aggregates in vitro [49] or differentiating into neurons after co-culture 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 vs. 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 co-polymerizes with both vimentin and desmin [57]. Nestin is also expressed in developing limb buds [58, 59], skeletal myoblasts during muscle regeneration [60], and in endothelial cells during development [61] and in 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 ionotropic N-methyl-D-aspartate (NMDA) 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 (LVA) 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 hetero-polymers 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-Genedebien 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 from 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 have 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 BrdU, a chemical mutagen, increases the multi-potency of human MSCs [88] and that rodent MSCs acquire the capacity to

form neurospheres-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, while 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 that a small percentage of MSCs localized to areas of lung injury resembled epithelial cells and co-purified 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 [101], sebaceous duct cells [102], and tubular epithelial cells in kidney [103, 140]. 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 co-culture 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 while 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 co-culture with airway epithelial cells in an air-liquid interface as evidenced by their columnar shape and expression of keratin 18, occludin and CTFR [102].

In contrast, several groups have reported that MSCs do not contribute significantly to the structural regeneration of epithelial cells in the post-ischemic kidney [103] or injured cornea [104]. Accordingly, it is difficult to develop a consensus opinion about MSC plasticity. A large number of variables are 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 latter case, plastic adherent populations elaborated from murine bone marrow are known to contain large number 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 to 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 precedes 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 re-organize 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 to identify 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 vs. host disease [123], myocardial infarction [124], and various neurological disorders [39]. However, in a number of such reports MSCs have effected 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 post-injection [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 regulates 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 sub populations 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 pro-angiogenic factors as well as proteins that modulate endothelial cell migration. Co-operatively, these factors induce capillary 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 neuro-regulatory 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 1 receptor antagonist [120]. This finding is consistent with the fact that IL-1 functions as 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 sub populations are identified and better characterized, their selective application to specific diseases may result in an enhanced therapeutic effect.

## CONCLUSIONS

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.

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