In vitro Differentiation Potential of Mesenchymal Stem Cells

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Adipose-derived stem cells · Differentiation ·
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Summary

Mesenchymal stem cells (MSCs) represent a class of multipotent progenitor cells that have been isolated from multiple tissue sites. Of these, adipose tissue and bone marrow offer advantages in terms of access, abundance, and the extent of their documentation in the literature. This review focuses on the in vitro differentiation capability of cells derived from adult human tissue. Multiple, independent studies have demonstrated that MSCs can commit to mesodermal (adipocyte, chondrocyte, hematopoietic support, myocyte, osteoblast, tenocyte), ectodermal (epithelial, glial, neural), and endodermal (hepatocyte, islet cell) lineages. The limitations and promises of these studies in the context of tissue engineering are discussed.

Schlüsselwörter

Stammzellen aus Fettgewebe · Differenzierung ·
Mesenchymale Stammzellen

Zusammenfassung

Mesenchymale Stammzellen (MSCs) sind multipotente Vorläuferzellen, die bisher aus verschiedenen Geweben isoliert wurden. Fettgewebe und Knochenmark gelten bezüglich des Gewebezugs, der Stammzellmengen und ihrer Dokumentation in der wissenschaftlichen Literatur als besonders vorteilhaft. Schwerpunkt dieser Literaturzusammenfassung ist die In-vitro-Differenzierungsfähigkeit menschlicher Gewebezellen. Mehrere unabhängige Studien berichten, dass MSCs zur Differenzierung in sowohl mesenchymale (Adipozyten, Chondrozyten, hämatopoetischen Unterstützungszellen, Myozyten, Osteoblasten, Tenozyten) als auch ektodermale (epitheliale, gliale, and neurale Zellen) als auch endodermale (Hepatozyten, Pankreasinseln) Zelllinien fähig sind. Die Limitationen und Aussichten dieser Studien im Kontext von Tissue Engineering werden diskutiert.

Introduction

Seminal studies by Friedenstein [1] and coworkers [2], Owen [3], Tavassoli and Crosby [4] and others first identified what were initially referred to as bone marrow-derived 'mechanocytes' or stromal fibroblasts. These adherent cells displayed multipotent differentiation properties in vitro and in vivo. Fur-

thermore, after Friedenstein and Lalykina [5] discovered the presence of multipotent progenitor cells in thymus and other lymphoid tissues, independent groups went on to document their presence within tissues throughout the body (table 1). While research initially focused on the traditional mesodermal differentiation pathways associated with the bone marrow microenvironment (adipogenesis, chondrogenesis, osteogene-

sis, and hematopoietic support [reviewed in 6–9], Caplan [10, 11] challenged existing dogma by introducing the concept of a ‘mesenchymal stem cell’ (MSC), a multipotent non-hematopoietic stem cell that is present in various adult tissues. He postulated that MSCs were present in the bone marrow and periosteum and were capable of differentiating along any mesodermal-associated pathway, including the myogenic and tendon lineages [12, 13]. The use of the stem cell label remains controversial [14], and some investigators in the field have argued that the term should be modified to ‘mesenchymal stromal cell’ as an alternative [15]. Regardless of the nomenclature, there is a wealth of publications confirming the presence of a similar type of cell in various sites throughout the body and evaluating the differentiation potential of MSCs along the mesodermal, ectodermal and endodermal pathways.

In this review, we highlight selected studies on the *in vitro* differentiation potential of MSCs isolated from the two most promising sources of adult stem cells, adipose tissue and bone marrow. Furthermore, we have focused on studies using chemical agents and biological growth factors to induce MSC differentiation rather than genetic engineering approaches. While the latter methods are fascinating, they will require substantial development before meeting regulatory requirements. Finally, while numerous studies have been performed on MSCs using a variety of animal models, we have concentrated on the human literature for this clinical audience.

Limitations and Promises of *in vitro* Analyses

In vitro studies of MSC differentiation face several limitations. First, analyses of biochemical characteristics do not necessarily translate to *in vivo* applicability. Consequently, it is critical to show that MSC differentiation can be manipulated and directed *in vivo* in accordance with functional tissue engineering principles. Specifically, the MSCs must express the complex properties required of each tissue type and integrate into the existing structure in a seamless manner. Second, *in vitro* findings may not accurately mimic the signal transduction pathways controlling MSC development *in vivo*. Isolated analysis of a particular cytokine’s effect on MSC differentiation *in vitro* may overlook important interactions with complementary or competing signaling pathways active under physiologic conditions. This may explain the discrepancies noted in the literature concerning the effects of bone morphogenetic proteins (BMPs) on adipogenesis and osteogenesis, for example [9]. Finally, it is always important to remember that observations with rodent MSCs, while providing excellent model systems, may not be predictive of the human response. Therefore, there is a continued need to focus on human MSC studies.

In spite of these limitations, the study of MSC differentiation has revolutionized our understanding of cell biology. There is now a greater appreciation of the plasticity of adult cells, and the concept of an ‘adult stem cell’ is gaining greater recogni-

Table 1. Sources of MSCs: An overview of the literature

Tissue	Reference(s)
Adipose	human [16, 26, 58, 123–128] non-human [129]
Bone marrow	human [10, 12, 18, 43, 130–132] non-human [1, 2, 129, 133–137]
Cartilage	human [138, 139] non-human [129, 140, 141]
Dental pulp	[17, 142–145]
Perichondrium	human [146] non-human [147, 148]
Skeletal muscle	non-human [129, 149–152]
Spleen	non-human [2, 137]
Synovium	[153, 154]
Tendon	human [155] non-human [89, 156]

tion and acceptance. It may be possible to ‘reprogram’ these adult stem cells using chemical or genetic approaches (see below). As such, they offer opportunities to explore questions in human biology that were formerly limited to pre-clinical animal models.

Human MSCs from adipose tissue and bone marrow have been characterized based on multiple criteria, including their surface immunophenotype, transcriptome, cytokine profile, and proteome [16–27]. While there is no consensus regarding a single surface antigen that identifies an MSC [28], a panel of several positive and negative markers has been identified [15]. The positive biomarkers include the CD73 (5' ectonucleotidase), CD90 (Thy1), and CD105 (endoglin) while the negative markers include those associated with hematopoietic lineages: myeloid (CD11b/14), lymphoid (CD19/ 79 α), and related progeny (CD45, HLA-DR) [15]. Additional criteria for defining an MSC are plastic adherence and the capability of differentiating along the adipogenic, chondrogenic, and osteogenic lineage pathways [15]. Data from analyses of human adipose and bone marrow tissues suggest that a donor’s age influences the frequency and/or proliferative rate of isolated MSCs [29, 30]. For further details on this topic, the reader is referred to the reviews entitled ‘Mesenchymal Stem Cells: Tissue Origin, Isolation and Culture’ [213] and ‘Phenotypic Characterization of Mesenchymal Stem Cells from Various Tissues’ [214] in this special issue of TRANSFUSION MEDICINE AND HEMOTHERAPY.

Mesodermal Lineage Potential

Hematopoietic Support

In vivo, the MSCs are responsible for establishing what has been referred to as the microenvironmental milieu or stem cell niche necessary to support hematopoietic events [31–33]. This function has been associated specifically with the osteoblast lineage as supported by the localization of hematopoietic stem cells (HSCs) to the bone-lining surface of

Table 2. In vitro mesenchymal lineage differentiation potential: highlights from the adipose- and bone marrow-derived MSCs literature

Lineage	Inductive factors	Adipose-derived MSCs	Bone marrow-derived MSCs
Adipocyte	dexamethasone, indomethacin, insulin, methylisobutylxanthine, thiazolidinedione	[26, 58, 59, 123]	[43, 157, 158]
Chondrocyte	ascorbate, bone morphogenetic protein 6, dexamethasone, transforming growth factor β	[26, 45, 70, 123, 125, 159–162]	[43, 162, 163] non-human [158, 164]
Endothelial	ascorbate, epidermal growth factor, fibroblast growth factor 2, vascular endothelial growth factor	[165–168]	[158, 169]
Hematopoietic support	co-culture models	[22, 36, 170]	[171–173]
Muscle (cardiac)	5-azacytadine	[77, 174, 175]	[176, 177] non-human [178, 179]
Muscle (skeletal)	low serum concentration, horse serum	[26, 123, 180–182]	non-human [183]
Muscle (smooth)		[79, 80]	[184, 185]
Osteoblast	ascorbate, bone morphogenetic protein, dexamethasone, 1,25 dihydroxy vitamin D3	[26, 123, 124, 126, 186, 187]	[43, 158]
Tendon	mechanical stimuli		non-human [188]

the marrow cavity [31, 32, 34, 35]. The MSCs are capable of supporting the proliferation and differentiation of HSCs in vitro [6–9, 22, 34, 36]. The MSCs act through direct cell:cell interactions mediated by surface adhesion molecules, surface delivery of growth factors, and paracrine release of cytokines [33]. Classical studies have demonstrated that antibodies to the MSC or stromal surface adhesion molecules CD9, CD29 and CD44, among others, interfere with hematopoietic events [37–40]. Likewise, the MSCs or stromal cells have been found to express the cytokines IL-6 and IL-7, macrophage colony stimulating factor, stromal-derived factor 1, and others that are associated with HSC proliferation, differentiation, and homing [22, 41, 42]. The adipose- and bone marrow-derived MSCs express a comparable, but not equivalent, surface immunophenotype based on flow cytometry [16, 25, 43–45], secrete a similar battery of cytokines [22, 46–48], and exhibit similar immunosuppressive properties [49–52]. Indeed, these immunosuppressive characteristics have led investigators to exciting studies exploring the utility of MSCs in the treatment of graft-versus-host disease and autoimmune conditions [53, 54]. These observations suggest that MSCs have potential clinical applications for in vitro expansion of HSCs and for in vivo enhancement and acceleration of HSC engraftment following transplantation.

Adipogenesis

The MSCs from adipose tissue and bone marrow can be induced to undergo adipogenesis by a number of stimuli (table 2). Direct comparisons indicate that cells isolated from

adipose tissue are as good as or better than those from bone marrow with respect to adipogenesis (table 3). Among the most commonly employed agents are those that increase intracellular levels of cAMP, such as the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX), a compound similar to the asthma therapeutic theophylline. Additional compounds are ligands for nuclear hormone receptors such as the glucocorticoid receptor (dexamethasone) and the peroxisome proliferator-activated receptor γ (PPAR γ ; e.g., rosiglitazone, the anti-diabetic insulin sensitizer AvandiaTM). The recent reports that diabetic patients on insulin sensitizers have an increased risk of fracture are entirely consistent with the mechanism of action of these nuclear receptor agonists driving adipogenesis at the expense of osteoblastogenesis [55]. The long-term use of PPAR γ ligands could have important clinical consequences that may only present after long-term treatment caused by a reduction in total bone volume and a reduced time to fracture threshold. Finally, most adipogenic differentiation cocktails include insulin as well. Together, these agents convert the MSCs from fibroblast-like stromal cells to oval, neutral-lipid droplet-containing cells within a 3- to 9-day period in vitro. The process can be enhanced by the addition of linoleic, palmitic and oleic fatty acids [56]. The resulting differentiated MSCs display biochemical features characteristic of mature adipocytes, including the expression of gene markers (fatty acid-binding protein 4, lipoprotein lipase), secretion of adipokines (adiponectin, leptin), and lipolytic response to adrenergic agonists [43, 57–59].

Table 3. Studies comparing the differentiation potential of adipose MSCs (A) and bone marrow MSCs (B)^a

Differentiation potential	References		
	adipogenesis	chondrogenesis	osteogenesis
A > B	[97, 189–192]	[189]	[189]
A = B	[26, 123, 193–198]	[26, 123, 194, 197]	[26, 123, 193–199]
B > A		[97, 162, 190, 191, 193, 196, 200–203]	[97, 190–192, 202]

^aA total of 19 studies have compared the differentiation potential of stem cells from adipose tissue and bone marrow. Three of these studies have been done using animal tissue (rat [191], rabbit [201] and mice [199]). Out of the 16 studies involving human tissue, 4 were done on patient-matched comparisons [97, 162, 193, 200], and out of the 4, only 2 studies compared adipogenic, osteogenic and chondrogenic differentiation potential of the stem cells, with different results as shown [97, 193]. Four out of the 16 studies on human tissue compared the differentiation potential of stem cells from adipose tissue and bone marrow, without making quantitative measurements [26, 123, 197, 198].

Osteogenesis

Likewise, the MSCs from adipose tissue and bone marrow can be induced to undergo osteogenesis (table 2). The majority of comparisons conclude that MSCs of bone marrow origin mineralize in vitro equally well as or better than those derived from adipose tissue (table 3). Continuous exposure of the MSCs to ligands for the glucocorticoid receptor (dexamethasone) and the vitamin D receptor (1,25 dihydroxy vitamin D3) together with ascorbic acid and β -glycerophosphate results in the mineralization of the extracellular matrix within a 3-week period. Alizarin red and von Kossa staining provide histochemical assays for the detection of calcium phosphate deposition. Additional biochemical assays include those for secreted osteocalcin and expression of the osteoblastic transcription factor, Cbfa1. These osteogenic responses can be further enhanced by the addition of the BMPs.

It has been hypothesized that MSC adipogenesis and osteogenesis are inversely related, i.e., that agents inducing adipogenesis do so at the expense of osteogenesis and vice versa [60–63]. Support for this argument comes from clinical studies, which have documented that the bone loss of osteoporosis is accompanied by increased marrow fat reserves. Furthermore, many agents promoting adipogenesis, such as the thiazolidinedione PPAR γ ligands, inhibit osteogenesis [64, 65]. Likewise, compounds such as alendronate, classically viewed as an osteoclastic regulator, may have an anabolic effect on MSCs by promoting osteogenesis while simultaneously inhibiting adipogenesis [66]. Nevertheless, exceptions do exist. For example, despite their association with osteogenesis, the BMPs have been noted to promote adipogenesis in MSC models, depending on culture conditions [67–69]. Thus, the adipocyte/osteoblast lineage switch remains complex and merits further investigation using both in vitro and in vivo models.

Chondrogenesis

In the presence of ascorbate, dexamethasone, and transforming growth factor β , MSCs express a chondrogenic phenotype

(table 2). In contrast to other lineages, chondrogenesis occurs most effectively when the MSCs are maintained in a three-dimensional configuration (i.e. pellet or micromass culture or within a hydrogel such as agarose or alginate), rather than as an adherent two-dimensional culture plate. The majority of comparisons demonstrate that the chondrogenic potential of bone marrow-derived MSCs is equal to or superior to that of adipose-derived cells under these standard differentiation conditions (table 3); however, it should be noted that the differentiation cocktails were designed almost exclusively in studies using bone marrow MSCs, and increasing evidence indicates that there are significant differences between bone marrow- and adipose-derived MSCs. For example, more recent analyses have shown that adipose MSCs displayed enhanced chondrogenesis with the addition of BMP6 to the differentiation cocktail, with suppression of a hypertrophic phenotype as measured by the down-regulation of type X collagen [70]. Conversely, bone marrow MSCs exhibit increased expression of type X collagen and a hypertrophic phenotype in response to BMP6 [71]. The chondrogenic and osteogenic capacity of MSCs can be further manipulated by introducing the cells into synthetic scaffolds, such as polycaprolactone, prior to implantation in vivo. [72]. Ultimately, the MSCs need to synthesize the major cartilaginous proteins, collagen II and aggrecan, in quantities sufficient to regenerate damaged cartilage in an articular joint while integrating with the underlying bone. The MSCs must achieve this goal to meet the functional tissue-engineering criteria defined by Butler et al. [73] for musculoskeletal repair. Thus, novel combinations of growth factors and scaffolds may provide the means to regulate the differentiation of MSCs for applications in the tissue-engineered repair or regeneration of articular cartilage. Similarly, other environmental factors such as the properties of the extracellular matrix [74], mechanical stimuli [75], or oxygen tension [76] can significantly influence the growth and chondrogenic differentiation of these cells.

Myogenesis

The adipose- and bone marrow-derived MSCs display the capacity to express biochemical markers characteristic of cardiac, skeletal, and smooth muscle myocytes (table 2). Exposure of MSCs to 5-azacytidine led to the expression of cardiac myocytes markers, including atrial natriuretic peptide and the transcription factor GATA4, as well as the presence of electrophysiologically active, beating cells [77]. Similar results have been achieved by co-culturing MSCs with cardiomyocytes or by incorporating cardiomyocyte protein extracts into MSCs directly [78]. Exposure of the MSCs to low serum concentrations or horse serum led to the expression of skeletal myocyte markers such as the transcription factor myogenin and the presence of multi-nucleated myotubes. Finally, MSCs maintained in serum-containing medium alone displayed characteristic markers of smooth muscle cells, such as α -smooth muscle actin, suggesting that in some cases spontaneous myogenic differentiation of MSCs is possible [79, 80]. In vivo, there are multiple mechanisms through which MSCs can promote myogenic repair. These include direct myogenic lineage differentiation, fusion to existing but damaged myocytes, release of paracrine cytokines/factors, and/or scavenging of reactive oxygen species. For excellent reviews covering the recent literature relating to the use of MSCs to treat myocardial infarction the reader is referred to [81, 82].

Tendons and Ligaments

Early reports in non-human models have documented the ability of bone marrow MSCs to display the cellular, nuclear morphological, and longitudinal alignment changes consistent with tenocytic differentiation [83–85]. Tendon properties could be improved by combining the MSCs with composite biomaterial scaffolds and mechanically loading the constructs in vitro using bioreactors. The addition of a collagen type I sponge helped to assimilate material stiffness to within the range of forces and tissue displacement experienced by patellar tendons in vivo [86]. While the MSC seeding density did not affect biomechanical properties significantly, it did lead to ectopic bone formation at cell preparations of >1 million cells/ml [87]; however, this undesired consequence could be reduced by lowering the cell-to-collagen ratio [88]. While few published reports have systematically explored the tenocytic differentiation of human MSCs from adipose or bone marrow origin, this area of research merits increased scrutiny. The recent isolation of multipotent stem cells from murine tendons may shed light on this subject [89].

Ectodermal Lineage Potential

Central Nervous System

Human, non-human primate, and murine MSCs display biochemical and morphological characteristics of neuronal-, and oligodendrocyte-like cells when cultured in the presence of

antioxidants and the absence of serum [26, 90–94]. Similar induction has been obtained in response to indomethacin, insulin, and methylisobutylxanthine [95, 96]. The MSCs express the neuronally associated markers nestin, NeuN, and intermediate filament. They also express the oligodendrocyte marker, glial fibrillary acidic protein (GFAP). Further studies with murine MSCs have detected the neuronally associated glutamate receptor subunits NR1 and NR2, MAP2, S-100, and β -III tubulin [97, 98]. The differentiated murine MSCs exhibited reduced viability in the presence of N-methyl D-aspartate (NMDA), consistent with a neuronal phenotype [94]. Rat MSCs have also been demonstrated to differentiate into olfactory ensheathing-like cells (OECs) when cultured on three-dimensional collagen scaffold in the presence of terminally differentiated OECs [99]. To date, no studies have clearly demonstrated that MSCs exhibit the full functionality profile of mature neuronal or glial cells. This area of research merits further investigation since studies of bone marrow MSCs suggest that the expression of neuronal biochemical features alone is not sufficient evidence to document true differentiation [100, 101]. Our group (Bunnell et al., unpublished observations) and others [100, 101] have data that indicate that both adipose- and bone marrow-derived MSCs express nestin and other markers in response to cytoskeletal disruption and extreme stress.

The release of neurotrophic factors by MSCs may also mediate the therapeutic efficacy observed in CNS disease models. MSCs have been shown to express a variety of neurotrophic factors that can mediate neuronal cell survival, induce proliferation of endogenous cells, and promote the regeneration of nerve fibers, including brain-derived neurotrophic factor, ciliary neurotrophic factor, nerve growth factor, and vascular endothelial growth factor [102–108]. Human adipose-derived MSCs promoted the growth and differentiation of isolated murine neural stem cells in a cell contact-dependent manner while murine 3T3-L1 adipocytes supported neurite outgrowths through the release of angiopoietin 1 [109–111]. Thus, paracrine factors released by MSCs or stimulated by their presence may account for the beneficial effects of MSC transplants on central nervous system injury models. Interrogation of the human adipose-derived MSC transcriptome identified expressed mRNAs encoding various cytokines, neurite-inducing factors and neural cell adhesion molecules (Bunnell et al., unpublished observations). Similar to bone marrow-derived MSCs, it is evident that adipose-derived MSCs may express neurotrophins and other potent neuroregulatory molecules. Thus, paracrine factors released by MSCs or stimulated by their presence may account for the beneficial effects of adipose tissue-derived MSC transplants on central nervous system injury models. Taken together these data raise the possibility of therapeutic applications for neural and glial tissue repair using MSCs, even though they are derived from mesenchymal germ layer instead of the ectodermal germ layer.

Table 4. In vitro epidermal and endodermal lineage differentiation potential: Highlights from the literature

Lineage	Inductive factors	Adipose-derived MSCs	Bone marrow-derived MSCs
Epithelial	all trans retinoic acid	[112]	[204]
B-Islet	nicotinamide, activin, extendin, pentagastrin, hepatocyte growth factor	[117]	[118,119]
Hepatocyte	hepatocyte growth factor, oncostatin M, fibroblast growth factor 2, nicotinamide	[114, 116, 205] non-human [206]	[113, 207, 208]
Neuronal/glia	antioxidants, indomethacin, insulin, isobutylmethylxanthine	[92–95, 128, 209]	[210–212]

Epithelial

The number of studies exploring epithelial differentiation potential of MSCs is limited (table 4). Human adipose MSCs have been noted to undergo epithelial cell differentiation in the presence of all-trans retinoic acid in vitro [112]. The MSCs displayed morphological changes characteristic of epithelial cells and expressed the lineage-specific marker cytokeratin 18 [112]. This remains an area for further investigation.

Endodermal Lineage Potential

Hepatic

Both adipose- and bone marrow-derived MSCs display biochemical characteristics of hepatocytes when cultured in the presence of hepatocyte growth factor (HGF), oncostatin M, and DMSO or in the presence of HGF, bFGF, and nicotinamide (table 4); these included albumin, α -fetoprotein, and urea production [113–115]. In a direct comparison, human adipose- and bone marrow-derived MSCs displayed similar hepatogenic differentiation in vitro [116]. It remains to be determined if MSCs can enhance hepatocyte differentiation through the delivery of paracrine factors or through some other mechanism.

Pancreatic

Adipose MSCs can display biochemical characteristics of pancreatic cells (table 4) [117]. In the absence of serum and the presence of nicotinamide and the growth factors activin, extendin, hepatocyte growth factor, and pentagastrin, MSCs expressed mRNAs for the pancreatic hormones glucagon, insulin, and somatostatin and the transcription factors isl-1, Ipf-1, Ngn-3, and Pax-6 [117]. Similar results have been achieved in bone marrow MSCs by genetic manipulation and/or co-culture with β -islet cells [118, 119]. Following transfection with a construct expressing the β -islet-associated transcription factor pancreatic duodenal homeobox1 (pdx1), MSCs expressed insulin and related pancreatic peptides. Furthermore, the MSCs were sensitive to environmental glucose

levels with respect to insulin release [119]. These preliminary studies relating to endodermal tissue offer promise for regenerative medical use of MSCs beyond the traditional mesenchymal pathways.

Genetic Advances

Recent advance in stem cell biology have provided encouragement in the ability to manipulate non-embryonic stem cells. Two groups recently reported that they have reprogrammed human skin cells into so-called induced pluripotent cells (iPCs) [120, 121]. Takahashi and Yamanaka [122] used a retrovirus to ferry into adult cells the same four genes they had previously employed to reprogram mouse cells: *OCT3/4*, *SOX2*, *KLF4*, and *c-MYC*. They reprogrammed cells taken from the facial skin of a 36-year-old woman and from the connective tissue of a 69-year-old man. Roughly one iPC cell line was produced for every 5,000 cells they treated with the technique, an efficiency that enabled them to produce several cell lines from each experiment. Yu et al. [121] obtained similar results using the transcription factor combination of OCT4, SOX2, NANOG, and LIN28 [121]. These studies set an important precedent that potentially provides a path to manipulate pluripotent cells from non-embryonic origin, such as adipose- and bone marrow-derived MSCs, towards desired cell phenotypes (i.e. osteoblasts, chondrocytes, myoblasts) and at the same time preventing differentiation towards cells of undesired phenotype (i.e. adipocytes).

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