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Review

The use of mesenchymal stem cells in tissue engineering

A global assessment

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Mesenchymal stem cells (MSCs) are of great interest to both clinicians and researchers for their great potential to enhance tissue engineering. Their ease of isolation, manipulability and potential for differentiation are specifically what have made them so attractive. These multipotent cells have been found to differentiate into cartilage, bone, fat, muscle, tendon, skin, hematopoietic-supporting stroma and neural tissue. Their diverse in vivo distribution includes bone marrow, adipose, periosteum, synovial membrane, skeletal muscle, dermis, pericytes, blood, trabecular bone, human umbilical cord, lung, dental pulp and periodontal ligament. Despite their frequent use in research, no standardized criteria exist for the identification of mesenchymal stem cells; The International Society for Cellular Therapy has sought to change this with a set of guidelines elucidating the major surface markers found on these cells. While many studies have shown MSCs to be just as effective as unipotent cells for certain types of tissue regeneration, limitations do exist due to their immunosuppressive properties. This paper serves as a review pertaining to these issues, as well as others related to the use of MSCs in tissue engineering.

Introduction

Some of the most promising and frequent research in the field of regenerative medicine has focused on the use of stem cells. These cells, by definition, are undifferentiated cells with significant self-renewal capabilities. Additionally, stem cells are able to proliferate and establish daughter cell lines for tissue generation.[1] However, stem cells are not only popular in research because of their self-renewal capabilities; their accessibility, expansibility, and in vitro and in vivo heterogeneity also make them extremely desirable.[2]

There are several types of stem cells, including totipotent, pluripotent and multipotent stem cells. Totipotent stem cells are those with the ability to establish daughter cell lines of any cell lineage in a given organism and include human embryonic stem cells. These cells, derived during the blastocyst stage of human development, possess the ability to become any of the over 200 different cell types in the human body.[3] Pluripotent stem cells have the same ability as multipotent cells, with the exception of the potential to form trophoblasts. Multipotent stem cells, however, are the most limited due to the fact that they can only produce daughter cells of a few specific tissue types.

A specific subtype of multipotent stem cells, mesenchymal stem cells (MSCs), are highly sought after in research due to their ease of isolation. The diverse in vivo distribution of MSCs includes bone marrow, adipose, periosteum, synovial membrane, skeletal muscle, dermis, pericytes, blood, trabecular bone, human umbilical cord, lung, dental pulp and periodontal ligament (Fig. 1).[4] It is also important to note that to this date, no significant difference has been observed between the MSCs in regard to their morphology and immune phenotype.[2]

While MSCs play a significant role in normal growth, they are also a vital component of adult tissue repair. It is this role of MSCs that has raised questions, primarily in regard to their ability to combat degenerative and age-related diseases.[5] To date, research has proven that MSCs aid in the regrowth of cartilage, bone, fat, muscle, tendon, skin, hematopoietic-supporting stroma and neural tissue.[7-13,16]

This review will compare some of the different types of MSCs to each other and to other cell types, as well as examine the established criteria for MSC identification, the signaling molecules involved in their differentiation, the various approaches for in vitro proliferation and in vivo delivery, and the potential limitations with their use in tissue engineering.

Bone Marrow-Derived MSCs (MDSCs) vs. Adipose-Derived MSCs (ADSCs)

Two of the most common sources from which MSCs are derived are bone marrow and adipose tissue. While both MDSCs and ADSCs have an equal potential to differentiate into cells and tissues of mesodermal origins (i.e., adipocytes, cartilage, bone and skeletal muscle), ADSCs have a distinct advantage: they are more readily accessible than bone marrow derived MSCs.[14] While comparative analysis of the two subtypes of MSCs has shown that there is no difference in regard to morphology, immune phenotype, isolation success and colony frequency, differences do arise in regard to osteogenic and chondrogenic differentiation.[15,16] In a study by

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Im et al.,[17] it was shown that ADSCs possess a lesser potential for osteogenesis and chondrogenesis than do MDSCs. However, MDSCs have a greater likelihood of experiencing partial growth arrest, as observed in a murine experimental model.[18] Furthermore, MDSCs also have a greater ability to differentiate into osteocytes and chondrocytes than do AMSCs.[15]

MSCs vs. Muscle Derived Stem Cells (MuDSCs) and Skeletal Muscle Satellite Cells

Human skeletal muscle contains multiple types of undifferentiated cell populations, including satellite cells and muscle derived stem cells (MuDSCs). Unlike satellite cells which are unipotent, MuDSCs are characterized by a broader differentiation capacity, similar to that of human MSCs.[19] MuDSCs have been shown to differentiate into myogenic, osteogenic, chondrogenic, adipogenic and hematopoietic cells.[20] Furthermore, MuDSCs have shown no signs of replicative senescence when cultured in vitro.[21]

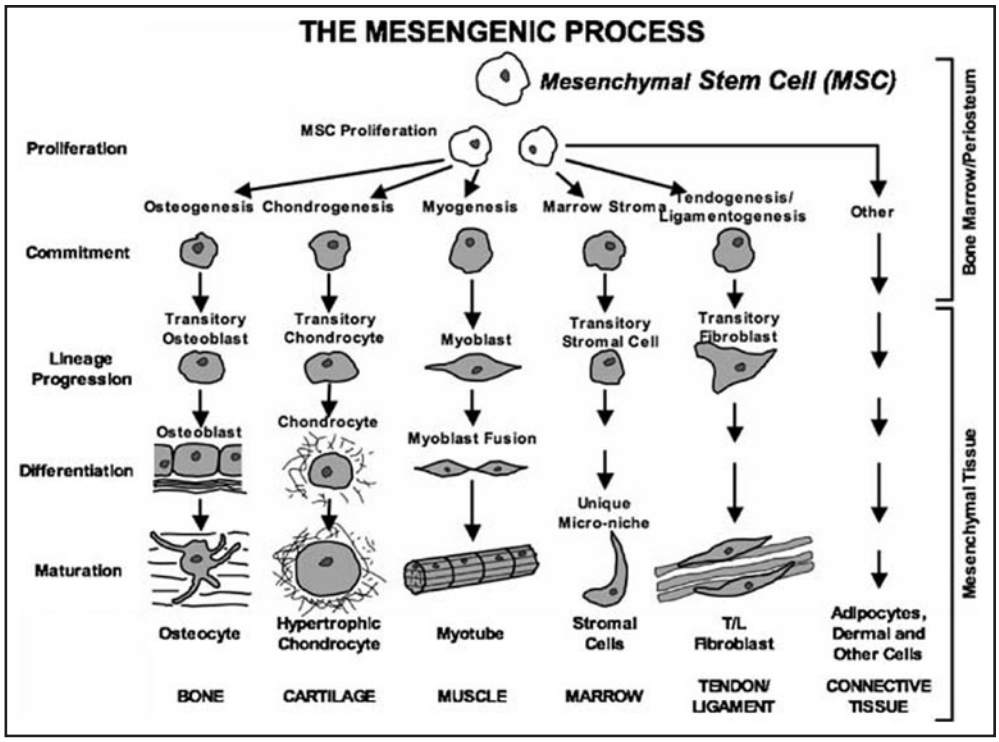

Figure 1. Flowchart elucidating possible commitment, lineage progression and maturation of mesenchymal stem cells. (Figure reproduced with permission from Caplan AI, Dennis JE. Mesenchymal Stem Cells as Trophic Mediators, J Cellular Biochemistry. Vol. 98, No. 5, 2006; pages 1076–1084. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.,).

Chan et al.,[22] studied the ability of MSCs to differentiate into skeletal muscle, in turn enabling a comparison of MSCs vs. satellite cells in regard to their myogenic potential. MSCs were able to assume a skeletal muscle phenotype under the appropriate conditions, which included exposure to galectin-1. This phenotype included long, multinucleated fibers that expressed both desmin and sarcomeric myosin. In other words, the skeletal muscle derived from the MSCs was histologically similar to that produced from satellite cells.

MDSCs and AMSCs vs. Epitenon Tenocytes, Sheath Fibroblasts

In a study investigating the use of MDSCs and AMSCs in flexor tendon tissue engineering, both cell types were compared to epitenon tenocytes and tendon sheath fibroblasts. Kryger et al.,[23] seeded acellularized allogenic tendons with both types of MSCs and epitendon tenocytes and tendon sheath fibroblasts in order to perform in vitro and in vivo assessment of the ability of each of the cells to engineer tendons. All cell types showed similar morphology, including elongated nuclei and spindle-shaped cytoplasm, which is indicative of fibroblast-like morphology. Additionally, all four cell types grew exponentially and reached confluence by day six. Staining indicated that the seeded tendon grafts were histologically indistinguishable between each of the different experimental groups. The similar growth characteristics observed in each of the four cell types enabled all of the reseeded tendon grafts to be successfully implanted in vivo. Not only did all grafts show viability at six weeks, but the in vivo implantation yielded greater scaffold repopulation of each cell type than the in vitro study. Because all results were indistinguishable, it was concluded that the use of MSCs is more practical than epitenon tenocytes and sheath fibroblasts for tissue engineering due to the ease at which they can be harvested.[23]

Criteria for MSC Identification

The International Society for Cellular Therapy has strongly encouraged the scientific community to adopt a set of criteria that standardizes the identification of MSCs.[24] The first criterion is that MSCs must be adherent to plastic when maintained in culture. Second, the MSCs must be positive for the surface antigens CD105, CD73 and CD90. Additionally, the MSCs must lack markers for monocytes, macrophages and B cells, as well as the expression of the haematopoietic antigens CD45 and CD34. The final criterion is that the MSCs must have the potential to differentiate into osteoblasts, adipocytes and chondrocytes under standard in vitro differentiating conditions. Furthermore, due to the plethora of names assigned to cells that are virtually all MSCs (i.e., marrow stromal cells, colony-forming unit fibroblasts, stromal precursor cells, bone marrow stromal cells), these guidelines will specifically categorize what is or is not an MSC.

While MSCs lack a unique marker that can be used for isolation, various surface proteins are present depending on MSC type (Table 1). Surface markers identified on MDSCs are collagen types I, II, III, IV, V, VI; growth factor receptors (bFGFR, PDGFR, EGFR, TGFβ1R/IIR); cell adhesion molecules (VCAM-1, ICAM-1/2, ALCAM-1, L-selectin, CD1056, CD44); chemokine receptors (IL-6, -7, -8, -11, -12, -13, -14, -15, -1α, 1R, 3R, 4R, 6R, 7R, CC, CXC receptors); proteoglycan; laminin; fibronectin; hyaluronate receptor; PDGFR; TNFIR; TNFIIR; TGFβ1R; TGFβIIR; IFNγR; bFGFR;

Table 1 **Surface markers found on marrow derived MSCs (MDSCs), adipose derived MSCs (ADSCs), muscle derived MSCs (MuDSCs)**

MDSCs	Collagen types I, II, III, IV, V, VI; bFGFR, PDGFR, EGFR, TGFβ1R/IIR; VCAM-1, ICAM-1/2, ALCAM-1, L-selectin, CD1056, CD44; IL-6, -7, -8, -11, -12, -13, -14, -15, -1α, 1R, 3R, 4R, 6R, 7R, CC, CXC receptors; proteoglycan; laminin; fibronectin; hyaluronate receptor; PDGFR; TNFIR; TNFIIR; TGFβ1R; TGFβIIR; IFNγR; bFGFR; EGFR; LIFR; G-CSFR; SCFR; Integrin subunits α1, α2, α3, α5, α6, αV, β1, β3, β4
ADSCs	tetraspan, aminopeptidase N, CALLA, integrin α5, β1, hyaluronate, complement protectin, endoglin, VCAM, ALCAM
MuDSCs	Sca-1, Bcl-2, CALLA, aminopeptidase N, CD34, and NCAM

EGFR; LIFR; G-CSFR; SCFR[5,8,25-29] Flouresence-Activated Cell Sorting (FACS) testing was performed by Majumdar et al.,[27] to identify the integrin subunits present on the surface. Integrin subunits α1, α2, α3, α5, α6, αV, β1, β3, β4 were all found. Surface markers found on AMSCs consist of tetraspan, aminopeptidase N, CALLA, integrin α5, integrin β1, hyaluronate, complement protectin, endoglin, VCAM, ALCAM.[30] MuDSCs contain the surface markers Sca-1, Bcl-2, CALLA, aminopeptidase N, CD34 and NCAM[31-33]

In studies using blocking antibodies, it has been shown that MSC propogation on collagen, laminin and fibronectin is mediated by integrin β1. It is thus thought that integrin β1 is the predominant mechanism for adhesion and proliferation on matrix proteins found in the bone marrow.[2] Bone gla protein (BGP) and decarboxylated bone gla protein (dBGP), like integrin β1, have been shown to have chemotactic activity. In a study by Lucas et al.,[34] these chemattractants were thought to facilitate the migration of MSCs to sites of bone resorption, a location where both compounds are present.

Scaffold Design for MSC Delivery

There are three components required for tissue engineering: viable cells, bioactive media (an inductive factor for tissue repair), and a matrix or scaffold. The scaffolds must be compatible with the cell type and inductive factor, and must have the appropriate bioactive and mechanical properties necessary to facilitate in vitro and in vivo cellular seeding and adhesion. Furthermore, the scaffold should not induce an inflammatory response and must have the ability to withstand compression and other forces that would occur during the repair and growth processes.[1] Some of the mechanical properties that must be considered are optimal porosity, pore interconnectivity and pore diameter.

It is unclear what the best choice of scaffold material is for effective MSC delivery. Over the past decade, numerous synthetic and natural scaffold materials have been studied. Synthetic scaffolds include poly-DL-lactic-co-glycolic acid (PLGA), polyglycolic acid (PGA) and poly-L-lactic acid (PLA).[2,35] Hyaluronic acid, silk scaffolds with paraffin porogens and nanofibrous hybrid scaffolds consisting of poly(ε-caprolactone)/poly(vinyl alcohol)/chitosan comprise the group of commonly studied natural scaffolds.

The quality of these scaffolds is determined by their ability to impact mechanical properties, cell responses and tissue formation. Synthetic scaffolds generally have good formability in regard to pore size, fiber diameter and degradation time. They also have great manipulability, thus making them an even more attractive cellular delivery device. Recent research has compared two types of PLGA synthetic scaffolds: smooth surfaced PLGA scaffolds versus a microcavity-rich surface. Greater alkaline phosphatase (ALP) expression, as well as a larger release of bone morphogenic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) was observed in the cells seeded on the microcavity-rich PLGA scaffold as opposed to the smooth surface substrate. These results demonstrate the enhanced osteogenic response of MSCs through the use of microcavity-rich scaffolds, which are more easily established in synthetic scaffolds.[35]

Despite the effectiveness of microcavity-rich synthetic scaffolds in the induction of tissue formation, their success can be limited due to their recognition by the body as foreign, which can ultimately catalyze an unwanted immune response. Furthermore, most lack cell recognition signals and have a low hydrophobicity, which prevents the uniform seeding of cells and the incorporation of growth factors in three dimensions.[36-39] Furthermore, the products resulting from the hydrolysis of these substrates can trigger an inflammatory response.[40]

Unlike synthetic scaffolds, natural scaffolds are composed of hydrophilic and native materials that enable cell interactions, therefore preventing the inflammatory response. The drawback to natural scaffolds, however, is their poor mechanical strength.[41] Additionally, it is difficult to control pore size on natural scaffolds.

There have, however, been attempts to create a natural scaffold that lacks these negative attributes. Uebersax et al.,[40] applied paraffin porogens to silk fibroin scaffolds, in hopes of establishing a natural scaffold with controllable pore sizes via the melting of the parrafin. This altered natural scaffold was considered an effective means of inducing osteogenic differentiation; significant calcium deposition, ALP activity and expression of CD71 and CD44 (a transmembrane hyaluronate receptor for osteopontin) were all observed in the altered natural scaffold as compared to controls.[40]

Microenvironment as a Regulator in MSC Differentiation

The microenvironment also greatly impacts organogenesis. This was exemplified in a study by Khan et al.,[42] comparing stem cell cultures in a hypoxic versus a normoxic environment. Under the hypoxic conditions, increased expression of HIF2α and HIF1α was oberserved, as well as the transcription factors SOX5, 6, 9 and aggrecan, versican and collagen types II, IX, X, XI. There was also an increased accumulation of proteogylcan as compared to that of the controls. This was demonstrative of the significance of oxygen tension regulation in the differentiation of MSCs.[42] While many studies have examined how MSC infiltration into a given region effects microenvironment, this study by Khan et al.,[42] is unique in that it evaluates how microenvironment impacts MSC differentiation.

Tendon Healing and MSCs

Given the multitude of reports documenting failure of the healing process following surgical repair of rotator cuff tendons, several recent studies have attempted to use MSCs to enhance the tendon healing.[43-45] Prior to their use in human beings, in vitro and

animal-model in vivo studies are necessary to determine the following:[46]

(1) Can MSC-enhanced tendon repairs form normal tendon tissue as opposed to scar tissue?

(2) Will the MSC-enhanced tendons have the same biomechanical characteristics as normal, uninjured tendon?

(3) Will MSC-enhanced tendon repairs affect the rate of tendon healing?

Thus far, a few studies have attempted to answer these questions.

Young and his group[47] were amongst the first to incorporate MSCs into a rabbit model of Achilles tendon repair. They treated sutures with MSCs, which were then used to repair a 1-cm defect. At 4, 8 and 12 weeks post-repair, the MSC-treated tendons exhibited improved stress and strain properties. Histologically, these tendons had improved collagen organization and larger cross sectional areas.

Chong et al.,[48] used a similar model to demonstrate an increased rate of healing using MSCs. They compared Achilles tendon repairs using bone-marrow derived MSCs to a control group. At three weeks after the repairs, the MSC-group demonstrated improved biomechanical and histological properties. By the 6- and 12-week time points, the properties were similar. Based on their results, the group concluded that MSCs can enhance the rate of tendon healing and maturation.

Ouyang and colleagues[44] were one of the first groups to perform in vitro work using MSCs with the eventual goal of enhancing rotator cuff tendon repair. Prior to their work, several studies documented the poor clinical results using allografts for large and massive rotator cuff repairs. One of the problems with the allografts used were the lack of viable cells on the cryopreserved scaffolds.[43] Ouyang et al.,[44] applied a sheet of MSCs to cryopresevered tendon allografts and cultured the complex. At three weeks, the MSCs had migrated into the tendon, and many of the MSCs had obtained a spindle-like appearance of tenocytes.

Juncosa-Melvin et al.,[45] altered the mechanical environments of MSCs, and their results also help promise for the eventual use of these cells for rotator cuff tendon repair. They implanted a collagen sponge-MSC complex into patellar tendon defects of rabbits. One group was exposed to mechanical stimulation, and the others were not. At 12 weeks after surgery, the maximum force, linear stiffness, maximum stiffness and linear modulus were all improved in the mechanical loading group. Histologically, both groups had excellent cellular alignment and resembled normal tendon. Given the improved biomechanical characteristics of the group exposed to mechanical loading, incorporating MSCs into rotator cuff repairs may allow for earlier postoperative mobilization.[46] At this point, there are no studies documenting the role of MSCs in tendon healing in human beings. However, the above studies have started to answers critical questions that will eventually lead to clinical studies.

Limitations in the Clinical Application of MSCs

While the potential role of MSCs to influence tissue engineering is undeniable, there are limitations that result from using MSCs. Although rare, in vivo fusion of MSCs to endogenous differentiated cells has been observed.[49] Furthermore, MSCs have displayed inhibitory effects on T-cell proliferation; they secrete high levels of interleukin-6 and VEGF, as well as down regulate MHC class II, CD40 and CD86 molecules on dendritic cells, all of which are directly correlated to the inhibition of T-cell proliferation.[2] In a study by Caplan and Dennis,[50] it was determined that MSCs secrete cytokines and other factors that suppress the immune response in addition to inhibiting apoptosis and fibrosis. Similarly, MSCs have also been shown to foster tumor growth in allogenic recipients, further elucidating the safety concerns that may limit the clinical application of MSCs.[51] It is only after these complications are resolved that the widespread clinical application of MSCs will occur.

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