Review Papers: Adult Mesenchymal Stem Cells for Tissue Engineering

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ABSTRACT

The identification of multipotential mesenchymal stem cells (MSCs) derived from adult human tissues such as bone marrow and connective tissues has provided exciting prospects for cell-based tissue engineering and regeneration. This review article focuses on the biology of MSCs, their differentiation potentials in vitro and in vivo, and their application in tissue engineering. Our current understanding of MSCs lags behind that of other stem cell types, such as hematopoietic stem cells. Future research should aim to define the cellular and molecular fingerprints of MSCs and elucidate their endogenous role(s) in normal and abnormal tissue functions.

1. Introduction

Despite the pluripotency of embryonic stem cells, legal and moral controversies concerning their use for therapeutic and clinical applications, have prompted active examination of the reservoirs of progenitor cells harboring within the adult organism. In principle, such unspecialized cells are considered to be quiescent, but capable of self-renewing. Their asymmetric division produces one identical daughter stem cell and a second progenitor cell that becomes committed to a lineage-specific differentiation program [1]. These cells remain in their "undifferentiated" state from suppression by some intrinsic or extrinsic factor, until stimulated. Such adult stem cells have been discovered and characterized in a multitude of tissues, suggesting the potential for therapeutic application in their host tissue [2, 3].

As these cells are capable of differentiation along specific lineages and being recruited to tissues in need, the promises for autologous clinical implantation or geneti-

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cally engineered stem cells for protein or drug delivery without the risk of immune rejection loom on the horizon. However, the success of future clinical applications depends critically upon a thorough understanding of the biology of these cells, and new findings are continuously being reported. For example, recent evidence suggests that the pluripotent stem cell, once thought to be restricted to the fates of a lineage hierarchy, is capable of transdifferentiation [4].

Some recent examples have shown the transformation of hematopoietic stem cells of bone marrow to hepatic oval cells [5–7], muscle satellite cells exhibit hematopoietic potential [8], neural stem cells have been shown to produce lineage-committed hematopoietic progenitors [9]: and mesenchymal stem cells from bone marrow have traveled to skeletal muscle [10], differentiated into neuronal tissue, supplied mesangial cells during repair processes [11], and given rise to cardiomyocytes in vitro [12]. These observations strongly imply a critical influence of microenvironmental cues on cell fate.

2. Sources of Mesenchymal Stem Cells

This review focuses on the adult mesenchymal stem cell (MSC), which has the potential to differentiate into chondrocytes, osteoblasts, adipocytes, fibroblasts, marrow stroma, and other tissues of mesenchymal origin. Interestingly, these MSCs reside in a diverse host of tissues throughout the adult organism and possess the ability to regenerate specific cell type for these tissues. Examples of these tissues include adipose tissue, periosteum synovial membrane, muscle, dermis, pericytes, blood [13], bone marrow [14], and most recently trabecular bone.

Currently, bone marrow aspirate is considered to be the most accessible and enriched source of MSCs, although trabecular bone may also be considered an alternative source, in view of recent efficient isolation of multipotential cells from this tissue [15]. Given the wide distribution of the sources of MSCs, the bone marrow stroma may be considered the source of these multipotent cells that gain access to various tissues via the circulation, subsequently adopting characteristics that meet the requirements of maintenance and repair of a specific tissue type. In fact, the presence of MSCs in tissues other than the marrow stroma strongly suggests the existence of cell populations with more limited capacity for differentiation; specifically, monopotent or bipotent cells may have differentiation potentials developmentally adapted to (and perhaps restricted to) the tissues in which they reside.

3. Characteristics of Mesenchymal Stem Cells

MSCs are described as multipotent because of their ability, even as clonally isolated cells, to differentiate into a variety of different cells/tissue lineages (Figure 1). However, in most studies, it remains to be determined whether true stem cells are present, or the population is a diverse mixture of lineage-specific progenitors. Inconsistency in published reports of the growth characteristics and differentiation potential of MSCs underscores the need for a functional definition of these cells. At present, no unifying definition as well as information exists on specific markers that define MSCs. While a unified definition has the ability to differentiate along specific mesenchymal lineages when induced to do so, to remain in a quiescent when induced to do so, to remain in a quiescent undifferentiated state until provided the signal to divide asymmetrically, and finally to undergo many more replicative cycles compared to normal and fully differentiated cells.

Some groups used the term “marrow stromal cell” interchangeably with “mesenchymal stem cell” [16]. While these two types of cell are likely to have a common ancestor, the stromal characteristic can be thought of as a committed lineage with limited potential for differentiation. Studies examining and comparing the morphology, phenotype, and in vitro functions of MSCs and marrow-derived stromal cells have shown that MSCs are more homogeneous and fibroblastoid, while the marrow-derived stromal cells are less homogeneous, with having both fibroblastic and hematopoietic characteristics to varying degrees. Although both cell types are able to support hematopoiesis, the undifferentiated MSCs are not as efficient, and while the cells display similar mRNA and cytokine profiles, their individual responses to IL-1 treatment differ [17].

Therefore, we propose that the stromal compartment of the bone marrow itself contains MSCs and that the stromal cell is actually an early differentiated progeny of the MSC. Despite improvements in long-term culture expansion, MSCs display finite life spans, uncharacteristic of immortalized stem cells. Although MSCs are present throughout life, their total number is inversely correlated to the age of the patient and depends upon the site of extraction and the systemic disease state [24]. Bruder et al. [18] characterized the long-term growth kinetics and osteogenic differentiation potential of MSCs aspirated from bone marrow of the iliac crest; the cells averaged 38±4 population doublings following extensive subcultivation and cryopreservation before they reached senescence.

Retroviral transduction of human MSCs with the human telomerase gene successfully extend the life span to more

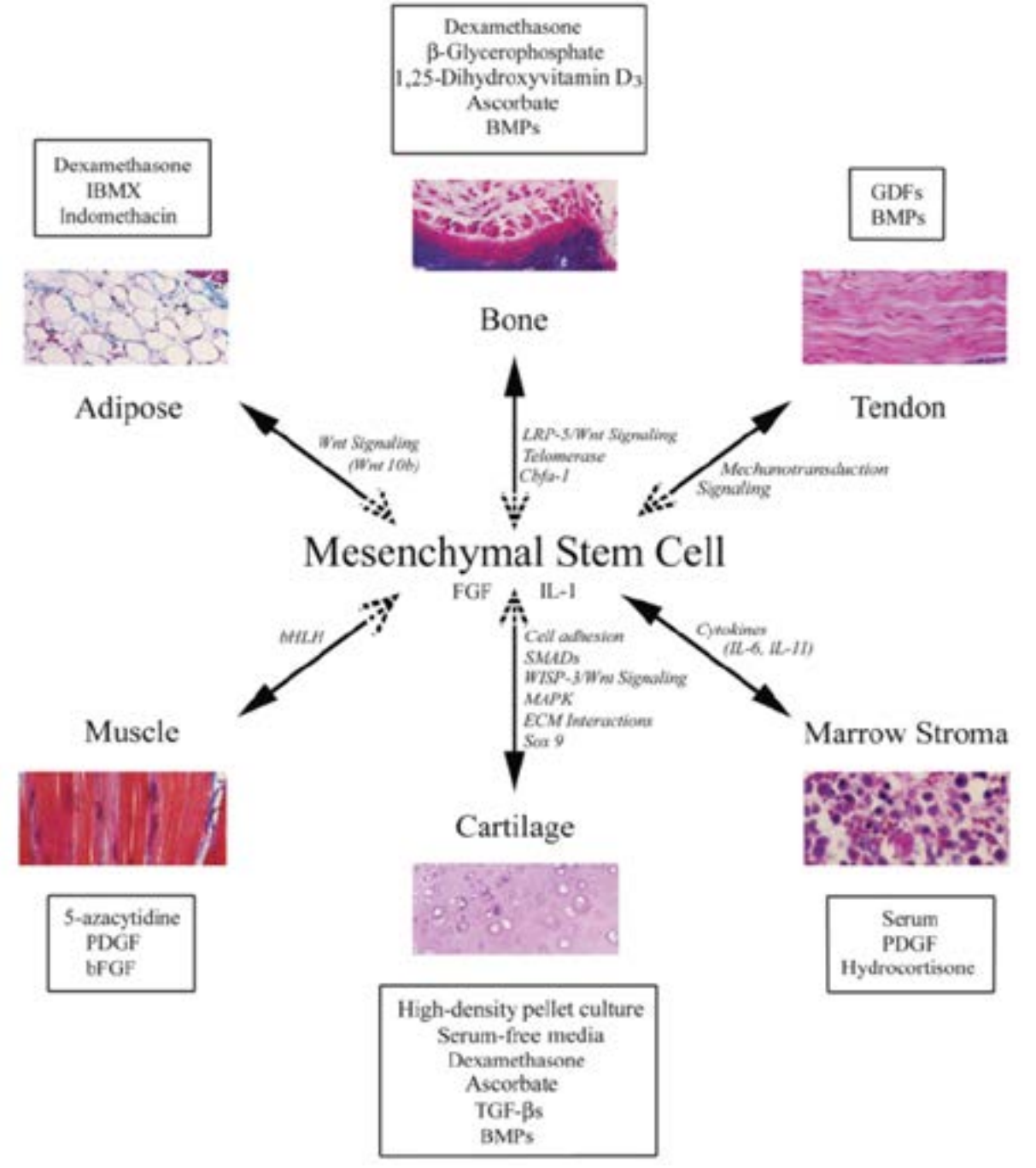

Figure 1. Depiction of some of in vitro culture conditions (boxed) that promote the respective differentiation process into a specific lineage. Signaling pathways and/or components or events involved in lineage-specific differentiation are in italics. See text for details. Dotted arrowheads denote potential 'reverse' differentiation events. Abbreviations: bFGF: basic Fibroblast Growth Factor; bHLH, basic Helix–Loop–Helix; BMP: Bone Morphogenetic Protein; Cbfa1: Core binding factor alpha 1; ECM: Extra Cellular Matrix; FGF: Fibroblast Growth Factor; GDF: Growth/Differentiation Factor; IBMX: 3-Isobutyl-1-MethylXanthine; LRP: Low-density lipoprotein Receptor-related Peptide; MAPK: Mitogen Activated Protein Kinase; PDGF: Platelet-Derived Growth Factor; SMAD: vertebrate homologue of Drosophila Mothers Against Decapentaplegic [22].

than 260 population doublings, while allowing the cells to remain stably undifferentiated with full multilineage differentiation potential. For the purpose of further elucidating the mechanisms regulating the lineage-specific differentiation pathways of MSCs, immortalized clonal cell lines have been established using the human papilloma virus E6/E7 genes with and without transduced telomerase reverse transcriptase [20]. Okamoto et al. have shown that

the immortalized parental population are composed of a heterogeneous combination of uni-, bi-, and tripotential progenitor cells. These findings again point to the intrinsic heterogeneity as well as the need for thorough characterization of the MSC population [21]. platelet-derived growth factor; SMAD, vertebrate homologue of Drosophila Mothers Against Decapentaplegic [22].

4. Discussion

To seriously consider the applications of MSCs for regeneration and tissue engineering, 2 key fundamental questions must be addressed: what exactly are these cells? and what is their endogenous function in their native tissue? Addressing the question of stem-cell identity requires examining the cellular and genetic signature of MSCs. This question needs to be addressed in a similar manner to current analyses of other populations of stem cells. Regarding the hematopoietic stem cell, techniques such as flow cytometry for analyzing specific cell-surface markers and methods like microarray analysis are applied to establish a phenotypic and genotypic fingerprint of this cell population [23]. Moreover, not only MSCs need to be examined, but also studies should include the cells that make up the niche or microenvironment that supports the survival and differentiation of stem cells [24]. These complementary approaches have been used to compare different groups of stem cells in order to identify core "stem" genes and to examine supportive tissue to understand what genes and pathways are involved not only in stem cell differentiation, but also in stem cell support and maintenance - some intriguing questions about the origins and functions of MSCs [25].

Are these cells a developmental remnant of early embryonic stem cells? If so, what mechanisms operate to allow this particular group of cells to escape developmental cues and remain undifferentiated in the adult organism? It is also known that the regenerative capacity of humans is very different from that of other metazoans and even different from that of other mammals. Are these differences in tissue-regenerative capacity related to the number of MSCs? For example, do axolotls, which are among the most efficient tissue regenerators, have MSCs, and if so, are they more abundant than in humans? In addition, what is the developmental or evolutionary advantage to the decrease in MSC number? Were these cells slowly recruited from the stem cell pool to contribute in increasing complexity and tissue organization of the human system? If so, how can we utilize the potential of our remaining stem cells for tissue regeneration and repair?

In conclusion, MSCs derived from adult tissue present an exciting progenitor cell source for applications of tissue engineering and regenerative medicine [26]. Modalities may include direct implantation and/or ex vivo tissue engineering, in combination with biocompatible, biomimetic, biomaterials, and or natural or recombinantly derived biologics. MSCs may also be considered for gene therapy applications for the delivery of genes or gene products [27]. Another intriguing prospect for the future is the use of MSCs to create 'off-the-shelf' tissue banks. To fully harness the potential of these cells, future studies should be directed to ascertain their cellular and molecular characteristics, as well as isolation, and expansion, and understanding the natural, endogenous role(s) of MSCs in normal and abnormal tissue functions [28].

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Conflict of Interest

The authors of this study declared no conflict of interests.

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