Stem Cell Considerations for the Clinician

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KEYWORDS

• Mesenchymal stem cells • Adipose-derived stem cells
• Bone marrow–derived stem cells • Nonunions • Osteoarthritis • Autologous
• Allogeneic • Paracrine

KEY POINTS

- Mesenchymal stem cells (MSCs) isolated from different tissues share many characteristics, such as the capability for multilineage differentiation, absence of HLA-DR expression, and possession of the markers CD105, CD73, and CD90, but may vary in expression of other markers, such as CD36 and CD106.
- In the United States, unpurified stem cells from bone marrow and other tissues can meet minimally manipulated classification as 361 tissue with exemption from Food and Drug Administration premarket review and regulation; however, enzymatic harvesting and culture expansion of MSCs are exclusive of 361 classification.
- Harvesting of MSCs from different anatomic sites yields varying cell numbers and proliferation rates, as exemplified by comparison of MSCs isolated from bone marrow and adipose tissues. Age and sex differences were observed with decreased proliferation and differentiation and increased senescence markers.
- Paracrine effects of soluble mediators and cell-to-cell interactions of MSCs affect innate and adaptive immunity and decrease inflammation.

INTRODUCTION

Over the past 60 years, evidence has accumulated supporting the existence of a multipotent adult stem cell population in the body that has the potential to differentiate into bone, cartilage, tendon, ligament, adipocytes, dermis, muscle, and connective tissue. These cells are now collectively grouped under the term mesenchymal stem cells (MSCs) or multipotent mesenchymal stromal cells. A large proportion of the studies on MSCs have involved the role of these cells in the development and repair of bone and cartilage, heightening interest in the clinical orthopaedic community. In 1966, intraperitoneal diffusion chambers implanted with mouse bone marrow cells

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demonstrated that undifferentiated "stem" cells were present and resulted in osteogenic foci of cells producing alkaline phosphatase (AlkP) and fibroblasts while hematopoietic cells were lost.[1] Interestingly, orthopaedic surgeons were already using viable cancellous bone chips containing these cells in fracture repair. In the first edition of *Campbell's Operative Orthopaedics* (1939), a recommended treatment of nonunions included a combination of stable fixation and packing of cancellous bone chips from the proximal tibia.[2] Even though the concept of stem cells as we know today was unknown at the time, early orthopaedic surgeons recognized the osteogenic effect of cancellous bone and bone marrow.

Today it is clear that stem cell supplementation offers a valuable tool for correcting some of the clinical challenges in treatment of musculoskeletal diseases and injury. Between 2006 and 2012, there was a threefold increase in the number of MSC product Investigational New Drug (IND) submissions to the Food and Drug Administration (FDA), resulting in clinical trials initiated worldwide (246 trials; source: http://www.clinicaltrials.gov). Although much of the initial research focused on bone marrow–derived MSCs (bmMSCs) with umbilical or placental sources serving as secondary sources, an increasing trend of adipose-derived MSC-based product INDs has occurred since 2011.[3] Many of these new INDs deal with MSCs destined for allogeneic use, with more than 80% using cryopreservation for storage of the MSC products to facilitate transport to the clinical site where they are used. Cell banking of cultured MSCs (35%) in these endeavors has also been denoted; however, one report showed reduced immunomodulatory function of thawed cryopreserved MSCs immediately after thawing that was recovered after subsequent in vitro culture.[4] The bioactivity of these products in the IND is variably described with molecular markers such as "secreted factors or expression of proteins on the surface of either the MSC or target cells (eg, T cells) that may be related to a given biological activity."[3]

MESENCHYMAL STEM CELL DEFINITION

What is the definition of this stem cell population and what are the differences between stem cell populations isolated from different tissues (bone marrow, adipose tissues, cord blood, muscle, synovium, dental pulp, muscle, and others)? Caplan[5,6] has stated that "All or most MSC arise in vivo from perivascular cells (pericytes) that are released from the damaged or inflamed blood vessels at the site of injury." If this is so, then tissues that have a poor vascular supply would heal poorly or not at all and this is supported by clinical observations of the mid to inner portions of the meniscal and articular cartilages. However, healing by fibroblast proliferation and scar formation and the regrowth of differentiated cells originating from stem cells that are specific to the function of the damage tissue are separate issues. Are stem cells from different tissues equivalent?

Review of the published literature on this question gives evidence to support shared characteristics of MSCs from different tissues, but also supports that variations are present as well. Perivascular MSCs from both bone marrow (BM) and dental pulp (DP) tissues localized immunohistochemically or isolated by immunoselection document that these cells do show expression of STRO1 an early marker of stem cells and CD146 an endothelial marker, but that a 3G5 antigen marker of pericytes was predominantly in the DP population and only in a small portion of the BM cells.[7] Another report observed that the MSC population derived from veins, artery, perivascular cells, or fibroblasts showed similarity of cell morphology and phenotypes established with 22 markers with heterogeneous expression of genes related to angiogenesis.[8] According to criteria set up by the Mesenchymal and Tissue Stem Cell Committee of