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Commentary

Stem Cells and Regenerative Therapies: Clarification of Terminology and Potential Applications in Aging and Neurodegenerative Disorders

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Abstract

The application of mesenchymal stem cells (MSCs) is a growing field in medicine, yet the terminology used in the literature remains heterogeneous. Proper characterization of cells used in clinical therapies is critical as the field continues to progress; in particular, the difference between MSCs and stromal vascular fraction cells (SVFCs) must be emphasized. MSCs have a variety of clinical applications, including serving in restorative and protective roles against aging and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Nevertheless, much remains unknown about MSCs and much research remains to be performed. As regenerative medicine continues to advance, an international registry of regenerative medicine interventions ought to be created, to allow for the systematic analysis of data within a controlled and accessible database.

Keywords

Mesenchymal stem cells; Stromal vascular fraction; Neurodegenerative disorders

Commentary

The application of mesenchymal stem cells (MSCs) in tissue and organ regeneration is one of the most rapidly expanding frontiers in medicine and technology. However, the terminology used to describe the origins of the MSCs has led to considerable confusion. In this article, we provide clarification of the nomenclature used for MSCs within scientific and lay literature. Accurate communication requires standardization of terminology as we continue to advance our understanding and characterization of MSCs as pluripotent cellular entities. Such standardization is particularly critical as we clarify the cellular and extracellular mechanisms responsible for tissue repair, and examine the clinical utilities of MSCs in fields such as aging and neurodegenerative disease.

Authors should be careful in defining the cellular product used as either stromal vascular fraction cells (SVFCs) or MSCs. SVFCs are a heterogeneous group of cells that include fibroblasts, vascular smooth muscle cells, endothelial cells, resident monocytes, lymphocytes, as well as MSCs. These cells reside in the stroma around the intima of capillaries [1]. Bone marrow and adipose tissue are the most common sources of SVFCs, though the fraction remains small. In adipose tissue, only 10% of all cells consist of SVFCs, with the rest consisting of mature adipocytes [2]. Thus, MSCs as characterized in the literature are isolated from the SVFCs and represent only one cell type out of many within that mixture. The mesenchymal stem cell population is by definition the multipotent or pluripotent stromal stem cell which exists *in vivo* as pericytes around the vasculature [1,3].

Among all potential MSC sources, the SVFCs of adipose tissue have emerged as some of the most suitable candidates for future tissue engineering and cell-based therapies. The ubiquity, ease of retrieval, minimally invasive harvesting procedures and lack of foreseeable ethical issues relating to these MSCs have all contributed to the extensive research on their mechanisms and applications [2,3]. The SVFCs can be isolated with simple enzymatic or mechanical techniques such as ultrasonic cavitation, and through further refinement with tissue culture and cellular engineering, allow the MSCs to express desired phenotypes, such as the secretion of growth factors, cytokines, matrix proteases and extracellular matrix molecules [1,3,4]. These MSCs further possess the capacity to differentiate into adipocytes, chondrocytes, osteoblasts, neurons, or myoblasts under appropriate stimuli and environmental conditions [5]. These MSCs meet the minimum criteria set forth by the International Society for Cellular Therapy (ISCT), which stipulate that cells must be simultaneously positive for CD105, CD73, and CD90, and negative for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II [2].

Notwithstanding the great advances in stem cell biology over the past decade, much remains unknown about the potential applications of MSCs and their mechanisms in patient cohorts. One key area involves the relationship between age and MSCs. Studies have long shown that alterations in MSC number, population doubling, and differential potential occur with respect to donor age in both human and animal models [5]. Similarly well-characterized is the loss of subcutaneous adipose tissue both quantitatively and functionally; with age there is accumulation of senescent cells, including stem cells and endothelial cells, an increase in circulating pro-inflammatory cytokines, and proliferative defects owing to changes in external signals originating in the microenvironment [3]. Thus, it is of little surprise that gene-expression profiles of human senescent adipose tissue (AT) specimens point to decreased MSC yields, growth kinetics, and differentiation capacities in older donors [3]. MSCs from older donors also have increased oxidative stress markers, reduced detoxification capabilities, slower growth rates and decreased angiogenic capacity [3]. Nevertheless, stem-cell therapies are becoming increasingly relevant in aging populations for regenerative purposes, and much remains unknown [3]. For instance, females appear to have their MSC potentials affected earlier than males, with greater individual differences noted in women after the age of 60, and in men only after the age of 80 [6]. While hypotheses abound on the potential role of female hormones post-menopause, such as the decrease in circulating estrogen, the potential roles of DNA methylation and epigenetics, as well as the likely detrimental effects of common co-morbidities such as osteoporosis can have on MSCs, further clinical and basic science

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research is clearly required [5,6]. For instance, no clinical studies have yet set out to address associations between sex, menopausal status, hormone replacement therapies, and MSC yields.

Geriatric patients in particular are those who stand to gain the most from regenerative medicine advances in the field of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's diseases (PD). With an ever-aging population, the number of AD patients is expected to increase to over 100 million cases by 2050 [7]. Research in new drugs and therapies is urgently needed. Several studies have shown promising results with the use of MSCs in animal models of AD, including palliative effects on the symptoms of dementia [8]. Studies in animal models of PD have also shown improved neurite regeneration with MSC-conditioned media, improved motor deficits and partially-restored dopaminergic marker expression in the striatum and substantia nigra, as well as the survival post-transplantation of neurons differentiated from MSCs [9,10]. The therapeutic role of MSCs in such neurodegenerative diseases is hypothesized to revolve around restorative and protective features, rather than the replacement of neuronal cells; one example is the ability of MSCs to activate microglia, induce amyloid-beta clearance, increase autophagy, and induce neurogenesis in AD models [8].

In summary, this article provides a recommendation on the nomenclature surrounding MSCs for both the scientific and patient communities, as well as some of the many clinical utilities of MSCs. Specifically, MSCs hold tremendous potential in the fields of aging and neurodegenerative disease due to their adipocyte, chondrocyte, osteoblastic, neuronal, or myoblastic potential. The ubiquity and ease of retrieval of MSCs from adipose tissue – with minimal morbidity to the patient – combined with the lack of foreseeable ethical obstacles further add to their appeal. As the field of regenerative medicine continues to grow, the authors strongly advocate for the creation of an international registry of regenerative medicine interventions, so as to allow for the systematic analysis of data within a controlled and accessible database. Such databases are abundant in other fields, and given the plethora of clinical and mechanistic literature within regenerative medicine in recent years, the timing is right for regenerative medicine to join their ranks as we navigate the future.

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