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Commentary

MSCs, but not mesenchymal stem cells

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ABSTRACT

Mesenchymal stem cells (MSCs) are prevalent within the human body and can be detected and isolated from nearly all tissues. The acronym MSCs is widely recognized as referring to adult stem cells with multipotent capabilities. Despite over 40 years of applications in research and clinical settings, the definition of MSCs as mesenchymal stem cells has faced scrutiny concerning their "stemness" and the underlying mechanisms of their therapeutic effects. In 2010, Dr. Arnold I. Caplan suggested redefining MSCs as "medicinal signaling cells" rather than mesenchymal stem cells. In this commentary, I concur with Dr. Caplan's view but further propose that MSCs be regarded as "master signaling cells." The primary therapeutic mechanism of MSCs is their signaling function. They respond to signals from immune cells to become activated and, in turn, act as signaling regulators for other cells. As master signaling cells, MSCs are multipotent stem cells present in almost all tissues, playing vital roles in regulating tissue homeostasis and facilitating tissue regeneration.

Key words: medicinal signaling cell, master signaling cell, mesenchymal stem cell, multiplepotent stem cell, stromal stem cell

The concept of mesenchymal stem cells (MSCs) is well-established in the stem cell research and application community, with "MSCs" commonly used as an abbreviation. However, there is ongoing debate regarding whether this term refers to mesenchymal stem cells, mesenchymal stromal cells, or multipotent stem cells. These terms all describe a type of cell first identified in the 1950s. The initial report of bone formation through bone marrow transplantation was documented in 1956[1]. Subsequent research by Friedenstein *et al.* (1966) identified osteogenesis from bone marrow during transplantation procedures[2]. Notably, in 1980, it was demonstrated that a suspension of marrow cells or fibroblasts derived from bone marrow could differentiate into bone and cartilage *in vivo*[3]. The concept of MSCs was further developed in a 1991 paper by Dr. Arnold Caplan, who described the isolation of a specific type of stem cell found in bone marrow[4].

In 1995, Drs. Wakitani and Saito, conducting research in Dr. Caplan's laboratory, reported the inducible differentiation of these cells into muscle cells and adipocytes[5,6]. Following this, Dr. Johnstone (1998) demonstrated that mesenchymal stem cells (MSCs) could differentiate into chondrocytes[7]. Additionally, Dr. Pittenger and colleagues (1999) provided evidence for the differentiation of MSCs into osteocytes, chondrocytes, and adipocytes[8]. In subsequent years, cells analogous to bone marrow-derived MSCs were successfully identified and isolated from diverse tissues such as adipose tissue[9], umbilical cord blood[10,11], umbilical cord[12], placenta[13], dental pulp[14], skin[15], and hair follicles[16]. In 2006, the International Society for Cellular Therapy (ISCT) established minimal criteria for defining MSCs, which included (1) adherence to plastic culture surfaces while exhibiting a fibroblast-like morphology, (2) the expression of surface markers CD105, CD73, and CD90, while lacking CD14, CD34, CD45, and HLA-DR, and (3) the capability to differentiate in vitro into osteoblasts, chondroblasts, and adipocytes[17]. Generally, these criteria reflect the two pivotal characteristics of stem cells: their ability to self-renew and differentiate. However, this standard has not yet definitively proven that the cells have the self-renewal capability, which remains one of the essential characteristics of stem cells.

Mesenchymal stem cells (MSCs) were initially employed for the treatment of bone and cartilage diseases[18–21]. Subsequently, the application of MSCs expanded to include a variety of conditions such as chronic obstructive pulmonary disease (COPD)[22,23], graft-versus-host disease[24], Crohn's disease[25], spinal cord injury[26], heart failure[27], and frailty[28]. Numerous studies have demonstrated the therapeutic efficacy of MSC transplantation, leading to the approval of specific treatments or drugs, such as Prochymal[29], Temcell HS[30], and Cartistem[31]. However, the

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therapeutic mechanism of MSCs appears to be independent of their stemness or differentiation capabilities. As a result, many scientists attribute the therapeutic effects of MSCs to alternative processes, particularly the secretion of factors such as secretomes and exosomes[32–34]. The release of components like growth factors, cytokines, and exosomes is deemed crucial for their therapeutic impact, contrasting with hematopoietic stem cells, whose efficacy results from differentiation into blood cells. Some studies also suggest that cell-to-cell interactions involving surface proteins significantly contribute to the therapeutic effectiveness of MSCs[34–36].

I have reviewed studies that provide evidence of mesenchymal stem cell (MSC) differentiation into cells with therapeutic potential, particularly non-mesenchymal cells such as lung cells, nerve cells, and beta cells; however, such investigations are exceedingly rare. Furthermore, in treating diseases associated with substantial tissue damage, such as bone defects and challenging regeneration scenarios, it appears more advantageous to utilize cell mixtures derived from bone marrow rather than bone marrow-derived MSCs[37]. The issues concerning the definitions and mechanisms of MSCs in therapeutic applications have generated substantial debate and raised critical questions. The divergence in therapeutic mechanisms from the traditional understanding of stem cells has led to the proposal of an alternative term by the originator of the concept: "medicinal signaling cell" (MSC)[38]. Subsequently, Douglas Sipp and colleagues advocated for clinics to refrain from using the term "mesenchymal stem cell" in marketing stem cell and regenerative medicine therapies[39]. Despite these recommendations, the notion of MSCs as mesenchymal stem cells is deeply entrenched in the scientific community and remains widespread in scientific publications.

Drawing from research experience, I propose redefining mesenchymal stem cells as "**master signaling cells**" (MSCs). This conceptualization implies that master signaling cells are fundamental across all tissues, including the blood. They are crucial for signaling tissue regeneration following damage, as they receive activation signals from inflammatory factors released by immune cells and subsequently transmit signals to facilitate regeneration. While I do not expect an immediate shift to the term "**master signaling cell**" from "mesenchymal stem cell," nor a change in the nomenclature when these cells are isolated from tissues, I aspire for this terminology to foster a more precise and comprehensive understanding of the therapeutic mechanisms and actual roles of these cells, ultimately helping to resolve continuous debates on their genuine therapeutic applications.

ABBREVIATIONS

None.

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The authors declare that they have no competing interests.

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