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# Mesenchymal stem cells: the truth about their nature, origin and potential use for therapy

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*A review of "The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine" Paolo Bianco, Xu Cao, Paul S Frenette, Jeremy J Mao, Pamela G Robey, Paul J Simmons, and Cun-Yu Wang; Nat Med 2013. 19:35.*

About 0.001% to 0.01% of the bone marrow compartment is comprised of mesenchymal stem cells (MSCs). MSCs are distinct from hematopoietic stem cells (which differentiate into blood lineage and immune cells) in that they differentiate into fibroblasts, chondrocytes, myocytes, adipocytes, or osteoblasts, and are involved in the maintenance and regeneration of connective tissues, cartilage, muscle, fat tissue and bone, respectively MSCs are multipotent, have limitless proliferative abilities, and can home to sites of tissue injury for repair [1, 2]. The microenvironment of solid tumors closely resembles that of injured tissue, producing chemokines that can recruit MSCs to the tumor site. There have been conflicting data as to whether MSCs promote or inhibit tumor growth at these sites and their function seems highly dependent on tissue context.

Because of their ability to mobilize to injury sites, gene therapy protocols have investigated the use of MSCs for targeted gene therapy of bone diseases, and more recently, tumor progression; yet the results have been disappointing [3]. There are several issues with the current approaches to MSC use for targeted therapies addressed in this review that must be addressed at the bench in order to produce more successful results with these multipotent cells.

Bianco et al. [4] have undertaken the task to address some of these issues in a new review about mesenchymal stem cells recently published in Nature Medicine. The authors first discuss what mesenchymal stem cells are and how they function. It was originally believed that MSCs could be isolated from any tissue type. Isolation includes analysis of specific cell surface markers and their ability to differentiate into bone-lineage in the appropriate culture media. Therefore, gene therapy protocols often used placental-derived MSCs or MSCs from lung tissue. As addressed by Bianco et al., placental-derived (or other tissue sources) MSCs satisfy the originally appreciated criteria, yet they are not true MSCs. The authors have previously shown that true MSCs (those isolated from the bone marrow compartment) are the only cells that naturally differentiate into bone lineage cells without media induction. The authors highlight a previous study in which bone marrow-derived MSCs were subcutaneously implanted into mice and over time, developed into a "miniature bone organ" consisting of bone cartilage (of chondrocytes), cortical bone (derived from osteoblasts), and a marrow compartment of hematopoietic stem cells (recruited by the MSCs, a known role for MSCs)[5]. MSCs derived from other tissues were not able to transform into bone tissue in this setting, despite their ability to differentiate in vitro. Collectively these findings emphasize that true MSCs must be able to naturally become bone tissues and thus should be identified as skeletal stem cells.

Next, the authors identify the most widely accepted cell surface markers for identification and purification of MSCs. Although many have classified a collection of markers (including STRO-1, CD105, and CD146), this review identifies a great misunderstanding in the proper selection markers. Although gene therapy protocols typically utilize human MSCs, the majority of investigations of MSC function in cancer studies

have utilized mouse-derived MSCs [6]. In this review, the authors delineate the species-specific differences in cell surface marker expression; previous reviews describe MSC cell surface as being cell-specific and rarely mention species-related differences. Furthermore, the authors describe the appropriate methods for pure isolation of MSCs. Collectively, this information is critical for understanding the function of mouse-derived MSCs. A great disconnect in translating the results from studies utilizing mouse-derived MSCs may lie in the fact that the cells were not true MSCs due to a lack of understanding of the proper tissue location for isolation, the appropriate method of isolation, and the correct surface markers from mouse cells (which are different from humans).

Last, the authors discuss the appropriate method of MSC delivery for investigating their mobilization to tissue injury sites and tumors. Most studies investigating MSC therapy, involved induction of tissue injury or injection of tumor cells into mice followed by intravenous (IV) injection of MSCs via the mouse tail. However venous circulation from the tail passes immediately through the lungs and, as discussed by the authors, cells can become lodged in the lungs. The authors mention that the majority of IV-injected MSCs lodge in the lungs, where they may cause extensive endothelial damage until being removed by the immune system[7, 8]. Although a small number may arrive at the injury or tumor site, the result does not allow for accurate analysis of MSC function and may be an important factor in the failure of clinical use of MSCs for therapy. They suggest direct implantation at the injury site; for example, intracardiac injection is the appropriate delivery method of cells to the bone and would likely be the best option for studies investigating MSC function in tumor progression in bone. Direct implantation is not always feasible for all studies, however this information highlights a critical aspect that should be considered when choosing the right model for MSC studies.

In short, MSCs are becoming more appreciated for their role in injury, bone-related diseases, and cancer progression. This has introduced a large number of studies investigating their potential as therapatic targets in biomedical research. Bianco et al. provide clarification to this well-appreciated field and highlight several anomalies in the science of MSCs that have likely contributed to inaccurate interpretations of their nature and function, and inevitably, the success of their use for therapy. The authors identify the true character these cells, the proper way to isolate them and some limitations of previously utilized delivery methods. With this review, Bianco et al. bring life into a potentially waning field that may lead to better developed therapies and more accurate investigations of how MSCs can be used clinically for patient therapies.

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