

Mesenchymal Stem Cells Markers

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Opinion

In the field of regenerative medicine, basic research and preclinical studies have been conducted to overcome clinical shortcomings with the use of stem cells, mesenchymal stem cells and adipose stem cells. They are present in adult tissues, including bone marrow, umbilical cord, umbilical cord blood and adipose tissue [1]. For many years, bone marrow-derived stem cells were the primary source of stem cells for tissue engineering applications. Russian-born Alexander A. Maximow in 1924 used extensive histological findings to identify a kind of spherical precursor cell in the mesenchyme, which can grow and differentiate into Different cell types. In late 1960's the scientists Ernest A. McCulloch and James E. Till reveal for the first time the clonal nature of bone marrow cells [2]. The challenge was to find those cells that can self-renew and differentiate into three cell types: bone, cartilage and fat (Figure 1).

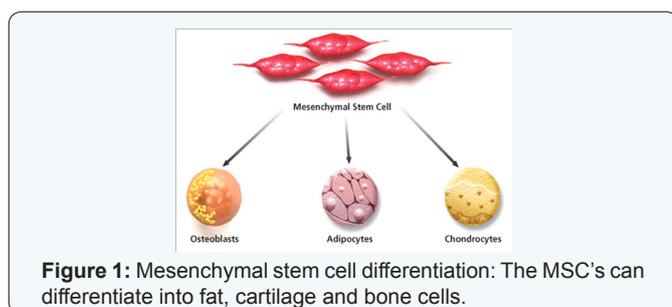


Figure 1: Mesenchymal stem cell differentiation: The MSC's can differentiate into fat, cartilage and bone cells.

The adipogenic differentiation is usually defined by the appearance of cells containing intracellular lipid droplets. Both AT-MS (ASC) and UC-MS (MSC) have been successfully differentiated into adipocytes. The chondrogenic differentiation capacity of MSC is evidenced by the formation of shiny cell-spheres expressing type II collagen in pellet cultures. Enhanced alkaline phosphatase expression and mineralization assayed by von Kossa or alizarin red staining indicates the occurrence of osteogenic differentiation [1,2].

The human mesenchymal stem cells (hMSC's) are typically isolated from the mononuclear layer of bone marrow after separation by centrifugation. The mononuclear cells were

cultured in medium with 10% fetal calf serum, and adhere to the walls.

Some of the hematopoietic cells adhere well, but over time in culture they are lost. Mesenchymal stem cells are characterized morphologically by a small cell body. The cell body containing a large, round nucleus surrounded by fine particles of chromatin in the nucleus, allowing clarity. The remain of the cell body containing a small amount of Golgi, mitochondria and polyribosome's (Figure 2) [2,4]. Mesenchymal stem cells (MSC's) are characterized by great "plasticity", i.e., have the ability to differentiate to form various cell types. For this reason it can be used in regenerative medicine to regenerate tissues and organs. Another important characteristic of the mesenchymal stem cell proliferation is the ability of these cells, to proliferate without losing their "plasticity"[2,3].

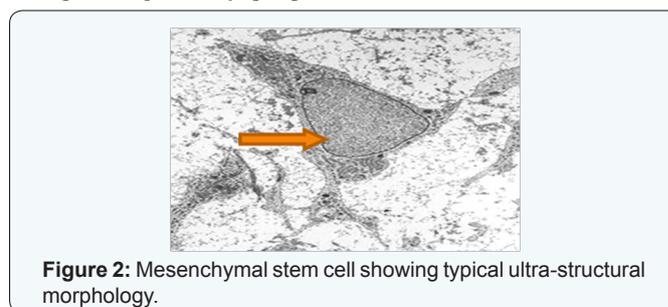


Figure 2: Mesenchymal stem cell showing typical ultra-structural morphology.

Beyond that, there is little we can say with confidence. Numerous studies have shown that human MSC's avoid self-recognition and interfere with the dendritic cells and T-cells and create an immunosuppressive microenvironment of the cytokines they secrete [5,6]. Other studies contradict some of these findings, reflecting the highly heterogeneous nature of MSC isolated and significant differences between the isolated cells are created by many different methods under development. The majority of modern techniques still use the approach CFU, wherein the bone marrow with or without ficoll spreads directly into cell culture plates or flasks. The mesenchymal stem cells, but not the red or hematopoietic cells adhere to the plastic medium within 24 to 48 hours. [7-9].

The major sources of human mesenchymal stem cells (MSC) can be distinguished between adult tissues, preferably bone marrow (BM), peripheral blood (PB) and adipose tissue (AT) and neonatal birth-associated tissues, including placenta (PL), umbilical cord (UC) and cord blood (CB) [1,2]. With flow cytometry sorting we marrow cells to specific surface markers, such as STRO -1, STRO-1 + cells, which are generally more uniform, and have higher capacity and higher rates of proliferation, differentiation, but the exact differences between STRO-1 + cells and MSC's they are not clear yet [1,10,11]. The ISCT (International Society of Cellular therapy), has proposed a set of standards for determining the MSC. A cell can be characterized as MSC's if displays plasticity under normal culture conditions and has a fibroblast-like morphology.

Moreover, it can be differentiated ex-vivo in bone, fat and cartilage. Phenotypically express a number of indicators, none of which is specific to the MSC's. It is generally accepted that adult human MSC's do not express hematopoietic markers (Cells must show <2% positivity for the expression of cell-surface antigens, Negative markers): CD45, CD34, CD14, CD11, CD80, CD86, CD40, CD31, CD18, or CD56, but do express (Cells must show >95% positivity for the expression of cell-surface antigens, Positive markers): CD105, CD73, CD44, CD90, CD71, CD106, CD166 and CD29 (Table 1 & 2). The cultured MSCs also expresses on their surface markers such as CD73, CD90 and CD105, while lacking the expression of CD11, CD14, CD19, CD34, CD45, CD79 and HLA-DR [1,2].

Table 1: Shows the positive and negative expression of MSC markers.

Positive Markers	Cells must express >95% positivity for cell surface antigen expression: CD29, CD44, CD73, CD90, CD105, CD166 & CD271.
Negative Markers	Cells must express <2% positivity for cell surface antigen expression: CD14, CD31, CD34, CD45, CD133 & Lin 1

Table 2: Shows the positive and negative expression according to major sources of human mesenchymal stem cells.

	Bone Marrow MSC	Adipose Tissue MSC	Peripheral Blood MSC
Positive Markers	CD13, CD44, CD73 (SH3), CD90, CD105 (SH2), CD166, STRO-1	CD9, CD13, CD29, CD44, CD54, CD73 (SH3), CD90, CD105 (SH2), CD106, CD146, CD166, HLA I, STRO-1	CD44, CD54, CD90, CD105 (SH2), CD166
Negative Markers	CD14, CD34, CD45	CD11b, CD14, CD19, CD31, CD45, CD79a, CD133, CD144, HLA-DR	CD14, CD34, CD45, CD31

The MSCs are a promising cell source because

- Differentiate into many different cell types in vitro.
- Relatively easy to proliferate in culture.

- Possess immunological traits.
3. Development of mesenchymal stem cells as medical therapies poses two potential problems

- Cells must be passaged repeatedly to ensure enough healthy cells available as treatment for a particular disease.
- MSCs may come from a variety of donors and could contain populations of cells that vary in their ability to differentiate, especially after repeated multiplication and passaging.

Overall Conclusion

- MSCs can differentiate into a variety of cell types.
- MSCs expression of cell-surface antigens must show >95% positivity and <2% negativity.
- Adult human MSC's do not express hematopoietic markers.
- Cultured MSCs also expresses on their surface markers
- They have the potential to treat a wide range of acute and degenerative diseases.
- MSCs are superior to other types of stem cells:
 - a. No ethical issues
 - b. Immune-privileged
- Autologous MSC could be used for the regeneration of human tissues

It is crucial to set standards in order to be safely characterized and use MSCs as potential therapies in regenerative medicine.

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