THE MESENCHYMAL STEM CELLS

Serban Comsa[1]

[1] Department of Microscopic Morphology Morphology/Histology, Angiogenesis Research Center Timisoara
"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

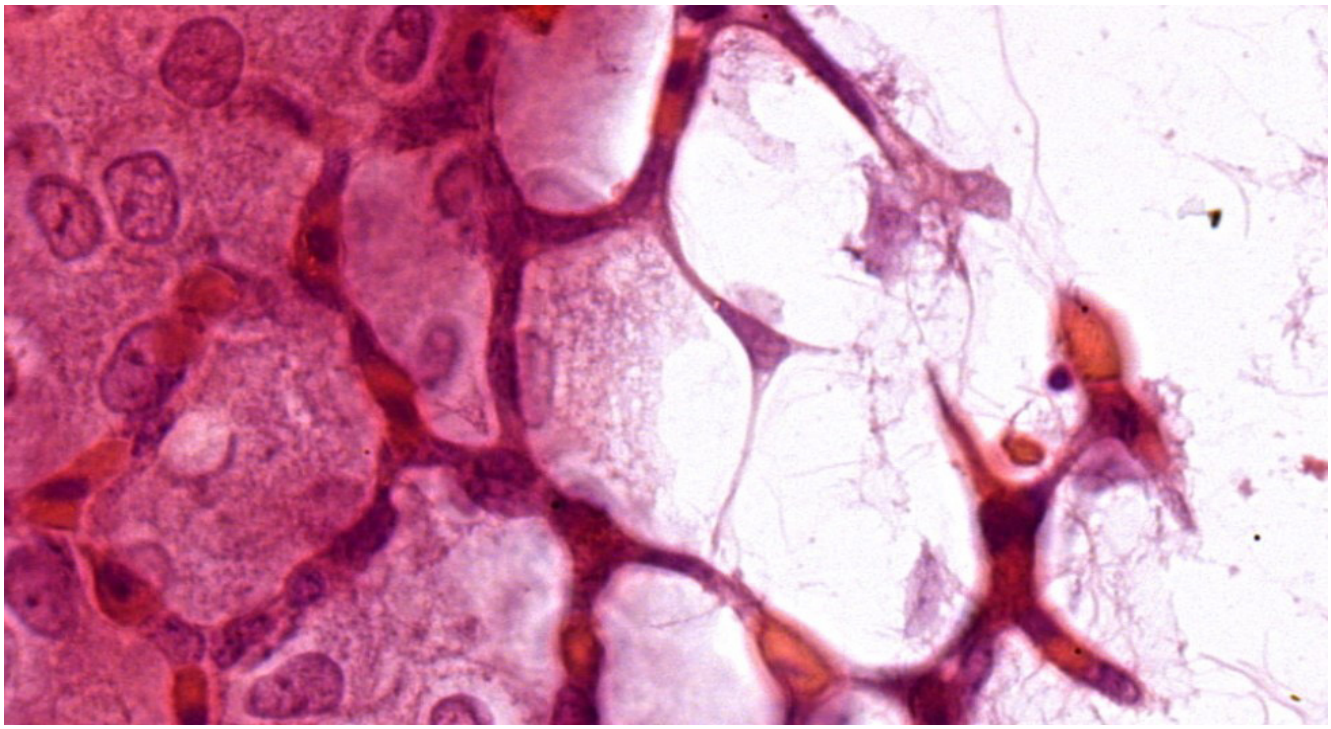

Figure:
Mesenchymal stem cells organizing into cappilary-like structures onto the chick embryo chorioallantoic

Mesenchymal stem cells (MSC) are non-haematopoietic cells that were first derived from the bone marrow and described approximately 40 years ago by Friedenstein et al. In 2006, the International Society for Cell Therapy defined the minimal criteria to define human MSC. They must adhere to plastic in culture and differentiate into osteocytes, chondrocytes and adipocytes. Additionally, they must express CD105, CD90 and CD73 and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules (1).
Other descriptive names for MSC populations in the literature include mesenchymal stromal cells, mesenchymal progenitor cells, multipotent mesenchymal stromal cells, bone marrow stromal cells, bone marrow-derived MSC, multipotent stromal cells, mesenchymal precursor cells, skeletal stem cells, as well as medicinal signaling cells (2).
Lately, MSC have generated substantial interest in the medical areas of transplant, regenerative medicine and cancer treatment because of their multi-potency and multi-functionality (3).
Due to their ability to restore tissue damage, promote regeneration and tissue homeostasis, in recent years MSC have become pivotal for therapies focused on heart damage repair. Additional studies, first in vitro and then in vivo, on animal models, of autoimmune diseases have proved that MSC are able to interfere with the proliferation, activation, and function of immune cells by altering both innate and adaptive immunity mechanisms. Despite being a powerful tool for clinical applications, they present limitations in terms of delivery, safety, and variability of therapeutic response (4), while their role in carcinogenesis remains a matter of controversy (3).

LOCATION

MSC can be identified in the vascular niche of the bone marrow and as perivascular or adventitial cells in a variety of foetal and post-natal tissues (5), demonstrating a tendency to remain close to the oxygen- and nutrient-rich perivascular area(1).
Although MSC are best known from their isolation and

culture from human bone marrow, similar cells have been isolated from such tissues as peripheral blood, cord blood, umbilical cord derived Wharton's jelly, adipose tissue, amniotic fluid, placenta, foetal tissues, dental pulp periosteum, synovial fluid and membrane, articular cartilage, skeletal muscle, dermis, lung and from a variety of other foetal and postnatal tissues. Additionally, MSC-like cells have been described in murine compact bone and the heart (5).

ORIGIN

Understanding the origin and the regenerative environment of MSC and manipulating their homing properties, are important for their efficacy in vascular repair for regenerative medicine therapies and tissue engineering approaches (5).

MSC represent a heterogeneous cell population due to their diverse origin from nearly all vascularized organs and tissues and exhibit migratory capability and regenerative potential (6).

Recently, a number of multipotent precursor cells potentially contributing to the MSC pool have been identified in vivo. Increasing evidence further suggests that MSC are anatomically and functionally associated with vascular/perivascular niches in various tissues. Following the hypothesis that blood vessels throughout the body serve as a systemic reservoir of multipotent stem/progenitor cells, researchers have identified, purified, and characterized distinct populations of MSC-like multilineage precursors from the vasculature of multiple human organs . These human blood vessel-derived precursor cell subsets, including pericytes, adventitial cells and myogenic endothelial cells, exhibit typical mesodermal multipotency in culture, but also demonstrate robust regenerative capacities in animal disease models. These precursor cell subsets, particularly pericytes and adventicial cells can be universally derived from definitive structures of blood vessel walls and represent active contributors to the MSC entity (7–9).

MORPHOLOGY

The first identified multipotent stromal precursor cell populations from the bone marrow were described as nonphagocytic, fibroblast-like in appearance and able to form adherent colonies that were henceforth termed "colony-forming units-fibroblastic" (CFU-F) for this population. Other studies revealed that bone marrow-derived MSC represent precursor cells for mesenchymal tissues, sharing a similar morphology. In vitro, colonies of MSC display heterogeneous morphological characteristics ranging from fibroblastoid to spindle-shaped or from large-flattened to small-round cells (2).

IMMUNOMORPHOLOGY

MSC populations have a natural variation in the expression of cell surface markers around a common mean. They are also dynamic and exhibit phenotypic variation over time, at in vivo – to –in vitro/in vitro-to –in vivo translation or other changes of their environment. Taken all together, the mollecular markers of MSC may be: CD29 (Integrin b1 chain 1), CD31 (Platelet endothelial cell adhesion molecule 1), CD34 (Hematopoietic progenitor cell antigen CD34, transmembrane phosphoglycoprotein), CD36 (Collagen Type I Receptor, Thrombospondin Receptor), CD44 (Hyaluronan receptor), CD49a (Integrin subunit alpha 1 chain), CD49b (Integrin subunit alpha 2 chain), CD49c (Integrin subunit alpha 3 chain), CD49d (Integrin subunit alpha 4 chain), CD49e (Integrin subunit alpha 5 chain), CD51 (Integrin subunit alpha V chain), CD54 (Intracellular adhesion molecule), CD58 (Lymphocyte function-associated antigen), CD61 (Integrin b3 chain), CD71 (Transferrin receptor), CD73 (Ecto-5'-nucleotidase), CD90 (Thy-1), CD102 (Intracellular adhesion molecule), CD104 (Integrin b4 chain), CD105 (Endoglin), TGFb R III), CD106 (Vascular cell adhesion molecule), CD120a (Tumor necrosis factor receptor 1A, TNF IR), CD120b (Tumor necrosis factor receptor type II, TNF IIR), CD121a (Interleukin-1 receptor), CD124 (Interleukin-4 receptor), CD140a (Platelet-derived growth factor receptor alpha), CD140b (Platelet-derived growth factor receptor beta), CD146 (Melanoma cell adhesion molecule), CD166 (Activated leukocyte cell adhesion molecule), CD200 (OX-2 membrane glycoprotein), CD221 (Insulin-like growth factor 1 receptor, IGF-R), CD271 (Nerve growth factor receptor, NGF-R), SSEA-4 (Stage specific embryonic antigen-4), STRO-1 (Stromal antigen 1), W8-B2/ MSCA-1 (MSC antigen 1) (2).

FUNCTIONS

There is great interest in using these cells in a wide variety of clinical domains, such as Neurology, Orthopaedics, Cardiology and Haematology. This interest arises from the following MSC characteristics: they have immunomodulatory capacities, they are multipotent and are thus possible effectors for tissue regeneration, and they tend to migrate to sites of tissue injury/inflammation. Additionally, MSC might escape immune recognition, although conflicting observations about this particular phenotype have been published. MSCs do not express MHC class □ antigens, but the expression of these molecules can be upregulated after exposure to inflammatory cytokines or during MSC differentiation. Currently, in Haematology, MSCs are mainly being tested for their ability to control graft-vs-host disease and to support haematopoiesis after haematopoietic stem cell transplantation (1).

As a key component of the bone marrow haemopoietic

As a key component of the bone marrow haemopoietic stem/progenitor cell niche, bone marrow MSC have also been shown to be organizers or regulators of haemopoietic stem cell function. While the localization of MSC adjacent to or within the vasculature might suggest a role in blood vessel formation by direct differentiation into endothelial cells and/or as supporting niche cells for vascular (re-) generation, it is also compatible with them being potential modulators of hostile injury microenvironments through their immunomodulatory and anti-inflammatory properties and their ability to limit inflammatory damage (5).

In addition, there have been reports that MSC have a procoagulant activity. MSC, particularly those that had been subjected to extended passaging and co-culture with activated lymphocytes, exhibit increased prothrombotic capacities; this effect is dose-dependent. It was also reported that MSC express functionally active tissue factor. When injected in the coronary arteries of a porcine myocardial infarction model, MSC determined a decreased in coronary flow reserve. This effect could be reversed by the co-administration of heparin, an antithrombin agent.

In recent years, MSC have been studied as vehicles to deliver anticancer treatments because there is evidence that they home to tumour sites. They can be induced to express anti-cancer proteins, to produce pro-drug activating enzymes, which ensures that the active drug will only be localized in the tumour, or to deliver oncolytic viruses (1).

Currently, the role of MSC in carcinogenesis is a matter of controversy. It has been reported that they favor tumor growth due to the immunosuppression. Also, MSC could enhance tumor metastatic potential since they can induce epithelia to mesenchyme transition. In contrast, other researchers have shown that MSC inhibit tumorigenesis (3). Anyway, some experiments in vivo and in vitro reported that adipose tissue MSC favor tumor growth by increasing extracellular matrix deposition and vascularization (10).

The angiogenic potential of MSC is an area of current and increasing interest. MSC have proven their involvement in promoting angiogenesis following tissue injury in several disease models and have recently been associated with vasculogenesis, as they were able to differentiate into endothelial cells and contribute to in vivo neovascularization, under optimized conditions (11). It seems that hypoxia serves to enhance differentiation of MSC towards the endothelial phenotype. Additionaly, a revised understanding of MSC-derived neovascularization contextualizes their behavior and utility as a hybrid endothelial-stromal cell type, with mixed characteristics of both populations (12).

The mechanism by which MSC contribute to tumor vessel formation is at least complex and not precisely known. MSC can participate in active tumor angiogenic processes as they are massively recruited by both differentiated endothelial cells and cancer cells. Data indicate a role for MSC in modulating the tumor microenvironment by its production of a large number of cytokines, growth factors and extracellular matrix proteins, expression of various cytokine and growth factor receptors, as well as by a (trans)-differentiation in endothelial-like and pericyte-like cells (13).

My personal contributions regarding the functions of MSC are detailed below. Together with my team, I have described the conditions that allow the assessment of chemotactic migration of adherent human MSC and have demonstrated that both tumor cells and VEGF alter the migration behavior of MSC in a transmigration model, indicating a role of tumor cell-derived VEGF to modulate the recruitment of MSC into sites of angiogenesis (14). Consecutively, I have described the conditions that allow the migration and organization of MSC into capillary-like structures (CLS) in a transmigration model, proving that both MCF-7 cells and VEGF stimulate MSC to form CLS, indicating a role for tumor-derived VEGF in modulating their recruitment into sites of tumor vasculogenesis in breast cancer (13). Further on, I have established an experimental model of breast cancer in vivo through the implantation of MCF-7 breast cancer cells onto the chick corioallantoic membrane (CAM) and I have demonstrated that MCF-7 cells recruit the mesenchymal cells of the CAM's mesoderm and most probably induce their differentiation through myofibroblast-like lineage or cells with a high vasculogenic potential, turning the mesoderm of the CAM into a surrogate tumor stroma (15). In a consecutive study onto CAM, I have shown that human MSC induce vasculogenesis and switch to an endothelial-like non-proliferative phenotype. They also stimulate the MSC originating in CAM to acquire a vasculogenic and pericyte-like phenotype, as the latter organize into CLS and express CD34 and SMA in the vasculogenic areas. Human MSC and CAM establish a genuine hotspot of vasculogenesis, which may evolve to a valuable experimental model for this research field (11).

MSC have been broadly studied in the last years, but there still are many unanswered questions regarding their functions. Understanding their complexity and versatility represents a challenge for the future research in the field.

REFERENCES

1. De Becker A, Van Riet I. Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? World J Stem Cells, 2016; 8(3):73–87.

2. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise Review: Multifaceted Characterization of Human Mesenchymal Stem Cells for Use in Regenerative Medicine. Stem Cells Transl Med, 2017; Dec;6(12):2173–85.

3. Bruna F, Arango-Rodríguez M, Plaza A, Espinoza I, Conget P. The administration of multipotent stromal cells at precancerous stage precludes tumor growth and epithelial dedifferentiation of oral squamous cell carcinoma. Stem Cell Res, 2017; 18:5–13. Available from:

4. Eleuteri S, Fierabracci A. Insights into the Secretome of Mesenchymal Stem Cells and Its Potential Applications. Int J Mol Sci, 2019; 20:4597.

5. Suzanne M.Watt, Francesca Gullo, Mark van der Garde, Daniel Markeson, Rosalba Camicia, Khoo CP, Zwaginga JJ. The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. Br Med Bull, 2013; 108:25–53.

6. Yang Y, Otte A, Hass R. Human Mesenchymal Stroma/Stem Cells Exchange Membrane Proteins and Alter Functionality. Stem Cells Dev, 2015; 24(10):1205–22.

7. Shafiee A, Patel J, Wong HY, Donovan P, Hutmacher DW, Fisk NM, et al. Priming of endothelial colony-forming cells in a mesenchymal niche improves engraftment and vasculogenic potential by initiating mesenchymal transition orchestrated by NOTCH signaling. FASEB J, 2017; Feb;31(2):610–24.

8. Shafiee A, Patel J, Lee JS, Hutmacher DW, Fisk NM, Khosrotehrani K. Mesenchymal stem/stromal cells enhance engraftment, vasculogenic and pro-angiogenic activities of endothelial colony forming cells in immunocompetent hosts. Sci Rep, 2017; Oct 19(1):13558.

9. Chen WCW, Park TS, Murray IR, Zimmerlin L, Lazzari L, Huard J, et al. Cellular Kinetics of Perivascular MSC Precursors. Stem Cells Int, 2013; 2013:983059.

10. Bielli A, Scioli MG, Gentile P, Agostinelli S, Tarquini C, Cervelli V, et al. Adult adipose-derived stem cells and breast cancer: a controversial relationship. Springerplus, 2014; 3:345.

11. Comşa Ş, Ceauşu RA, Popescu R, Cîmpean AM, Raica M. The human mesenchymal stem cells and the chick embryo chorioallantoic membrane: The key and the lock in revealing vasculogenesis. In Vivo, 2017; 31:1139–44.

12. Rytlewski JA, Alejandra Aldon M, Lewis EW SL. Mechanisms of Tubulogenesis and Endothelial Phenotype Expression by MSCs. Microvasc Res, 2015; May;99:26–35.

13. Comşa S, Ciuculescu F, Raica M. Mesenchymal stem cell-tumor cell cooperation in breast cancer vasculogenesis. Mol Med Rep, 2012; 5(5):1175–80.

14. Comşa S, Ciuculescu F, Henschler R, Raica M. MCF7-MSC co-culture assay: approach to assess the co-operation between MCF-7s and MSCs in tumor-induced angiogenesis. Rom J Morphol Embryol, 2011; 52(3 Suppl):1071–6.

15. Comşa Ş, Popescu R, Avram Ş, Ceauşu RA, Cîmpean AM, Raica M. Bevacizumab Modulation of the Interaction Between the MCF-7 Cell Line and the Chick Embryo Chorioallantoic Membrane. In Vivo, 2017; 31:199–204.