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Review Article

Mesencchymal Stem Cells: Sources and Properties in Regenerative Medicine

Jorge Luis Maria Ruiz*, Débora Levy and Sérgio Paulo Bydlowski

Laboratory of Genetics and Molecular Hematology (LIM31), University of São Paulo School of Medicine, Brazil

***Corresponding author**

Jorge Luis Maria Ruiz, University of São Paulo School of Medicine, Av. Dr. Enéas de Carvalho Aguiar, 155, 1st Floor, Room 43, 05403-000 São Paulo, SP, Brazil, Tel: +55-11-26619553; Email: jorgeruiz@usp.br

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Abstract

Stem cells application in regenerative medicine is the new goal on stem cell research. However, still exist some problems to use stem cells safely mainly by immune rejection and by cancer development issues. One type of stem cells, the mesenchymal stem cells are promising therapeutic cells that shown unique immunomodulatory properties. On the other hand, some issues regarding MSCs participation on cancer promotion or cancer inhibition remain to be elucidated. In this review, we address the current knowledge about interaction between MSCs and cancer cells.

INTRODUCTION

Mesenchymal stem cells (MSCs)

Today, are known various types of stem cells (SCs) with therapeutic potential, these are being classified by age (adult or embryonic) or potency (totipotent, pluripotent or multipotent, and unipotent). Some of these cells are currently being isolated and used in clinical protocols for the treatment of various types of disease.

Especially, one type of SC are gaining space in research, the Mesenchymal Stem Cells (MSCs), that were defined by the International Society for Cellular Therapy (ISCT) as multipotent mesenchymal stromal cells with the following properties: adherence to plastic culture surface, co-expression of mesenchymal markers, such as CD73 and CD90 and CD105, the absence of characteristic hematopoietic cells antigens plus the ability to differentiate *in vitro* into osteoblasts, adipocytes and condroblastos [1]. These cells are versatile group of non-hematopoietic stem cells with high potential for proliferation and differentiation founded in various tissues (Figure 1). Characteristics such as easy for isolation, high proliferation capacity *in vitro*, coupled with high potential for cell differentiation have generated great interest in its therapeutic use in regenerative medicine [2].

MSCs derived from bone marrow [BM] were first described in 1976 by Friedenstein and col. and still remain most often SC type used, in research and clinical, as support for hematopoietic stem cells in bone marrow transplants [3,4]. Subsequently were identified some multipotent cells that meet the criteria for MSCs in other adult tissues, as in adipose tissue [5], periphery blood [6] and dental pulp [7]. Moreover, in the last years MSCs were isolated too from fetal and neonatal tissues such as blood for umbilical cord [8], placenta [9], amniotic fluid [10-12] and Wharton's jelly [13,14].

Although adult tissues, such as bone marrow, are the most used as source of MSCs, neonatal tissues have been gaining popularity in research because their advantages. Generally, these tissues are being discarded after birth and MSCs can be obtained by non-invasive techniques, without causing morbidity for the donors. Since MSCs founded in neonatal tissues become from a younger tissue is assumed that this cells have less passages [cells division numbers] than as becoming from adult tissues, but this assumption still remain unproved. However, despite its uniform morphology and immunophenotype, MSCs from different tissues may exert different biological activities when infused *in vivo*. Recent studies showed that MSCs isolated from neonatal tissues have additional capabilities compared to those derived from adult tissues, such as increased proliferation, increased differentiation potential and longer useful life [15].

Currently, the main applications of MSCs are in transplants, especially in hematopoietic stem cells transplantation after cancer chemotherapy. Here, they serve as support for HSCs that have the function of reconstitute the hematopoietic system damaged by chemotherapy treatment [2,16-20]. When MSCs are used as co-adjuvant in transplantation, it have an additional advantage, the power to regulate the immune system, which prevents the rejection of transplanted tissue by the immune system [21,22]. Complementarily, it has been observed that MSCs can attenuate the effects of graft vs. host disease, which results in the main cause of failure in bone marrow transplantation [4,23]. These characteristics will be discussed below.

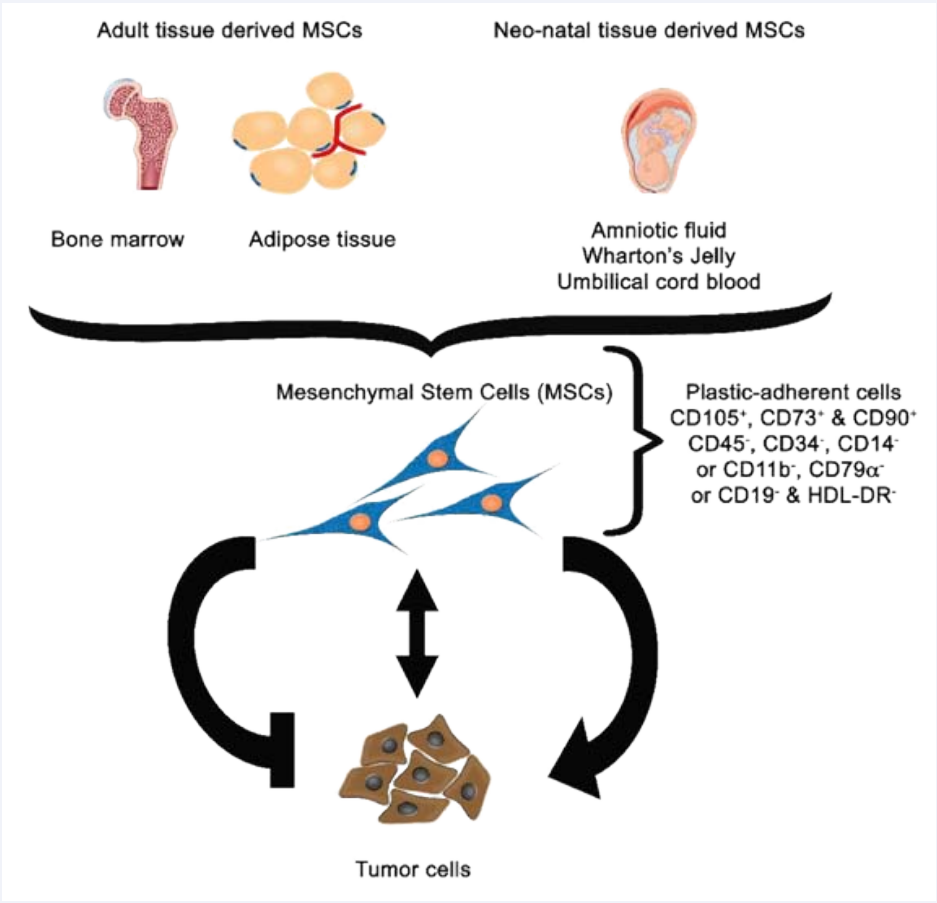

Figure 1 Origin of mesenchymal stem cells and interaction with tumor cells. Both direct interaction or secreted substances, MSCs can inhibit or enhance tumor cell proliferation.

IMMUNOMODULATORY PROPERTIES OF MSCS

Studies of the mechanisms of action of MSCs indicate that these cells have the ability to induce immune system anergy. The immunoregulatory effect seems to be mediated by cell-cell contact and through the release of soluble mediators that influence the microenvironment in which these cells are placed [21]. Furthermore, due to the lack of expression of histocompatibility molecules, MSCs have a minimal or absent immunogenic activity [24]. This "immune-privileged state" showed by MSCs [immunosuppressive activity with low immunogenicity] has been mainly associated with poor antigen expression of Major Histocompatibility Complex [MHC] class I, as well as the lack of determinants of MHC class II and co-stimulatory molecules like CD80, CD86, CD40, and CD40L [21,25]. Experimental models of cytotoxicity mediated by natural killer [NK] cells showed that MSCs are able to escape and inactivate cellular NK cells cytotoxicity, suggesting that there would be no interaction between NK cells and MSCs in hosts transplanted, either autologous or allogeneic MSCs [26].

Other T lymphocytes also have inhibited their proliferation by the MSC, upon activation of the PD-1 (Programmed Death-1) that leads to inhibition of T cell receptor already inhibiting proliferation of B-lymphocytes. It is sensitive to factors secreted by MSCs, but independent of the PD-1. [27] MSCs express surface molecules, including CD90 (Thy-1), CD106 (vascular cell adhesion molecule-1), the intercellular adhesion molecule 1 (ICAM-1), ICAM-2 and CD166 (activated leukocyte cell adhesion molecule, Alcam) having cognate connections with T cells. Furthermore, constitutively produce varying amounts of immunologically active soluble agents, including transforming growth factor-β[TGF -β] , hepatocyte growth factor (HGF), IL-2, IL-8, IL-10, and indoleamine 2,3-dioxygenase, nitric oxide [NO] and prostaglandin E2 [25,28].

Thus, still are poorly understood the mechanisms underlying the interaction between MSCs and immune cells mechanisms, although it is believed that are mediated both by direct cell-cell interaction and by the secreted factors [20].

MESENCHYMAL STEM CELLS AND CANCER

MSCs express chemokine receptors and adhesion molecules that enable their preferential migration (homing) to injured sites and tumors *in vivo* in response to gradients of chemokines [24,29,30]. In damages tissues, MSCs have a regenerative effect while in tumors, the effects still remains controversial [31]. Some studies have shown that MSCs support tumor growth, and for other hand others work suggest that MSCs can have antitumor effects inhibiting cell proliferation in primary tumors like as Kaposi's sarcoma [31-34].

Several studies have reported that bone marrow derived from MSCs increment the *in vivo* growth of colon tumor cells, melanoma and lymphoma, and contribute to the survival of cells in follicular lymphoma B cells derived from human tumors.[35-37] This protective effect was found increased when MSCs were pretreated TNF family members, like tumor necrosis factor alpha [TNF-α] and lymphotoxin -α1β2 [35,38].

In vivo experiments showed that when MSCs are injected in mice, the interaction with tumor cells begins with the migration of MSCs to the tumor due to the gradient of cytokines, as previously mentioned. However, other interactions remain unclear or controversial. Tumor cells [TC] can induce MSCs to secrete stimulating factors to support itself, and moreover, have been observed that angiogenic factors secreted by MSCs act on tumor vasculature and formation of fibrillar tissue thereby sustaining the growth of the same [39,40].

Controversially, other groups have reported that factors derived from stem cells can induce differentiation of the tumor or directly kill tumor cells as demonstrated mainly *in vitro* [34,36,41,42]. In a highly inflammatory and angiogenic model of Kaposi's sarcoma, MSCs inhibited tumor growth in xenografic tumors, even though this result was not found for MSCs from the umbilical cord. The use of athymic mice (nude) in these experiments suggests that the results are not related to the power of immunoregulatory MSCs [32].

The MSCs derived from fetal skin inhibited the growth of breast cancer cells MCF-7 in vitro. Besides, the treatment with MSCs derived conditioned medium (CM) on these tumor cells resulted in downregulation β of survival factors such as -catenin, c-Myc and survivin. These effects were mediated by DKK-1 protein (related protein-1), an β inhibitor of -catenin pathway signaling, which is secreted by MSCs [36,43].

Adipose-derived MSCs have also been reported to inhibit the proliferation of primary leukemia cells. This effect was mediated by soluble DKK-1, which is regulated by transcription factor Nanog [36]. Also, MSCs were able to suppress pancreatic tumors by modifying the cell cycle progression in culture *in vitro*, where an increase of the G1 phase was found leading to the arrest of this cellular cycle phase [44].

Moreover, a few studies reported that MSCs could turn into malignant cells and form tumors when injected *in vivo*. Although these data have to be taken with caution because several researchers have found that these "called tumor MSCs" were actually cross-contamined with tumor cell line [45,46].

MESENCHYMAL STEM CELLS, BONE MARROW TRANSPLANTATION AND HEMATOLOGICAL TUMORS

Controversial data highlight the need for detailed studies to avoid side effects and to maximize the potential of MSCs. Bone marrow transplantation of HSC need a high match between donor and receptor that difficulty success and get enough donators. In these procedures, when are used MSCs as co-adjuvant is believed that MSCs supports hematopoiesis [17]. Studies in animals have shown that transplantation of HSC can repair the damage tissue and MSCs can generate a tissue microenvironment favorable for hematopoiesis, thus improving the transplant outcome [4,6,16,19,47]. More significantly is the ability of MSCs to reduce the effects of graft vs host disease preventing rejection and improving the outcomes [48].

Although beneficial properties of MSCs are known, some studies have brought to light certain dangers of using MSCs in transplantation. As being the increase of cancer recurrence in patients transplanted with MSCs and HSC regarding those were transplanted with HSCs [49]. On the other hand, as seen above, MSCs may modulate and inhibit several types of lymphocytes such as NK cells [26], T cells [27] and B lymphocytes [27]. Others works have found that MSCs can also inhibit hematological tumor cells, as well as non-Hodgkin lymphoma [50] or enhance the proliferation of other tumor cell types such as follicular lymphoma [35], mainly through an increase of anti-apoptotic proteins like Bcl-2.

This indicates that the behavior of MSCs is very related to the environment in which they find themselves and their origin (adult or embryonic); but little is known about the underlying molecular mechanisms linking MSCs to the tumor microenvironment or how MSCs could regulate tumor cell phenotypes.

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