Bol Med Hosp Infant Mex. 2016;xxx(xx):xxx–xxx

Boletín Médico del
Hospital Infantil de México

www.elsevier.es/bmhim

REVIEW ARTICLE

Participation of mesenchymal stem cells in the regulation of immune response and cancer development

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Received 24 September 2016; accepted 24 October 2016

KEYWORDS
Mesenchymal stem cells;
Cancer;
Immunosuppression;
Tumor microenvironment

Abstract The relevance of the microenvironment in the initiation, promotion, and progression of cancer has been postulated. Mesenchymal stem cells (MSCs) have been identified as important components of the tumor stroma, which are capable of affecting the development of cancer through various mechanisms. In particular, MSCs immunosuppressive properties play an important role. It has been shown that bone marrow-derived and other healthy tissues-derived MSCs are capable of regulating the immune response by promoting the activation, maturation, proliferation, differentiation, and effector function of cells of the immune system, such as neutrophils, macrophages, dendritic cells, natural killer cells (NK) and T-lymphocytes. Similar mechanisms have been identified in MSCs associated with different types of tumors, where they generate an immunosuppressive microenvironment by decreasing the cytotoxic activity of T-lymphocytes and NK cells, skew macrophage differentiation towards an M2 phenotype, and decrease the secretion of Th1-type cytokines. Also, the cytokines, chemokines, and factors secreted by the transformed cells or other cells from the tumor stroma are capable of modulating the functions of MSCs.

PALABRAS CLAVE
Células troncales mesenquimales;
Cáncer;
Inmunosupresión;
Microambiente tumoral

Participación de las células troncales mesenquimales en la regulación de la respuesta inmune y desarrollo de cáncer

Resumen Se ha postulado la relevancia del microambiente en la iniciación, promoción y progresión del cáncer. Las células troncales mesenquimales (MSC, del inglés *mesenchymal stem cells*) se han identificado como un componente fundamental del estroma tumoral. Estas son capaces de favorecer el desarrollo del cáncer mediante varios mecanismos. En particular, sus propiedades inmunosupresoras juegan un papel importante. Se ha demostrado que las MSC

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http://dx.doi.org/10.1016/j.bmhimx.2016.10.003

Please cite this article in press as: Castro-Manrreza ME. Participation of mesenchymal stem cells in the regulation of immune response and cancer development. Bol Med Hosp Infant Mex. 2016. http://dx.doi.org/10.1016/j.bmhimx.2016.10.003

de médula ósea y otros tejidos sanos son capaces de regular la respuesta inmune al afectar la activación, maduración, proliferación, diferenciación y función efectora de las células del sistema inmune, como neutrófilos, macrófagos, células dendríticas, células NK y linfocitos T. Mecanismos similares se han identificado en las MSC asociadas con diferentes tipos de tumores, donde estas se encargan de generar un microambiente inmunosupresor al disminuir la actividad citotóxica de linfocitos T y células NK, polarizar a los macrófagos hacia un fenotipo M2, y disminuir el patrón de secreción de citocinas tipo Th1. Asimismo, las citocinas, quimiocinas y factores secretados por las células transformadas u otras células del estroma tumoral son capaces de modular las funciones de las MSC.

1. Introduction

Despite the efforts in the development of new strategies against cancer, many cases remain unresponsive to chemotherapy, radiotherapy and immunotherapy treatments, whose main target are the neoplastic cells; however, several studies have evidenced the importance of the tumor microenvironment in the initiation, promotion, and progression of cancer. The tumor microenvironment has several components, such as transformed cells, leukocytes, fibroblasts, endothelial cells, pericytes and mesenchymal stem cells (MSCs). These cells are responsible for the secretion of cytokines, chemokines, peptides, metalloproteases and components of the extracellular matrix, which altogether contribute to the generation of a permissive microenvironment for the development of neoplasia.[1]

In this context, the interaction between transformed cells and tumor stromal cells occurs through cell-cell contact and secreted factors, which act in an autocrine and a paracrine form. It has been shown that in response to signals generated by transformed cells, cellular components of the tumor stroma can proliferate, differentiate, migrate, secrete cytokines, chemokines and growth factors, remodel the extracellular matrix, induce angiogenesis, and recruit cells of the immune system. These are important processes that favor the progression of cancer.

Inflammation plays a key role in all stages of cancer development. Due to their persistence, the areas where a tumor develops are considered as *wounds that do not heal*. They are characterized by the presence of immune cells, such as dendritic cells (DC), macrophages, neutrophils, eosinophils, T-lymphocytes, and natural killer cells (NK); as well as cytokines, such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 (IL-1), and transforming growth factor-β (TGF-β). It has been shown that the inflammatory tumor microenvironment favors the migration of MSCs to these sites,[2–5] where they stimulate the development of the tumor through the following mechanisms:

1. MSCs are precursors of approximately 20% of the tumor-associated fibroblasts (TAFs), which express α-smooth muscle actin (αSMA).[2] The exposure of bone marrow or adipose tissue-derived MSCs to tumor cells produced factors such as TNFα and IL-1β, induce their differentiation towards TAFs,[3,6] capable of secreting pro-inflammatory chemokines (CCL2/MCP-1, CXCL8/IL-8, and CCL5/RANTES) that stimulate the development of the tumor.[7]
2. MSCs promote angiogenesis: pro-inflammatory cytokines like IFNγ and TNFα, normally expressed in the tumor microenvironment, activate MSCs to express the hypoxia-inducible factor 1-alpha (HIF1α), and secrete high amounts of vascular endothelial growth factor (VEGF).[8,9]
3. MSCs secrete trophic factors promote chemoresistance[10] and the maintenance of tumor-initiated cells.[11,12]
4. MSCs stimulate the epithelium-mesenchyme transition, the invasion and metastasis of tumor cells through the secretion of CXCL12/SDF-1, CCL1, CCL8/IL-8, IL-6 and prostaglandin E2 (PGE_2).[3,13] In carcinoma cells, MSCs decrease the expression of the epithelial marker E-cadherin and induce the expression of mesenchymal markers such as fibronectin and vimentin, as well as the transcription factor snail.[13] In addition, it has been shown that MSCs-secreted TGF-β participates in the migration of breast cancer cells.[14]
5. MSCs are capable of regulating the immune response.

In this review, we focused on the analysis of the immunosuppressive capacity of MSCs and the effect of this feature in the development of a tumor.

2. Mesenchymal stem cells

MSCs are adult pluripotent stem cells originally isolated from bone marrow (BM).[15] Currently, their isolation from different tissues have been achieved, but until now an MSCs marker has not been defined. Therefore, the International Society of Cell Therapy has established a series of guidelines to define these cells. It is necessary that MSCs show the following characteristics: positive expression of CD105, CD73, CD90; low levels of HLA-I and negative for HLA-II, CD11b, CD14, CD34, CD45, and CD31; likewise, these cells must possess adipogenic, osteogenic and chondrogenic differentiation capacity.[16,17]

3. Immunosuppressive properties of MSCs

Immunosuppressive properties of MSCs have been demonstrated using different *in vitro* and *in vivo* study models.

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