Cancer Treatment Reviews 39 (2013) 180–188

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

Mesenchymal stem cell signaling in cancer progression

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ARTICLE INFO

Article history:
Received 20 October 2011
Received in revised form 9 March 2012
Accepted 13 March 2012

Keywords:
Mesenchymal stem cells
Cancer
Tumor microenvironment
Tumor stroma
PI3K/Akt pathway

ABSTRACT

Mesenchymal (multipotent) stem/stromal cells (MSCs) may affect cancer progression through a number of secreted factors triggering activation of various cell signaling pathways. Depending on receptor status, phosphatase and tensin homolog (PTEN) status, or Wnt activation in the cancer cells, the signals may either result in increased growth and metastasis or lead to inhibition of growth with increased cell death. Thus, MSCs can play a dual role in cancer progression depending on the cellular context wherein they reside. The phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway has a central role in regulating tumor growth, and several MSC secreted factors stimulate activation of this pathway. A comprehensive understanding of the signals regulating MSC–tumor cross-talk is highly important for the development of MSCs as potential therapeutic vehicles. Thus, the presented review focuses on factors released by MSCs and on the dual role they may have on various stages of tumorigenesis.

Introduction

During the last decade considerable focus has been given to MSCs based on their biological properties, such as their potential capacity to replace diseased cells in various organs and their potential use as suppressors for graft-versus-host disease due to immunomodulatory functions. Also, their homing ability to tumor tissue makes them promising vectors for cancer therapy. However, the use of MSCs in cancer treatment has been met by a general concern related to the biosafety of using MSCs. This concern has been supported by various reports indicating that MSCs may be involved in cancer initiation *in vivo*[1–5] and also by the suggestion that MSCs may spontaneously transform into malignant cells *in vitro*.[6–12] A recent report has also shown fusion between MSCs and gastrointestinal epithelial cells, suggesting the generation of a more cancer prone cell type.[13] However, based on the information available there is currently no solid evidence supporting spontaneous *in vitro* transformation of human MSCs.[14–16]

The field of MSC research is quite confusing both with respect to the definition of MSCs as well as by contradicting reports regarding the role of MSCs in cancer development. It is clear that MSCs secrete a number of paracrine factors that may influence tumor growth; however, the cellular mechanisms induced by these factors are poorly understood. Also variations in experimental designs and a mixed use of cell lines impede the interpretation of the role of MSCs in tumor development. Here we present a critical review focusing on the function of MSCs in the tumor stroma and on various model systems used to study MSC–tumor cell interactions. Emphasis will be given to cell signaling pathways that are induced during cross-talk between tumor cells and MSCs, and also on how these pathways act as negative or positive regulators of tumor growth and metastasis.

Activation of MSCs in the tumor stroma

The tumor stroma, involving tumor–host cellular interactions, plays an important role in tumor growth, angiogenesis, and metastasis.[17,18] It consists of a complex extracellular matrix wherein fibroblasts, immune and inflammatory cells, fat cells and blood-vessels reside. Activated fibroblasts (also designated myofibroblasts) in the tumor stroma are commonly referred to as carcinoma-associated fibroblasts (CAFs) or tumor associated fibroblasts (TAFs). It has been suggested that CAFs/TAFs can be derived from MSCs,[19–22] and in many studies they may in fact represent the same cells, since in most instances neither of the cell populations are specifically selected for by the isolation protocols used. This view is supported by reports demonstrating that MSCs can undergo myofibroblast differentiation upon transforming growth factor β1 (TGFβ1) stimulation.[20,21,23] TGFβ1 stimulation can generate hypomethylated MSCs that show alterations in gene expression profiles towards myofibroblast signatures expressing markers such as alpha-smooth muscle actin (α-SMA), tenascin-C and fibroblast surface protein (FSP), as well as increased expression and secretion of growth stimulating factors such as chemokine (C–C motif)

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http://dx.doi.org/10.1016/j.ctrv.2012.03.005

ligand 5 (CCL5)/RANTES and stromal-derived-factor-1 (SDF-1)[19–21] (Fig. 1). Similarly, CAFs are more hypomethylated than normal stromal cells[24] and it has been estimated that a minimum 20% of CAFs originate from MSCs.[20] Yet, MSCs seem to possess a greater tendency to enhance tumor sphere formation and tumor initiation than tumor-activated or normal myofibroblasts.[20,25,26]

MSCs are distributed in a variety of tissues such as the bone marrow (BM), fat, bone, cartilage, and muscle.[27] In the following sections we will use MSCs as a common name for these cells irrespective of the tissue source, while BM-MSCs will be used to specifically describe bone marrow-derived MSCs and ASCs refers to adipose-derived MSCs.

MSC–tumor cell cross-talk

Interactions between MSCs and tumor cells involves a number of MSC secreted signaling molecules that may stimulate various signaling pathways, in particular related to cell growth and apoptosis regulation in the tumor cells. However, the tumor–MSC cross-talk is complex, also involving signaling from tumor cells that stimulates MSCs as well as MSC activation of inflammatory cells and angiogenesis by recruitment of endothelial cells. The various signaling molecules and pathways at the different stages of tumorigenesis will be discussed in the following paragraphs.

Involvement of MSCs in tumor initiation and early tumor growth

To fully understand the mechanisms of transformation of a normal cell into a cancer cell has been a major focus in cancer research. The assumption that the tumor-initiating cell has stem cell properties has lead to the cancer stem cell (CSC) hypothesis, and considerable efforts have been made to define the CSCs by various cell surface markers. For a transformed cell to become a cancer-initiating cell, it has to avoid the immune system and survive and proliferate in a defined microenvironment. MSCs may contribute to such an environment, since they can have a regulatory role on immune cells by altering the cytokine secretion profile toward an anti-inflammatory environment.[28] For instance, in allogenic mice, immunosuppressive MSCs may prevent tumor cell rejection by the immune system promoting tumor cell growth,[29] a property potentially mediated by the generation of regulatory T-cells (Tregs). Recently it has been shown that MSCs can protect breast cancer cells by increasing Tregs and reduce the activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTL),[30] which are known to be responsible for tumor cell destruction. Consequently, it has been hypothesized that MSCs can protect a sub-set of low-proliferating tumor cells from chemotherapy, and these tumor cells can remain dormant in the BM for years before resurging.

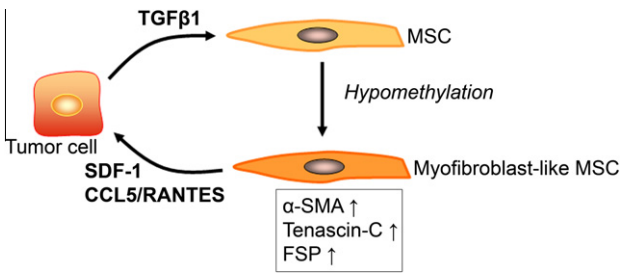

Fig. 1. Generation of tumor associated MSCs. Tumor cell secreted TGFβ1 induce hypomethylation and a more myofibroblastic gene signature in MSCs, with upregulated expression of α-SMA, tenascin-C and FSP. Tumor stimulation also induce enhanced secretion of MSC produced CCL5/RANTES and SDF-1, which may act in a paracrine way to stimulate tumor growth and survival.

One of the biological functions of MSCs is to provide a stromal compartment for hematopoietic cells in the bone marrow, where stemness is maintained in a so-called bone marrow niche.[31] In parallel to this, it has been proposed that CSCs reside in a CSC niche.[32,33] MSCs in the bone marrow may actively participate in the generation of such a niche, which can be relocated to the tumor site by CXCR4 signaling and thereby stimulate tumor growth.[20] MSCs in the tumor niche express IL-6, Wnt5α, BMP4, and Gremlin-1, and the latter has been suggested as a marker for MSCs in the bone marrow or within the tumor niche.[20] Gremlin-1 is involved in maintenance of the stem cell pool, and may promote CSC self-renewal.[34] Tumor cell secreted TGFβ and SDF-1α may serve as attractants recruiting MSCs to the tumor niche.[20]

MSCs may also impose tumor initiating effects through secretion of growth factors that stimulates sphere formation or growth of CSC-like cells. One of the MSC-secreted factors is IL-6 which can stimulate increased sphere formation and support tumor initiation through activation of the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway[25,35] where in particular activation of the transcription activator STAT3 seem to be important for oncogenesis.[36] Also, in relation to breast cancer, it has been shown that MSCs can stimulate mammosphere formation[37–39] partly through epidermal growth factor (EGF) secretion with a subsequent activation of the PI3K/Akt survival pathway.[38] Also, in the context of CSC-like populations and MSCs, it has been shown that tumor growth can be accelerated by a cytokine network involving C–X–C chemokine ligand type 7 (CXCL7) and IL-6.[40]

It has also been suggested that MSCs can become the tumor initiating cells of various types of sarcomas.[2–5] For instance, it has been shown that stimulation with the Wnt inhibitor Dickkopf-1 (Dkk-1) can increase proliferation of MSCs and render them more liable to undergo transformation.[3] It has also been suggested that MSCs may be the origin of some gastric cancers, either by Helicobacter-associated transformation[1] or fusion with gastrointestinal epithelial cells,[13] although, this has not been conclusively demonstrated.

In contrast, hTERT immortalized fetal dermis-derived hMSCs (Z3-MSCs) have been shown to inhibit colony formation of the breast cancer cell line MCF-7 and the hepatocellular carcinoma cell line H7402, as well as causing delayed tumor formation in severe combined immunodeficiency (SCID) mice.[41,42] Furthermore, animal xenograft studies indicate that tumor formation is accompanied by MSC-associated necrosis.[41–43] In another study it was shown that co-injection of BM-MSCs with Skov-3 ovarian cancer cells in mice lead to an initial delay in tumor growth, whereas at later stages of tumor progression larger tumor volumes were observed leading to a shorter survival.[22] This controversy between observations of necrosis formation and delayed tumor stimulation can potentially be explained by the production of necrotic products that can initiate an environment that is preferential for cancer survival and regrowth.[44]

In summary, there is at present little mechanistic information into how MSCs affect the early steps of tumorigenesis, although several studies indicate an active role of MSCs in immune suppression and niche formation, which represents important elements in tumor cell survival and colonization. Both MSCs and tumor cells express IL-6, and this cytokine is involved in niche formation and growth of CSC-like cell populations. The MSC secreted factors described to be involved in tumor initiation and early tumor growth are summarized in Fig. 2.

Involvement of MSCs in tumor growth

A current controversy is reflected in the fact that tumor growth can both be stimulated and inhibited by various MSC secreted factors. The stimulatory and inhibitory effects may represent a