Chapter 4

# Multipotent Stromal Cells in a Tumor Microenvironment

Flavia Alejandra Bruna

Additional information is available at the end of the chapter

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**Abstract**

Multipotent mesenchymal stromal cells [also referred to as mesenchymal stem cells (MSCs)] as was previously described, are a heterogeneous subset of stromal cells with regenerative potential. Their present tropism for inflamed sites including tumors lesion may be adverse or therapeutic effects arising from MSC administration; in this context, their potential for producing trophic and immunomodulatory factors raises the question as to whether MSCs promote or interact with a tumor microenvironment. Previous studies show a paradoxical effect regarding MSCs, which seems to depend on isolation and expansion, cells source, dose and both route and timing of administration. The occurrence of neoplastic transformation in ex vivo expanded MSCs after a long-term culture has been reported, however, this event has been subsequently described as uncommon, with an estimated frequency of $<10^{-9}$. Furthermore, neither ectopic tissue formation nor MSC-originating tumors have ever been reported so far in hundreds of patients treated with MSC therapy. The biosafety of these cells, both in precancerous and cancerous environments, has been little investigated to date. We found in an animal model of oral cancer that locally or systemically administered allogeneic MSCs do not aggravate the progression of precancerous lesions. Moreover, they preclude cancer progression and tumor growth, particularly at papilloma stage.

**Keywords:** mesenchymal stem cells, multipotent mesenchymal stromal cells, tumoral microenvironment, cancer

## 1. Introduction: Properties of the MSC

Mesenchymal stem cells (MSCs) are a promising source for cell therapy in regenerative medicine. The therapeutic properties of MSCs are related to their potentials for transdifferentiation, immunomodulation, and trophic factor secretion. Investigators have isolated MSCs from many

different tissues, including bone marrow, adipose tissue, umbilical cord blood, peripheral blood, dermis, liver, skin, and skeletal muscle [1–4]. Previously it has been reported that MSCs from different sources (adipose tissue, bone marrow, kidney, muscle, etc.) share characteristics properties (i.e., expression of cell surface antigens, immunomodulatory capability, and tropism toward tumor) [5–8]. On the other hand, it has been reported that MSCs isolated from different sources can be found into tumor microenvironments, and depending on the level of commitment to a certain lineage by MSCs, they can be transdifferentiated faster to certain cell types depending on the source [9]. The MSCs from different source express a distinct set of genes, which is a reflection of its commitment related to their potential of differentiation (including adipocytes, osteocytes, chondrocytes, hepatocytes, fibroblasts, and pericytes) [10, 11]. MSCs can be expanded until five passages preserving their therapeutic potential for use in clinical applications [12, 13]. Additionally, the transdifferentiation of MSCs has rarely been observed in animal models [14]. Regarding the immunomodulator potential, it has been reported that MSCs can secrete various immunomodulators, such as nitric oxide (NO), prostaglandin (PGE2), indoleamine 2,3-dioxygenase (IDO), interleukin (IL)-6, IL-10, and HLA-G [12, 13]. Regarding the immunomodulatory potential of MSCs, there are molecules that can moderate the immune response such as nitric oxide (NO), prostaglandin (PGE2), indoleamine 2,3-dioxygenase (IDO), interleukin (IL)-6, IL-10, and histocompatibility antigen class I, G (HLA-G). These soluble factors modify the function of immune cells and induce T regulatory cells activation ([14]). In addition, MSCs can suppress immune cell activation via cell-to-cell contact. MSCs can also inhibit the proliferation of effector T cells by activating programmed cell death pathways such as apoptosis by the interaction of programmed death signal molecules type 1 (PD-1) with their related ligands PD-L1 and PD-L2. On the other hand, it has been reported that MSCs can induce T cell anergy by inhibiting the expression of CD80 and CD86 in antigen-presenting cells [15–17]. Among the wide range of factors that MSCs secrete, are modulators that can regulate inflammation, apoptosis, angiogenesis, fibrosis, and tissue regeneration [18]. In addition, previous studies reported that MSCs produce trophic factors that promote cell survival (SDF-1, HGF, IGF-1), cell proliferation (EGF, HGF, NGF, TGF-$\alpha$), and angiogenesis (VEGF) [19, 20]. Faced with the signal of damaged tissue, MSCs can migrate to the site of injury (homing) by sensing chemoattractant gradients of cytokines secreted by the extracellular stromal matrix (MEC) and spreading through the peripheral blood to all the organisms [21–24]. At the site of injury, MSCs are stimulated and activated by local damage and repair factors, such as hypoxia, the cytokine environment, and Toll-like receptor ligands. This cascade of stimuli as a whole promotes the production and the release of abundant growth factors that converge to increase tissue regeneration [28, 29]. In contrast to the use of MSCs in regenerative medicine, recent data suggest that MSCs may increase tumorigenesis or inhibit tumorigenesis [25, 26]. In the tumor microenvironment, the tumor tries to avoid recognition by the immune system while secreting inflammatory mediators to establish and maintain a constant state of inflammation [27]. In addition, the correlation between normal cells, cancer cells, and the matrix within the tumor microenvironments has gained increasing attention, especially because these interactions contribute to certain hallmarks of cancer, such as immunomodulation, angiogenesis, invasion and metastasis, and apoptotic resistance [28–30]. Regarding, if the MSCs promote or suppress tumor development, in several studies shown that MSCs perform homing the tumor microenvironment and then promote the formation of

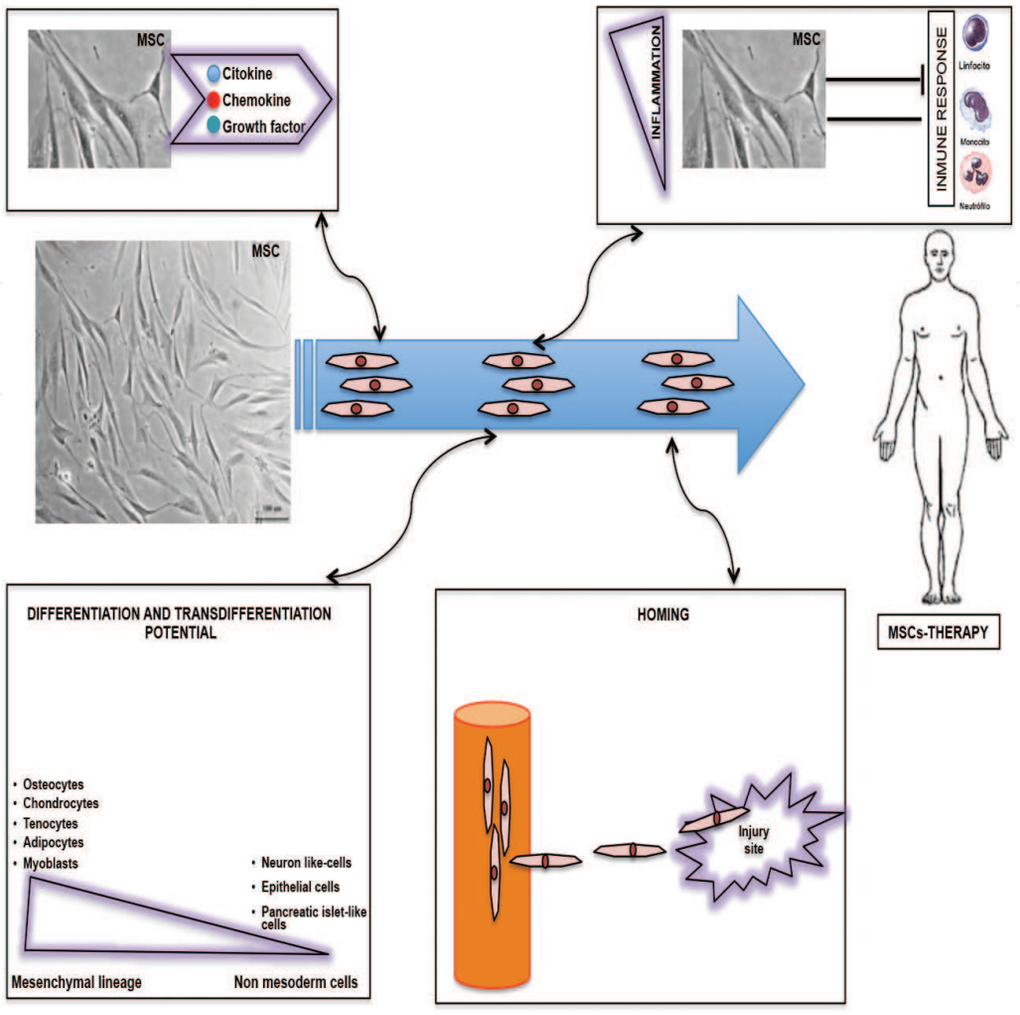


**Figure 1.** MSC effects in clinical use. The therapeutic potential of MSCs relies on several unique properties as: (i) the capacity to differentiate into various cell lineage, (ii) the ability to secrete paracrine factors initiating healing and regeneration in the surrounding cells, (iii) the ability to reduce inflammation and regulate immune response and to migrate to the exact site of injury.

tumor blood vessels, improving the fibrovascular network and suppressing immune responses, modulating thus the tumor response to antitumor therapy [31–35]. Unlike its tumor-promoting abilities, MSCs can also suppress tumor growth by inhibiting proliferation-related signaling pathways, such as AKT, PI3K, and Wnt, by the secretion of proapoptotic molecules such as Dikkopf type 1 (Dkk1) inhibiting the progression of the cell cycle; in turn, they can negatively regulate the X-linked inhibitor of the apoptosis protein (XIAP) and suppression of angiogenesis [31, 36, 37] (**Figure 1**). In this chapter, we will analyze how MSCs can contribute to tumorigenesis, including (i) transition to tumor-associated fibroblasts; (ii) suppression of the immune response; (iii) promotion of angiogenesis; (iv) stimulation of epithelial-mesenchymal transition (EMT); (v) through contribution to the tumor microenvironment; (vi) inhibition of tumor cell apoptosis; through contribution to the tumor microenvironment; (vi) inhibition of tumor cell apoptosis, and (vii) promotion of tumor metastasis.

## 2. MSC and cancer: how they relate?

### 2.1. MSCs can induce epithelial-mesenchymal transition

The epithelial-mesenchymal transition (EMT) is a process characterized by downregulation of proteins associated with cell adhesion present in epithelial cells such as E-cadherin, γ-catenin/plakoglobin, and zonula occludens-1. In turn, it triggers an upregulation of proteins related to the mesenchymal phenotype, such as N-cadherin, vimentin, fibronectin, and alpha smooth muscle actin [38, 39]. The EMT is present during organogenesis and wound healing. EMT has also been described during the development of epithelial tumors, which is associated with a more undifferentiated and metastatic phenotype (poor prognosis) [40]. There are accumulated evidence that suggests that a defective EMT promotes tumor invasion, metastasis, and chemoresistance to medications [41]. In many tumors, the presence of cytokines such as HGF, EGF, PDGF, and TGF-β produced and released by the stroma associated with the tumor, act by inducing EMT and favoring processes such as metastasis [42, 43]. Interestingly, it has been reported that these factors are secreted by MSCs [44] and that they can activate a number of transcription factors of genes that promote EMT, such as Snail, Slug, zinc finger E-box binding homeobox 1 (ZEB1), and Twist related protein-1 (TWIST) to transmit EMT promotion signals [45–47]. A recent study demonstrated the activation of specific genes to induce EMT in breast cancer cell lines when they were co-cultured with MSCs and a decrease in expression of genes related to epithelial differentiation [48]. MSCs also improve the ability to trigger the metastatic cascade in colon cancer cell lines through high expression of EMT-associated genes (ZEB1, ZEB2, Slug, Snail, and Twist-1), in a cell-cell-dependent manner. It should be noted that the decrease in the expression of the E-cadherin gene is related to EMT [48]. In breast cancer cell lines, it has been described that MSCs produce leptin which results in an increase in the expression of EMT genes and associated with metastasis (SERPINE1, MMP-2, and IL-6). On the other hand, in SCID/beige mice co-injected with MCF-7 breast cancer cells and with MSCs containing leptin shRNA, a decrease in the leptin levels produced by the MSCs was observed and consequently a reduction in the tumor volume MCF7 and less metastatic lesions in liver and lung [49]. Other authors have reported that MSCs can fuse with different cancer cells and unleash the classic characteristics of EMT [50–52].

### 2.2. MSCs can induce transition to tumor-associated fibroblast

*MSC to fibroblasts associated with tumors*: The tumors consist of cancer cells and different stromal cells that form the tumor cell medium [53]. The tumor stroma consists of an extracellular matrix scaffold (MEC) populated by stromal cells that include fibroblasts, immune cells, and endothelial cells. Fibroblasts can be activated in the tumor stroma and activated fibroblasts (also called myofibroblasts) are called carcinoma-associated fibroblasts (CAF) or tumor-associated fibroblasts (TAF). CAF/TAF are abundant in most invasive tumors and are mainly composed of cells expressing smooth muscle actin α (α-SMA) [54]. These cells can secrete SDF-1 with the consequent promotion of tumor growth and angiogenesis [55], which binds to CXCR4 expressed by tumor cells [55]. Recently, it was reported that MSCs could differentiate into CAFs/TAFs [24, 56, 57]. In fact, MSCs can differentiate into CAF/TAF and increase the production of α-SMA, tenascin-C and fibroblast surface protein (FSP), CCL5/RANTES, and

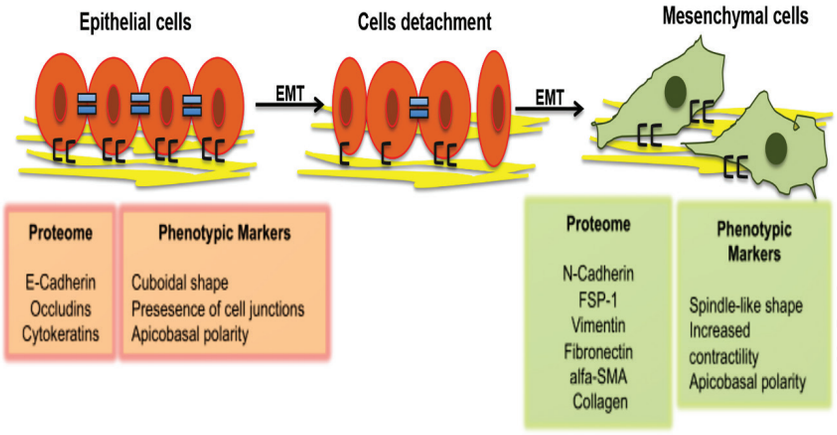


**Figure 2.** Figure illustrating the epithelial-mesenchymal transition.

SDF-1 by stimulating tumor growth through contribution of angiogenesis and the production of tumor stimulating growth factors [37, 61–63] (**Figure 2**).

### 2.3. MSCs in tumor microenvironments can modulate the immune response

*Immune response in tumor microenvironments*: In addition to protecting the host from external invaders, the immune system recognizes tumor antigens and eliminates malignant tumors [58]. Therefore, tumor growth, invasion, and metastasis are important aspects of the tumor's immune escape mechanism [59, 60]. During tumor initiation, TAMs and MSCs migrate to the tumor microenvironments. TAMs act as the main inflammatory component of the tumor microenvironment [61, 62]. In contrast, TAMs can show antitumor activities linked to the M1 phenotype via IFN-γ, TNF-α, TGF-β, PGE2, and IL-10 [72, 77–82]. Also, M1 TAMs secrete free oxygen radicals, nitrogen radicals, and pro-inflammatory interleukins (e.g., IL-1β, IL-6, IL-12, IL-23, and TNF-β) facilitating the killing of tumoral cells. The MSCs can be activated by the pro-inflammatory cytokines IFN-γ, TNF-α, or IL-1βn in tumor microenvironments [30, 52, 69, 83, 84]; additionally, the tumor cells and M2 produce immunomodulatory molecules, such as IDO, PGE2, IL-6, IL-10, HLA-G5, and NO [64, 65]. IDO is the critical rate-limiting enzyme of tryptophan catabolism through the kynurenine pathway, resulting in tryptophan depletion and halting the growth of various cells. In tumor microenvironments, MSCs can be activated by pro-inflammatory cytokines IFN-γ, TNF-α, or IL-1β [66, 67]. Within the immunomodulatory molecules secreted by MSCs, Prostaglandin E2 (PGE2) has a multifunctional role in pathological processes including the regulation of inflammation and cancer. The production of PGE2 by MSCs increases after stimulation with TNF-α or IFN-γ. In addition, PGE2 increases the level of expression of IL-10 and decreases the expression of TNF-α, IFN-γ, and IL-12 in cells of the developing immune system and of macrophages [68, 69]. PGE2 regulates the secretion of IFN-γ and IL-4 in Th1 and Th2 cells, respectively, and promotes proliferation of Treg cells [19]. It has been reported that IL-6 secreted by MSCs inhibits monocyte differentiation toward CD and decreases the activation capacity of CD to T cells [70, 71]. In addition, IL-6 secreted by MSCs resulted in a delay in apoptosis of lymphocytes and neutrophils [72, 73]. Another important molecule in the moderation of the immune response is nitric oxide (NO). NO is produced by inducible NO synthase (iNOS) through stimulation by inflammatory factors such as IL-1, IFN-γ, and TNF- α [72, 74] and also inhibits the functions of T cells [75]. In contrast to

the reported evidence that MSCs can suppress the immune response, Ohlsson et al. reported that administration of tumor cells and MSCs simultaneously caused an increase in the inflammatory component in the stroma, mainly composed of granulocytes and monocytes, whereas when administered separately, this was not observed [75]. In a rat-induced colon cancer model, it was observed that the colon tumor cells inoculated in a gelatin matrix, when implanted subcutaneously, developed larger tumors than animals that surgically received colon cancer cells combined with MSCs. MSCs inhibited rat colon carcinoma by increasing the leukocyte infiltrate [75]. It was observed that the increase in infiltrations of both granulocytes and macrophages was much higher in rats co-injected with tumor cell lines and MSCs than in rats injected with tumors without MSCs. These data suggested that MSCs had pro-inflammatory effects in this model. In this same work, a greater degree of infiltration of granulocytes and macrophages was observed, but to a lesser extent, when only MSCs were added to the gelatin. [75].

### 2.4. MSCs may promote tumor growth

The tumor microenvironment, is composed of cancer cells, noncancerous cells, and stromal cells, all this as a whole influences the growth of the tumor [28]. The tumor stroma hosts many types of cells, as well as MEC. These cells include different types of immune cells, fibroblasts, endothelial cells, and myofibroblasts [28]. MSCs perform homing at tumor sites and then integrate into the tumor stroma [76, 77]. These cells interact with each other and with cancer cells, resulting in the promotion of tumor growth. The ability of MSCs to promote tumor growth and metastasis was demonstrated in murine models of breast cancer with similar results from cancer cells co-implanted with MSCs [24, 78, 79]. In turn, it was observed that allogenic mice transplanted with B16 melanoma cells did not in the development of tumors when B16 cells were co-injected with MSCs [80]. This finding indicates that MSCs exert essential immunosuppressive and antitumor effects at the onset of the tumor. Human bone marrow-derived MSCs have increased the growth of estrogen receptor-alpha (Er$\alpha$) positive breast cancer cell lines: T47D, BT474, and ZR-75-1, in an in vitro three-dimensional tumor environment assay, in contrast, have had no effect on the ER$\alpha$ negative cell line MDA-MB-231 [81]. Nonetheless, the growth rate of (another ER$\alpha$ negative cell line) was high in the presence of human MSCs [81]. Another study showed both human fetal MSCs transplanted subcutaneously into BALB/c-nu/nu mice with human adipose-derived MSCs alone or together with cell lines F6 (human mesenchymal stem cells F6) or SW480 (human colon adenocarcinoma cell line) in a ratio 1:1 or 1:10, favoring the growth of these tumor cell lines [79]. Other authors reported that tumor cells procured from primary breast cancer were grown in the presence of human bone marrow-derived MSCs (ratio 1:1). Additionally, this was tested on secondary mice, where a greater tumor-producing ability compared with the cells obtained from primary tumors and grown in the absence of MSCs was observed [82]. In addition, tumor incidence and/or size [83, 84] as well as tumor vascularization [30] increased when breast, lung, colon, or prostate tumor cells were co-injected with MSCs independent of the source of origin from the same. Similar results were observed with MSCs derived from adipose tissue or human bone marrow. The same was demonstrated with tumor cells of osteosarcoma, melanoma, and glioma [85]. Another interesting observation relates to adipose tissue adjacent to the tumor implant (e.g., lung cancer models or to Kaposi's sarcoma xenografts), where a substantial increase in

tumor size was observed along with the appearance of stromal cells of the implant; MSCs derived from adipose tissue may promote tumor growth [86].

The innate tropism of MSCs to injured sites, including established tumors, has been widely reported, although the mechanism behind it has not yet been fully elucidated that the proinflammatory cytokines secreted by the reactive stroma are involved [24]. The most accepted explanation to date is that the tumors behave as unresolved wounds since their stroma closely resemble the healing granulation tissue and produce cytokines, chemokines, and other chemotactic agents [27] and the chemotactic properties of MSC are similar to those of leukocytes [87, 88]. The tropism of MSCs for tumors has been widely studied and exploited with very good results for the supply of antitumor drugs in animal models of lung and breast cancer, melanoma, and glioma [88].

Like any other cell in culture, when long-term MSCs are manipulated in vitro, they can have chromosomal aberrations and produce tumors in healthy animals because they undergo cell crisis [89]; this has been observed mainly in mouse cells, which require extensive cultures to produce a significant number of MSCs free of hematopoiesis [90]. For example, it has been demonstrated that the intravenous administration of MSCs derived from bone marrow in NOC/SCID mice generates cellular aggregates that are retained in the pulmonary capillaries, forming emboli when they are injected in large quantities. Once lodged in the capillaries, they expand and invade the lung parenchyma and form tumor nodules [90]. These lesions rarely contain lung epithelial cells, but have the characteristics of cartilage and immature bone that resembles a well differentiated osteosarcoma. However, until now, no type of transformation has been demonstrated by human MSCs adequately expanded ex vivo for cell therapy (no more than five passages) [90]. The Canadian Trial Critical Care Trials Group recently reported a meta-analysis of randomized, nonrandomized, controlled, and uncontrolled clinical trials, phase I and phase II, where they found no reports associating the administration of autologous or allogeneic MSCs and tumor formation in 36 clinical studies [91]. However, a longer follow-up is necessary to evaluate the tumorigenic potential of human MSCs.

### 2.5. MSCs might promote metastasis

Along with the increasing number of cancer metastasis mechanisms being discovered, it has been reported that MSCs can induce metastasis in vitro and in vivo [78, 83, 92, 93]. Previous studies showed when human breast cancer cells were co-incubated with MSCs, the gene expression of onco and proto-oncogenes in breast cancer cells was upregulated [48]. These molecular and morphological alterations were accompanied by a metastatic phenotype. Breast cancer cells induce the motility of tumor cells through the secretion of CCL5, increasing invasiveness and metastatic potentials [83]. The invasion mediated by CCL5/RANTES is also closely related to the increased activity of matrix metalloproteinase 9 (MMP-9) [94].

On the contrary, it has been shown that the increase in metastatic capacity when MSCs are co-injected with tumor cells is reversed when the MSCs are injected in a different site from the tumor and this anti-metastatic effect by the MSCs remains independent of tumor distance [83]. Other mechanisms, such as the induction of EMT, the regulation of CSC, and the displacement of mesenchymal niches are also implicated in tumor metastasis [95]. Breast cancer cells co-cultured with MSCs derived from human bone marrow (ratio 1:1) upregulate the expression of

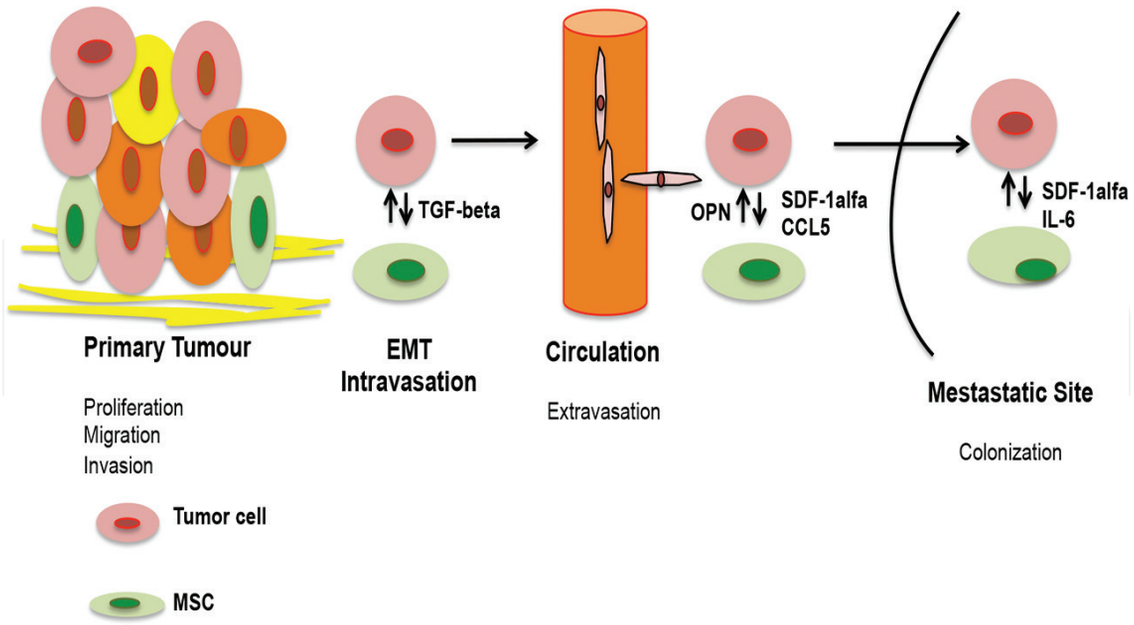


**Figure 3.** Interaction of tumor cells with MSCs during cancer progression. MSCs can interact with tumor cells at the primary site of the tumor and during metastasis by promoting cancer progression and invasion. One of the mechanisms involved in these processes is that MSCs induce EMT in tumor cells through close cell-cell contact, which could be due in part to the secretion of TGF-β [38, 82]. Studies have shown that secretion of osteopontin (OPN) by tumor cells, induces MSCs to secrete chemokine (motif CC) ligand 5 (CCL5) by stimulating the metastasis of the cancer cell through interaction with its specific chemokine receptor CC type 5 (CCR5) [84]. The migration of tumor cells to and from the metastatic site is mediated by SDF-1, a factor secreted by bone marrow MSCs, which interacts with the CXC receptor chemokine receptor type 4 (CXCR4) expressed in human tumor cell lines of the breast and prostate [33, 101, 102] (adapted from Sarah M. Ridge, Francis J. Sullivan and Sharon A. Glynn. Mesenchymal Stem Cells key players in cancer. Molecular Cancer, Feb. 2017 13:31 1-10. https://doi.org/10.1186/s12943-017-0597-8).

oncogenes and proto-oncogenes associated with tissue invasion, angiogenesis, and apoptosis (i.e., N-cadherin, vimentin, Twist, Snail, and E-cadherin) [48]. These molecular changes have been accompanied by morphological and growth alterations, which are characteristics of a more metastatic phenotype. It has been seen that $0.5 \times 10^5$ breast cancer cells co-injected subcutaneously with $1.3 \times 10^6$ MSCs derived from human bone marrow have significantly increased the rate of lung metastases in NOD/SCID mice. This effect was lost when the MSCs derived from bone marrow were injected separately from the tumor cells [83]. On the other hand, it has been shown that MSCs derived from bone marrow facilitate cancer cells [MCF-7, T47D low invasive cell lines, and factor 1 derived from stromal cells (SDF-1) null MDA-MB-231 highly aggressive] target to the bone marrow and modify the metastatic niche through the secretion of trophic factor (SDF-1 and CXCR4) and improved neovascularization in a xenogeneic mouse model (**Figure 3**) [96].

### 2.6. MSCs might inhibit tumor growth

MSCs can not only secrete cell regenerative factors continuously but also secrete factors in response to other various stimuli [97]. Tumor progression is accompanied by hypoxia, starvation, and inflammation. Although many studies have shown that MSCs have tumor promoting properties, many other studies have shown that MSCs have tumor suppressor properties

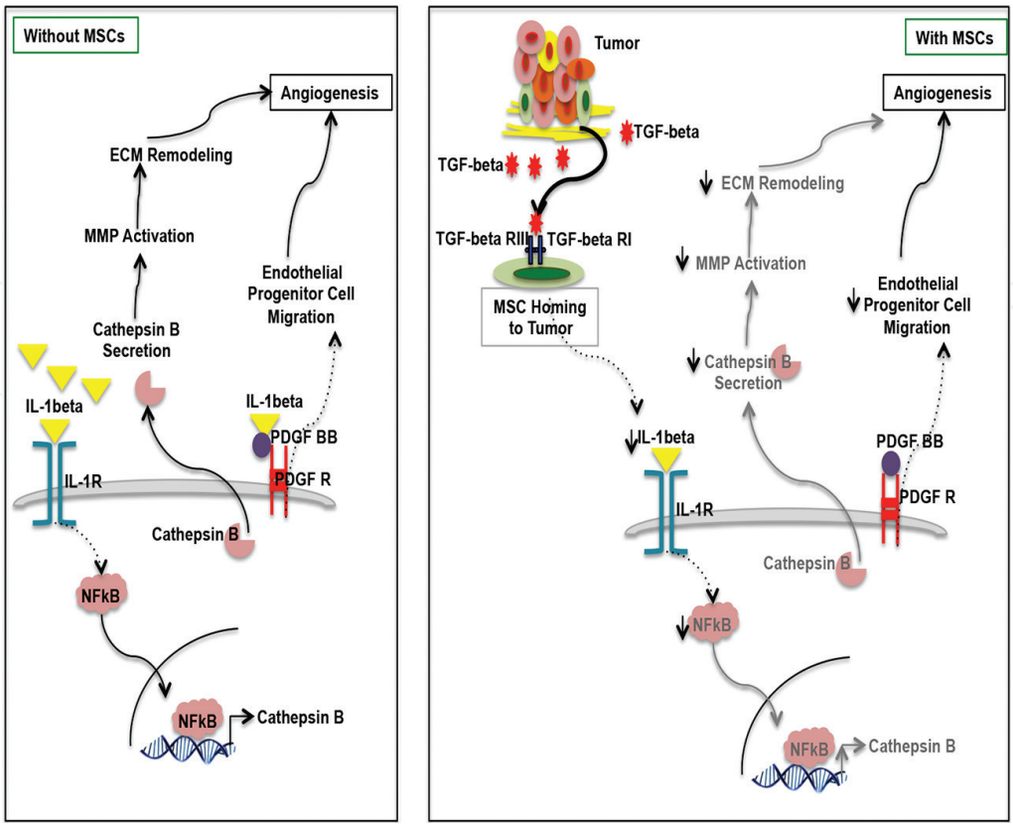


**Figure 4.** Mesenchymal stem cells can perform homing to the tumor environment. Studies in murine models of gliomas have reported that they can be directed to the tumor site through TGF-beta signaling and, once there, they can suppress angiogenesis within the tumor microenvironment. The proposed mechanisms are the following in sequential order: (1) the glioma microenvironment contains high levels of the proangiogenic cytokine, IL-1 beta. (2) Signaling through the NF-kappa B axis increases the expression of Cathepsin B and activates extracellular matrix remodeling programs that promote angiogenesis. (3) The increase in beta IL-1 potentiates the signaling of PDGF-BB, which promotes the migration of endothelial progenitor cells. (4) Glioma stem cells within a tumor secrete TGF-beta and recruit MSCs through TGF-beta RII and the endoglin/CD105 co-receptor. (5) Within the glioma microenvironment, the presence of MSCs reduces the levels of beta IL-1, negatively regulating Cathepsin B and decreasing PDGF R-beta signaling. It is believed that the downregulation of these signaling cascades in the presence of MSCs inhibits angiogenesis, reduces the density of microvessels and suppresses glioma growth. (Adapted from: https://www.rndsystems.com/resources/articles/mesenchymal-stem-cells-exhibit-tgf-beta-dependent-tropism-gliomas-and-inhibit-angiogenesis).

(**Figure 1**) (reviewed in [30]). In this regard, it is believed that MSCs suppress tumor growth by increasing the infiltration of inflammatory cells [97], inhibit angiogenesis [34], suppress Wnt and AKT signaling, and induce cell cycle arrest and apoptosis [32, 35, 36]. Recently, Ryu et al. reported that when the MSCs derived from adipose tissue were cultured at a high cell density, they synthesized IFN-beta, which then suppressed the growth of MCF-7 cells [98]. In addition, MSCs prepared with IFN-gamma or cultured with three-dimensional systems can express TRAIL, which induces specific apoptosis of tumor cells [97, 99]. In particular, it was demonstrated that in vitro culture of MSCs under hypoxic conditions increased cell proliferation. In addition, the expression of Rex-1 and Oct-4 was increased, leading to the conclusion that MSC scion was increased during hypoxia [100]. In addition, under hypoxic and starvation conditions, MSCs can survive through autophagy and release many antiapoptotic or pro-survival factors such as VEGF, FGF-2, PDGF, HGF, brain-derived neurotropic factor

(BDNF), SDF-1, IGF-1 and IGF-2, transforming growth factor-beta (TGF-b), and IGF-2 binding protein (IGFBP-2) [101, 102]. These factors inhibit the apoptosis of tumor cells and promote tumor proliferation, whereas normal MSCs do not acquire these properties. In addition to the mitogenic properties of growth factors secreted by MSCs, VEGF and FGF-2 can mediate Bcl-2 expression, delaying apoptosis [103], while indirect angiogenic factors can induce VEGF expression and FGF-2 [104]. In addition, SDF-1 was reported to prevent drug-induced apoptosis of chronic lymphocytic leukemia (CLL) cells [105]. In addition, VEGF, FGF-2, HGF, and IGF-1 expressed by MSCs have been reported to stimulate angiogenic and antiapoptotic effects after hypoxic conditioning [101, 106]. Although little is known about how MSCs under hypoxic conditions exert support effects on tumor cells directly, growth factors stimulated by MSCs, stimulated by hypoxia, can provide tumor support effects in the tumor microenvironment through angiogenic and antiapoptotic effects (**Figure 4**).

### 2.7. MSCs can induce apoptosis of cancer cells and endothelial cells

Depending on the microenvironment, MSCs can exert an antiproliferative effect. Lu et al. demonstrated that MSCs had an inhibitory effect on mouse tumor hepatoma cells in a cell-dependent manner through the activation of intrinsic caspase 3 pathway [107]. Lu et al. reported that MSCs increased p21 gene expression, involved in the arrest of the cell cycle. These data demonstrate that MSCs exerted tumor inhibitory effects in the absence of host immunosuppression, inducing arrest of the G0/G1 phase and apoptosis of cancer cells [107]. The same tumor suppressor activity by MSCs was observed in xenografted SCID mice with disseminated non-Hodgkin lymphoma [108]. A single injection of MSCs which increased the survival of the animals included those who presented more aggressive lymphomas. In turn, significant induction of endothelial cell apoptosis was observed when co-cultured with MSCs, suggesting that MSCs exert anti-angiogenic activity through endothelial cell apoptosis [108]. These findings were consistent with the results reported by Karnoub et al. where they demonstrated that MSCs exhibited potent anti-angiogenic activity in Kaposi's sarcomas with high vascularity and endothelial cell cultures in vitro by inducing apoptosis of tumor epithelial and endothelial cells through the Dkk-1 protein [32, 34]. Additionally, Dasari et al. reported that downregulation of the antiapoptotic inhibitor, inhibitor of the apoptosis protein linked to X (XIAP), in the presence of human umbilical cord blood-derived mesenchymal stem cell (hUCBSC) induced apoptosis of glioma cells and xenograft by the activation of caspase-3 and caspase-9 [109]. Recently, MSCs cultured at high density express IFN type I, which leads to cell death of breast cancer cells, MCF-7 and MDR-MB-231 cells [98]. In addition, MSCs prepared with IFN-gamma or cultured with three-dimensional systems can express TRAIL, which induces specific apoptosis of tumor cells. [97, 98].

### 2.8. Regulation of cell cycle by MSC

MSCs secrete a variety of cytokines that induce cell cycle arrest of tumor cells, albeit transiently, at the G1 phase through expression of Cyclin A, Cyclin E, Cyclin D2, and p27KIP1 [31, 107, 110]. Human stromal cells of adipose tissue (ADSC) and its conditioned culture medium can suppress tumor growth [107]. In addition, the cell culture medium conditioned by ADSC stimulated the necrosis of the cancer cells after the arrest of the G1 phase in the absence of

apoptosis. Finally, when ADSC was introduced in pancreatic adenocarcinoma, the tumor did not grow [107]. Similarly, tumor cells that were cultured with MSC in vitro were also stopped in the G1 phase [111]. However, when the nonobese diabetic-severe combined immunodeficient mice were injected with MSCs and tumor cells, their growth was more increased compared to the injection of tumor cells alone. Although it has been reported that MSCs can induce arrest of the cell cycle of tumor cells in vitro, little is known about the exact mechanisms. In our experiment, the delay or arrest of the cell cycle can be induced in certain types of tumor cells and under certain co-culture conditions (type of medium, cell concentration, or co-culture time). While we cannot explain the exact mechanism (s), several studies performed by different groups, including hours, have shown that the arrest of the tumor cell cycle occurs. It has been shown that MSCs derived from human bone marrow interfere in vitro with small cell lung cancer (A549), esophageal cancer (Eca-109), Kaposi's sarcoma, and proliferative kinetics of the leukemic cell line [112]. The above was not only observed when $0.5 \times 10^5$ tumor cells were cultured together with $0.5 \times 10^5$ MSCs derived from human bone marrow but also when exposed to medium conditioned by MSC; the cells were stopped during the G1 phase of the cell cycle in both cases by the negative regulation of Cyclin D2 and the induction of apoptosis [111]. MSCs from other sources, including MSCs derived from human fetal skin and MSCs derived from adipose tissue, have also inhibited the growth of human liver cancer cell lines [32], breast cancer (MCF-7) [111], and primary leukemic cells by reducing their proliferation, colony formation, and oncogene expression [30, 32]. Intravenous injection of $4 \times 10^6$ MSCs derived from human bone marrow in nude mice carrying Kaposi's sarcoma has inhibited the growth of tumor cells [32]. A similar effect has been observed in an animal model of hepatocellular carcinoma and pancreatic tumors, since the alteration of cell cycle progression has led to the decrease of cell proliferation [30, 31]; the same has happened with melanoma due to increased apoptosis of capillaries [34], and the growth of colon carcinoma in rats has been inhibited when rat EMFs (cell line MPC1cE) were co-mapped with tumor cells in a relationship 1:1 or 1:10 [33]. MSCs derived from human fetal skin (Z3 cell line) also delayed liver tumor growth and decreased tumor size when injected with the same number of cells from the H7402 cell line in SCID mice [36]. Injection of MSCs derived from human adipose tissue ($1 \times 10^3$ cells/$mm^3$) into established pancreatic cancer xenografts has led to apoptosis and the abrogation of tumor growth in nude (nude) Swiss mice [31]. The role of MSCs in cancer remains paradoxical. Evidence to date has suggested that they are pro as well as antitumorigenic [113–115] and such discrepancy seems to depend on the isolation and expansion conditions, the source and dose of the cell, the route of administration, and the model tumor used.

### 2.9. MSCs and regulation of cellular signaling

The main signaling pathway involved in the control of cell survival is the pathway of phosphoinositide 3-kinase (PI3K)/AKT and WNT/beta-catenin. The activation of this pathway induces proliferation, growth, and migration, and increases cellular metabolism [116–118]. In the biology of a tumor cell, numerous studies have reported the requirement for the activation of the AKT-signaling cascade for the migration, invasion, and survival of tumor cells. Additionally, the WNT pathway has also been associated with the development of various types of carcinomas, including breast, liver, colon, skin, stomach, and ovary [119]. In a murine

model of Kaposi's sarcoma, Kakhoo et al. reported that MSCs injected intravenously were able to migrate to the tumor and inhibit tumor cell proliferation by inhibiting AKT [32]. On the other hand, they observed in glioma cells that PTEN was upregulated in the presence of HUCBSCs, with the consequent downregulation of AKT [109]. In addition to inhibiting the PI3K/AKT pathway, MSCs can also suppress the WNT/beta-catenin pathway through the induced expression of the pro-apoptotic protein DKK-1 [31, 36, 37]. These recent findings demonstrated that beta-catenin can be negatively regulated in different human carcinoma cell lines (hepatocellular, H7402 and HepG2, breast, MCF-7, hematopoietic, K562 and HL60) by the secretion of DKK-1 by the MSCs. On the other hand, when the activity of DKK-1 was inhibited by the use of anti-DKK-1 neutralizing antibodies or interfering RNA, the inhibitory effects of MSCs on tumor progression disappeared [31, 36, 37].

## 3. Conclusions

Although therapy with MSC in regenerative medicine is considered feasible and safe, the literature reported to date reveals dicrepancies respect to the MSCs impact in the tumor microenvironment. This paradoxical effect could be attributed to the differences in the experimental conditions of isolation and expansion, the source and dose of cells used, the route of administration and its timing, and the host characteristics. This chapter highlights the mechanisms of the effects of tumor support or suppression mediated by the MSCs and analyzes the possible mechanisms involved. MSCs demonstrate a tropism for tumors and once they interact with each other and with cancer cells, they promote tumor growth by: inmunosuppression; promotion of angiogenesis; epithelial-mesenchymal transition; inhibition of apoptosis; and promotion of metastasis. In contrast, many studies have reported that MSCs can prevent tumor growth by increasing leukocyte infiltration, inhibiting angiogenesis, suppressing Wnt and AKT signaling. Further investigations are necessary to establish the biosecurity of cell therapy in the presence of precancerous lesions.

## Conflict of interest

The author discloses no potential conflicts of interest.

## Notes/Thanks/Other declarations

Not applicable.

## Appendices and nomenclature

| | |
|---|---|
| NO | nitric oxide |
| PGE2 | prostaglandin |

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| | |
|---|---|
| IDO | indoleamine 2,3-dioxygenase |
| IL-6 | interleukin-6 |
| IL-10 | interleukin-6 |
| HLA-G | histocompatibility antigen, class I, G |
| PD-1/2 | programmed death-1/2 |
| PD-L1/2 | programmed death-1/2 ligand |
| CD80 | T-lymphocyte activation antigen CD80 |
| CD86 | T-lymphocyte activation antigen CD86 |
| SDF-1 | stromal derived factor-1 |
| HGF | Hepatocyte Growth Factor |
| IGF-1 | insulin dependent growth factor-1 |
| EGF | epithelial growth factor |
| NGF | neurotrophic growth factor |
| TGF-$\alpha$ | transforming growth factor-alpha |
| VEGF | vascular endothelial growth factor |
| ECM | stromal extracellular matrix |
| MSCs | multipotent stromal mesenchymal stem cells |
| AKT | Serine-threonine kinase |
| PI3K | Phosphoinositide 3-kinase |
| Wnt | Wingless-Type MMTV Integration Site Family, Member 1 |
| XIAP | X-linked inhibitor of apoptosis protein |
| EMT | epithelial–mesenchymal transition |
| PDGF | platelet derived growth factor |
| TGF-$\beta$ | transforming growth factor-beta |
| ZEB1/2 | zinc finger E-box binding homeobox 1/2 |
| TWIST | twist related protein-1 |
| SERPINE1 | serpin family E member 1 |
| MMP-2 | metalloproteinase-2 |
| SCID | severe combined immunodeficiency |
| CAFs | carcinoma-associated fibroblasts |

| | |
|---|---|
| TAFs | tumor-associated fibroblasts |
| $\alpha$-SMA | $\alpha$-smooth muscle actin |
| FSP | fibroblast surface protein |
| CCL5/RANTES | chemokine (C-C motif) ligand 5 |
| DCs | dendritic cells |
| IgG | immunoglobulin G |
| NK | natural killer cells |
| TNF-$\alpha$ | tumor necrosis factor-alpha |
| IFN-$\gamma$ | interferon-gamma |
| MHC-class I/II | major histocompatibility complex |
| Er$\alpha$ | estrogen receptor-alpha |

## Author details

Flavia Alejandra Bruna[1,2]*

*Address all correspondence to: flabruna@gmail.com

1 Instituto de Biología y Medicina Experimental de Cuyo, Technological Scientific Center CONICET, Mendoza, Argentina

2 Centro de Medicina Regenerativa, Universidad del Desarrollo, Santiago, Chile

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