

# Mesenchymal Stem Cell: A Hard Nut to Crack in Cancer Development

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## Abstract

Tumors are surrounded by various types of cells, including mesenchymal cells, immune cells, and vascular and lymphatic endothelial cells. In this context, it has been recognized that cell-to-cell communication in the tumor microenvironment is a dynamic mechanism that exerts significant effects on progression of carcinogenesis. Over the last decade, the discoveries that mesenchymal stem cells (MSCs) can migrate to sites of inflammation and neoplasia have been the subject of a growing interest due to their potential application in regenerative medicine and gene delivery. In particular, based on the report that MSCs are incorporated into tumor tissues, the impact of MSCs on tumor growth has been extensively investigated. Despite intense research, it is highly debatable whether MSCs are friends or foes of tumor. In this mini-review, I will introduce the contradicting observations on the role of MSCs in tumorigenesis and discuss why this discrepancy has been reported.

## Keywords

Mesenchymal stem cells; Stem cells; Tumor microenvironment; Cancer-associated fibroblasts; Cancer progression

## Abbreviations

VEGF: Vascular Endothelial Growth Factor; FGF-2: Fibroblast Growth Factor-2; Ang-1: Angiopoietin-1; ERK1/2: Extracellular Signal-Regulated Kinase1/2; Th2: T helper2; TGF- $\beta$ 1: Transforming Growth Factor- $\beta$ 1; SDF-1 $\alpha$ : Stromal Cell-Derived Factor-1 $\alpha$ ; CCL5: Chemokine (C-C motif) ligand 5; CXCL16: C-X-C motif Chemokine 16; CXCR6: Chemokine (C-X-C motif) Receptor 6; IL-1 $\beta$ : Interleukin-1 $\beta$ ; PDGF-BB: Platelet-Derived Growth Factor-BB; PCNA: Proliferating Cell Nuclear Antigen; DKK-1: Dickkopf-1; WNT: Wingless and int-1; bFGF: basic Fibroblast Growth Factor; EGF: Epidermal Growth Factor; HGF: Hepatocyte Growth Factor; MMP-2: Matrix Metalloproteinase-2

## Characteristics of Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are generally characterized by their differentiation potential into mesodermal lineages, such as adipocytes, chondrocytes, and osteoblasts [1,2]. However, there is accumulating evidence that MSCs also give rise to a wide variety of non-mesodermal cell types, including epithelial cells, endothelial cells (ECs), and neuronal cells [3,4]. Traditionally, primary MSCs have been isolated from bone marrow [5].

It should be noted that MSCs in bone marrow are comprised of a heterogeneous population of cells having stem-cell-like properties that enable them to differentiate into bone, cartilage, and hematopoietic supporting tissues [6]. MSCs can be distinguished from hematopoietic stem cells, their counterpart in the bone marrow, in that they are spindle-shaped and adherent cells expressing cell surface markers CD29, CD73, CD90, and CD105, but lacking hematopoietic markers, including CD11b, CD34, and CD45 [7]. In addition, it is well-documented that MSCs can be obtained from other fetal and adult tissues, such as umbilical cords, adipose tissues, and dental pulps [8,9]. In particular, adipose-derived stem cells (ASCs) can be easily isolated from adipose tissues [10]. Even though ASCs share many cell surface markers with bone marrow-derived MSCs, ASCs exhibit unique characteristics, including differences in CD markers and gene expression profiles. Furthermore, different methods employed to obtain ASCs affect the proportions of various cell types and different cell culture conditions exert remarkable effects on ASC gene expression patterns, suggesting that ASCs used in studies may have different properties [11]. Also, it becomes increasingly clear that environmental cues and epigenetic remodeling, such as DNA methylation and histone modifications, play an important role in differentiation and fate of MSCs [12]. Thus, it should be noted that all MSCs cannot be regarded as an identical cell type.

Recently, a growing body of literature supports the concept that MSCs play a significant role in modulating the immune system. MSCs have been shown to counteract inflammation by suppressing the host immune responses. Glennie et al. [13] demonstrated that mouse bone marrow-derived MSCs inhibited T cell proliferation by down-regulating cyclin D2 expression. Similarly, MSCs isolated from human bone marrow induced cell cycle arrest in B cells and dendritic cells [14,15]. The mechanisms underlying the immunosuppressive effect of MSCs are not fully understood. Ren et al. [16] suggested that MSC-mediated immune suppression might be exerted through the concerted action of cytokine-induced chemokines and nitric oxide (NO). In this study, the authors showed that chemokines promoted lymphocyte migration into proximity with MSCs and T cell responsiveness was impaired due to NO from MSCs. Based on the discoveries that MSCs modify the immune responses, the potential application of MSCs in treatment of immune-mediated diseases has been tested in a variety of experimental models [17]. Bartholomew et al. [18] first showed that intravenous administration of baboon MSCs prolonged skin graft survival *in vivo*. Indeed, Le Blanc et al. [19,20] subsequently reported successful treatments of severe acute graft-versus-host disease by transplanting MSCs in patients.

Intriguingly, accumulating evidence indicates that MSCs are able to migrate into injured tissues and tumors [21]. Since the process of tumor development is highly associated with chronic inflammation and many of the soluble factors secreted from wounds are also discovered in the tumor microenvironment, it is speculated that MSCs may home into tumor tissues in a similar way that they migrate toward wound sites [21,22]. Indeed, a number of studies have reported that MSCs are preferentially recruited by the tumor microenvironment, implying that MSCs may have profound effects on tumor development. Additionally, it has been shown that MSCs can migrate from a neighboring source, such as adipose tissues, and from a distant location via circulation, including bone marrow [23-25]. Based on these exciting findings, the role of MSCs in tumor progression has been intensely investigated. Despite all these efforts, however, our current understanding of the relationship between MSCs and tumor cells is still limited and the results in studies are controversial.

### Mscs as Friends of Cancer

Numerous studies report that MSCs support tumorigenesis and several main mechanisms by which MSCs contribute to tumor pathogenesis have been proposed.

### Angiogenesis Support

MSCs have been suggested to promote tumor progression by supporting tumor vasculature. Recent studies report that MSCs serve as a potent inducer of angiogenesis by secreting various pro-angiogenic factors, including VEGF, FGF-2, and Ang-1 [26,27]. Furthermore, it is found that MSCs give rise to endothelial-like cells, enhancing neovascularization and vascular density [28-30]. Zhang et al. [31] showed that transplantation of rabbit bone marrow MSCs into tumor tissues were able to differentiate into vascular ECs, thus fostering angiogenesis. Additionally, MSCs have been reported to differentiate into pericytes which envelop the surface of the vascular tube and support the vasculature [32]. Indeed, a population of ASCs resides in a periendothelial location and plays a critical role in vascular stabilization by interacting with ECs [33]. Furthermore, pericytes isolated from diverse human organs retain a MSC-like population, suggesting that MSCs are able to contribute to angiogenesis [34]. Currently, it has been documented that extracellular vesicles (EVs) secreted from cells deliver bioactive molecules, such as proteins, lipids, and nucleic acids, to adjacent cells, suggesting that EVs may act as a key mediator of cell-to-cell communication [35]. In this context, recent work showed that EVs derived from human bone marrow MSCs promoted angiogenesis in tumors by stimulating the ERK1/2 pathway *in vivo* [36].

### Immunomodulatory Effects

As discussed above, MSCs are generally thought to exert immunosuppressive effects. Even though this immunosuppressive property of MSCs provides new opportunities for treating immune-mediated diseases, such as rheumatoid arthritis, it is possible that a suppressed immune system by MSCs may lead to a higher incidence of tumor formation [37,38]. Djouad et al. [39] injected MSCs systematically to investigate whether MSCs enhanced tumor growth by suppressing the immune system *in vivo*. In this study, they found that co-injection of melanoma cells and MSCs resulted in tumor progression in allogeneic mice, implying that systemic immunosuppression was induced by MSCs. Moreover, MSCs have been suggested to recruit and maintain regulatory T cells (Tregs), which confers a growth advantage to tumors [40]. Recent work reported that MSCs derived from bone marrow induced Tregs by producing Th2 cytokines and TGF- $\beta$ 1, thus enhancing breast cancer growth [41].

### Contribution to Tumor Stroma

The involvement of MSCs in tumor progression is not restricted to their ability to promote angiogenesis and modulate the immune responses [42]. It has been suggested that cancer-associated fibroblasts (CAFs) are partially derived from MSCs that reside in regional sources or bone marrow [25,43]. It is well-established that tumor cells stimulate their neighboring cells to create a favorable environment for their survival and growth [44]. Currently, a number of studies demonstrate that these tumor cell-educated CAFs promote tumor progression in various cancer types. It was found that CAFs stimulate angiogenesis, cancer cell proliferation, and invasion, suggesting the significant role of CAFs in enhancing carcinogenesis [45-47]. Some evidence indicates that MSCs are progenitors of tumor stroma. Quante et al. [25] showed that using an inflammation-induced gastric cancer model, some of the CAFs were generated from MSCs and they were recruited to the tumor microenvironment in a TGF- $\beta$ - and SDF-1 $\alpha$ -dependent manner. In addition, Jotzu et al. [43] suggested that human ASCs might provide a source of CAFs. In this study, the authors reported that a large amount of ASCs differentiated into CAF-like cells through the TGF- $\beta$ 1 signaling pathway when exposed to conditioned media from MDA-MB-231 and MCF7 human breast cancer cell lines.

### Induction of Epithelial-Mesenchymal Transition and Metastasis

It has been suggested that MSCs may trigger epithelial-mesenchymal transition (EMT). It is well-documented that EMT plays a critical role in the malignant characteristics of tumors by increasing local invasion and distant metastasis [48]. Indeed, EMT is now recognized as a source of CAFs, facilitating cancer progression [49]. Previous study reported that co-culture of pancreatic cancer cells and human bone marrow MSCs promoted tumorigenesis by facilitating EMT via Notch signaling [50]. Moreover, Martin et al. [51] demonstrated that in a breast cancer model, co-culture of human bone marrow MSCs resulted in up-regulation of EMT-specific markers, such as N-cadherin, Vimentin, Twist, and Snail. MSCs have also been reported to contribute to metastasis. Karnoub et al. [52] showed that CCL5 secreted from MSCs caused breast cancer cells to disseminate from their origin and metastasize to lung. A recent study elegantly elucidated how MSCs promoted cancer progression and metastasis using a prostate cancer model [53]. They showed that CXCL16 secreted from prostate cancer recruited bone marrow MSCs and the CXCL16/CXCR6 signaling triggered the conversion of MSCs into CAFs which expressed CXCL12. Subsequently, CAFs induced EMT via CXCL12/CXCR4 axis, thus enhancing metastasis.

### Mscs as Foes of Cancer

Despite the reports that MSCs facilitate tumor development, a number of observations contradictorily suggest that MSCs suppress tumorigenesis.

## Inhibition of Angiogenesis

Intriguingly enough, it has been reported that MSCs also impair angiogenesis under certain conditions. A study demonstrated that administration of human bone marrow MSCs strongly inhibited vascular network formation through the VE-cadherin/ $\beta$ -catenin signaling pathway [54]. Otsu et al. [55] observed that MSCs isolated from rat and mouse bone marrow were able to damage capillary structures in a concentration-dependent manner. The data showed that MSCs intercalated between ECs, releasing reactive oxygen species which were cytotoxic to ECs. Moreover, they found that MSCs effectively abrogated growth of tumor vasculature in a melanoma model. Recent work demonstrated that co-administration of glioma cells and human bone marrow MSCs caused impairment of vascular density and tumor development [56]. The results exhibited reduced expression of PDGF-BB and IL-1 $\beta$  in this co-culture system, implying that the anti-tumor effect of MSCs might be related to suppression of angiogenesis by MSCs. Furthermore, mouse bone marrow MSC-derived EVs greatly down-regulated expression of VEGF in breast cancer cells, which led to inhibition of angiogenesis *in vitro* and *in vivo* [57]. The results demonstrated that MSC-derived EVs shuttled miR-16, a microRNA known to target VEGF, and miR-16 was implicated in the anti-angiogenic effect of MSC-derived EVs.

## Induction of Anti-Proliferation and Apoptosis

Some evidence indicates that MSCs can elicit anti-proliferation and apoptosis in cancer cells, thus suppressing tumor development. One study reported that systemically injected human bone marrow MSCs migrated toward tumor tissues and potently suppressed tumor progression in a Kaposi's sarcoma model [58]. The molecular mechanism underlying this tumor growth inhibitory effect of MSCs was involved in suppression of the AKT activity. Additionally, Qiao et al. [59] demonstrated that human MSCs inhibited the malignant characteristics of H7402 and HepG2 human liver cancer cell lines. In this study, they showed that conditioned medium from MSCs down-regulated expression of Bcl-2, c-Myc, PCNA, and surviving in tumors, which led to increased apoptosis. Interestingly, it has been reported that MSCs attenuate cell proliferation not only in solid tumors, but also in liquid tumors. Zhu et al. [60] observed that MSCs from human adipose tissue exerted inhibitory effects on proliferation of K562 human leukemia cell line and primary leukemic hematopoietic progenitors from patients. The authors found that DKK-1 released from MSCs negatively regulated the WNT signaling pathway, highlighting anti-proliferation effects of MSC on tumors. Lu et al. [61] explored the growth inhibitory impact of bone marrow-derived MSCs on tumor cells using H22 murine hepatoma, YAC-1 and EL-4 lymphoma, and INS-1 rat insulinoma cell lines. The results showed that MSCs up-regulated p21 and caspase-3 in these different types of cancer cells, inducing G0/G1 phase arrest and apoptosis of cancer cells. In addition, Bruno et al. [62] demonstrated that human bone marrow MSC-derived EVs inhibited various types of tumor progression *in vitro* and *in vivo*. They treated MSC-derived EVs with HepG2 hepatoma, Kaposi's sarcoma, and Skov-3 ovarian tumor cell line and MSC-derived EVs elicited cell cycle arrest in all cell lines and increased apoptosis in HepG2 and Kaposi's cells and necrosis in Skov-3 cells.

## Suppression of EMT and Metastasis

In direct contradiction to the studies reporting that MSCs trigger EMT and metastasis, a couple of studies have suggested that MSCs may inhibit EMT and metastasis. Chang et al. [63] showed that human bone marrow MSCs cultured with various growth factors, including bFGF, EGF, and ascorbic acid 2-phosphate, increased the secretion of HGF. HGF from the conditioned MSCs specifically counteracted the actions of TGF- $\beta$ 1, thus suppressing TGF- $\beta$ 1-induced EMT in a chronic kidney disease model. Furthermore, Li et al. [64] evaluated the effect of human bone marrow MSCs on hepatocellular carcinoma (HCC) using MHCC97-H cells which have a high metastatic potential. Surprisingly, the authors found that MSCs significantly enhanced proliferation of HCC cells, but inhibited their invasiveness and metastasis *in vitro* and *in vivo* by down-regulating expression of TGF- $\beta$ 1 and MMP-2.

## Do Mscs Support or Suppress Cancer?

As discussed above, MSCs have been regarded as a double-edged sword in terms of carcinogenesis, suggesting that we are still far from understanding the myriad functions of this jack-of-all-trades. Interestingly, one study even reported that human bone marrow MSCs induced apoptosis of tumor cells *in vitro*, but promoted tumor growth *in vivo* [65]. Thus, it seems reasonable to say that MSCs can be pro- or anti-tumorigenic in a context-dependent manner even though some review papers are somewhat biased to one viewpoint. Indeed, this discrepancy within the literature might be explained by some factors. First, the findings that MSCs secrete a wide variety of growth factors, cytokines, and EVs containing bioactive molecules might account for the inconsistent results. Multifunctional MSCs interact with tumors and their neighboring cells, such as immune cells, in a myriad of ways. Thus, it is likely that their impact on tumor progression cannot be simplified. Secondly, artificial experimental conditions and technical issues may lead to the different results in the studies. Obviously, the number of the MSCs systematically injected or transplanted in many studies is not physiologically relevant. Additionally, the injection timing of MSCs varies greatly. Thirdly, MSCs are heterogeneous. As noted before, MSCs can be obtained from different sources, conferring variability in MSCs. It is also possible that the characteristics of MSCs alter during continuous subcultivation, contributing to the conflicting findings. Finally, tissue- and species-specific effects should not be excluded.

## Conclusions

The tumor microenvironment is comprised of a variety of cells. Intercellular interaction between cancer and adjacent cells in the tumor tissues has grabbed the attention of the research community. Based on the accumulating evidence that MSCs migrate and incorporate into tumor tissues, a great deal of research has focused on the role of MSCs in the tumor microenvironment. To date, the role of MSCs in carcinogenesis has been tested in a variety of experimental models and no simple principle can be applied. Whether MSCs support or suppress tumorigenesis, however, it is clear that MSCs exert profound effects on the tumor microenvironment. Thus, in order to harness MSCs as a novel therapeutic strategy, a more careful approach is needed.

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## Competing Interest Statement

Author has no conflict of interest

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