

Review Article



Bidirectional and Opposite Effects of Naïve Mesenchymal Stem Cells on Tumor Growth and Progression

Faramarz Rahmatizadeh^{1,2,3}, Shiva Gholizadeh-Ghaleh Aziz⁴, Khodadad Khodadadi⁵, Maryam Lale Ataei^{2,6}, Esmail Ebrahimie^{7,8}, Jafar Soleimani Rad^{6,9*}, Maryam Pashaiasl^{3,6,9,10*}

¹Department of Molecular Medicine, Faculty of Advanced Medical Science, Tabriz University of Medical Science, Tabriz, Iran.

²Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.

³Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

⁴Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran.

⁵Murdoch Children's Research Institute, Royal Children's Hospital, The University of Melbourne, Melbourne, Australia.

⁶Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

⁷Adelaide Medical School, University of Adelaide, Adelaide, Australia.

⁸School of Animal and Veterinary Sciences, University of Adelaide, Adelaide, Australia.

⁹Department of Reproductive Biology, Faculty of Advanced Medical Science, Tabriz University of Medical Science, Tabriz, Iran.

¹⁰Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Article info

Article History:

Received: 17 May 2019

Revised: 31 July 2019

Accepted: 13 Aug. 2019

published: 24 Oct. 2019

Keywords:

- Mesenchymal stem cells
- Dual effects
- Bidirectional effects
- Anti-tumor
- Cell-cell interactions
- Secretory factors
- Tumor progression

Abstract

Cancer has long been considered as a heterogeneous population of uncontrolled proliferation of different transformed cell types. The recent findings concerning tumorigenesis have highlighted the fact that tumors can progress through tight relationships among tumor cells, cellular, and non-cellular components which are present within tumor tissues. In recent years, studies have shown that mesenchymal stem cells (MSCs) are essential components of non-tumor cells within the tumor tissues that can strongly affect tumor development. Several forms of MSCs have been identified within tumor stroma. Naïve (innate) mesenchymal stem cells (N-MSCs) derived from different sources are mostly recruited into the tumor stroma. N-MSCs exert dual and divergent effects on tumor growth through different conditions and factors such as toll-like receptor priming (TLR-priming), which is the primary underlying causes of opposite effects. Moreover, MSCs also have the contrary effects by various molecular mechanisms relying on direct cell-to-cell connections and indirect communications through the autocrine, paracrine routes, and tumor microenvironment (TME).

Overall, cell-based therapies will hold great promise to provide novel anticancer treatments. However, the application of intact MSCs in cancer treatment can theoretically cause adverse clinical outcomes. It is essential that to extensively analysis the effective factors and conditions in which underlying mechanisms are adopted by MSCs when encounter with cancer.

The aim is to review the cellular and molecular mechanisms underlying the dual effects of MSCs followed by the importance of polarization of MSCs through priming of TLRs.

Introduction

Mesenchymal stem cells (MSCs) are multipotent, self-renewing, and heterogeneous population of mesenchymal progenitor cells which exhibit at least three main characteristics based upon the minimal definition criteria recommended to define human MSCs by The International Society for Cell and Gene Therapy (ISCT, Europe), approved in 2006 and outlined as below:

First, MSCs have a physical property of plastic adherence when they are maintained under defined culture conditions.

Second, MSCs exhibit specific cell surface markers like CD73, CD90, CD105, and negative expression of CD14, CD45, CD34, and human leukocyte antigen (HLA)- DR.

Third, MSCs also have an intrinsic ability to differentiate into chondroblasts, adipocytes, and osteoblasts in vitro conditions.^{1,2}

So far, MSCs have been derived and purified from many different sources such as embryonic/fetal and non-embryonic sources of connective tissues.³⁻⁵

Indeed, MSCs obtained from different sources have shown many different behavioral and biological

*Corresponding Authors: Jafar Soleimani Rad and Maryam Pashaiasl, Tel: +98 41 33348573, Email: Soleimanirj@yahoo.com, Pashaim@tbzmed.ac.ir

characteristics that might be more closely related to their origins.⁶⁻⁹ The most obvious biological differences among MSCs are listed below:

They may present different cell surface marker profiles, genetic diversities, broad differentiation potential, and may show different proliferation rates. MSCs have an inherent tendency to migrate toward inflammatory sites, primary tumor sites and metastatic foci via chemotaxis.^{10,11} Only a minor subpopulation of non-tumor cells within the tumor tissues are MSCs and this has been estimated to be about 0.01-1.1 percent of the total number of cells.¹² Despite the fact that, almost a small number of MSCs are present in the tumor tissues they have important role in determining the fate of tumor cells.^{13,14} There are three main types of MSCs within tumor stroma including: (1) N- MSCs or normal MSCs, hereinafter referred to as MSCs, (2) Tumor tissue-educated MSCs or tumor associated MSCs (TA-MSCs), and (3) cancer-associated fibroblasts (CAFs).^{15,16}

Wide range of heterogeneity also exists among different tumor tissues. Hence, not only host individuals have unique conditions but also each tumor type has its own unique characteristics^{17,18} that may be altered dynamically at different stages of tumor progression.¹⁹ The distinct differences among different types of tumors are termed inter- and intra- tumor heterogeneity that have a correlation with genetic and epigenetic modifications in tumor cells.²⁰ Taken together, during tumor progression the heterogeneous and innate population of MSCs (which has unique properties and functions) can engraft within tumors, and consequently interact with highly heterogeneous components of tumor microenvironments (TMEs). These components are made of various different combinations of tumor tissues such as bulk tumor cells as well as non-tumor-initiating cells. Therefore, it has been predicted that the different MSCs may exert multiple effects on various tumor types.²¹⁻²⁴ Moreover, previous experimental results have shown that MSCs have dual effects on tumor growth and progression. Thus, they may exhibit pro- and anti-tumorigenic activities when confronting with cancers through cytokines, chemokines, growth factors, and many different factors indirectly or via direct cell-to-cell connections.²⁵⁻³² Obviously, there are so many variables which may subsequently determine the functional effects of MSCs on tumor development.³³ For instance, variations that exist in MSCs isolated from different sources, the cross-contamination of MSCs with cancer cell lines, their behavior in a time and concentration dependent manner, the effects of route of MSC administration, the influence of different toll-like receptors (TLRs) on MSCs, and predicting MSC behaviors at different time points are more important than other conditions and factors.³³⁻³⁷ As a result, the dual and opposite effects of MSCs on tumor progression can restrict the utilization of these cells in the field of cell-based cancer therapies.³⁸ In order to overcome the major impediments to identify definitive solutions for cell-based

cancer therapies which are more effective, it is necessary to gain in depth the knowledge of the possible underlying molecular mechanisms through which MSCs can exert their opposite effects on tumor cells. Moreover, we have emphasized the importance of a new paradigm which can promote the anti-tumor effects of MSCs via stimulation of TLR4. This concept has indicated that TLR4-priming results in polarization of MSCs into a pro-inflammatory phenotype or MSC 1 which has shown to exhibit anti-tumor properties.^{33,39}

Tumor-promoting effects of MSCs

There is empirical evidence to demonstrate that MSCs pose supportive effects on tumor growth and progression.^{40,41} These cells have been identified that can promote tumor growth and progression in mouse models of gastric cancer, gliomas, colon cancer, subcutaneous breast tumors, prostate cancer, ovarian cancer, head and neck cancer *in vitro*.^{23,42-49} Besides, the supportive effects of MSCs (through using different molecular mechanisms) have an impact on all three major steps of tumorigenesis process which consists of initiation, promotion, and progression.⁴¹

The promotion of tumor growth by modulating immune responses

MSCs derived from various sources have a profound impact on innate and adaptive immune responses that finally may result in the promotion of tumor progression.⁵⁰ The regulatory effects of MSCs are exerted on immune responses through direct cell-cell communication and indirectly by the release of particular secreted factors such as nitric oxide (NO), transforming growth factor beta (TGF- β), prostaglandin E2 (PGE2), Interleukin (IL)-6, indoleamine-2, 3-dioxygenase (IDO), interleukin (IL)-10, and HLA-G5 (Figure 1).⁵¹⁻⁵⁶

Tumor-associated macrophages (TAMs) are considered as the decisive components of TME that have an influence on immune responses and might be involved in tumor-related inflammation.⁵⁷ TAMs have at least two different states of polarization in the TME including the classically activated M1 macrophage phenotype and alternatively activated M2 macrophage phenotype.⁵⁸ The polarization of TAMs can be derived toward an M1-like phenotype that exerts noticeable pro-inflammatory and anti-tumor activities. On the contrary, when TAMs switch to the M2 phenotype display pro-tumor activities and may be involved in the resolution of tumor inflammation. MSCs can reciprocally modulate the polarization of TAMs toward the M2 phenotype that can promote tumor progression.⁵⁹ The other effects of MSCs on innate immune cells that are associated with the enhancement of tumor progression include reduction in proliferation, differentiation, activation, and functions of natural killer (NK) cells through expression of PGE2, TGF- β 1, and IDO.⁶⁰ Also, cytokine-activated MSCs can suppress

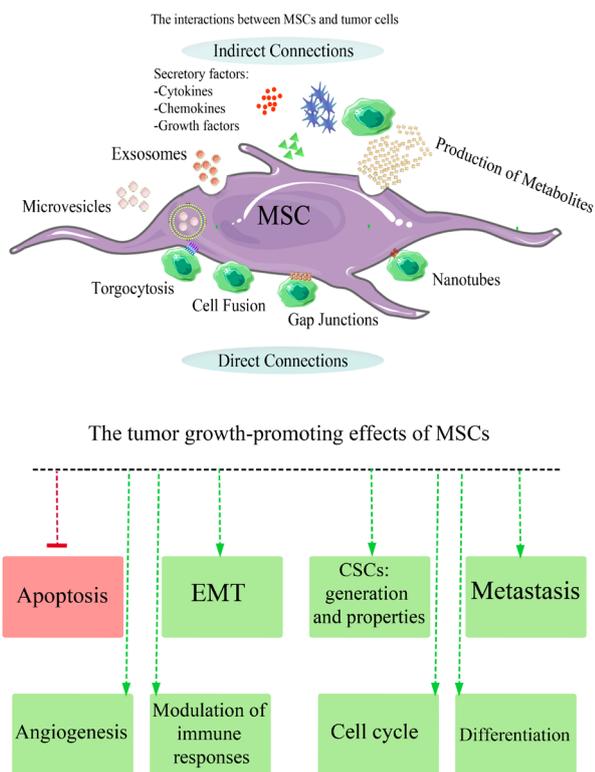


Figure 1. Different types of communication between MSCs and tumor cells and various mechanisms adopted by these cells to promote tumor growth and progression directly and indirectly. EMT, Epithelial –to– Mesenchymal transition; CSCs, Cancer Stem cells; MSCs, Mesenchymal Stem cells.

maturation, migration, and antigen-presentation capacity of monocyte derived dendritic cells.^{51,61,62} MSCs can block degranulation of the mast cells and prevent oxidative burst and apoptosis of human neutrophil.⁶³

Additionally, MSCs are able to modulate adaptive immune responses and promote the tumor progression through multiple mechanisms.⁶⁴ These cells have significant effects on T-lymphocytes and the induction of T-cell clonal energy. In this regard, MSCs also inhibit both CD4+ and CD8+ T-lymphocyte proliferation through direct contact. These cells also secrete a large number of different growth factors that result in cell cycle arrest in G1/G0 phase. MSCs not only can reduce the number of CD8+ and CD4+ T lymphocytes but also inhibit the production of interferon-alpha (IFN- α), interferon-gamma (IFN- γ), and interleukin (IL)-1 which are secreted by T-cells.^{61,65-70} However, MSCs do not exert their inhibitory effects on CD4+ T-cells which are activated through IFN- γ .⁷¹ Programmed cell death-1 (PD-1) pathway plays a critical role in regulating T-cell homeostasis and activation. These cells can directly activate the PD-1 pathway via cell-to-cell communication between T-cells and MSCs or indirectly through secretion of PD-1 specific ligands including B7-H1 (PD-L1/CD274) and B7-DC (PD-L2/CD273). The lineages are able to suppress CD4+ T-cells, downregulate IL-2, induce irreversible hyporesponsive state and cell death.⁷² MSCs also reduce the number of

T-cells through expression of Fas ligand (FasL)⁷³ (Figure 1) and are capable of suppressing the activation of CTLs and skew the differentiation pattern of naïve CD4+ T-cells (Th0) into T-helper type1 cells (Th1), T-helper type 2 cells (Th2), and T-helper type 17 cells (Th17) that finally result in the production of Th2 cells and enhanced the release of IL-4.^{74,75} In addition, MSCs may help to improve the production of CD8+ or CD4+ regulatory T-cells (Tregs).^{52,76} Taken together, they skew the Th1/Th2 cytokine balance toward Th2 (or an anti-inflammatory state) in tumor stroma.^{77,78} Furthermore, MSCs showed inhibition effects on multiple aspects of B lymphocyte activity including proliferation, functions, chemokine receptor expression patterns, and differentiation into antibody-secreting cells.^{79,80}

Differentiation and transdifferentiation of MSCs into other cell lineages

The tumor mass consists of a highly diverse and heterogeneous cell population include bulk tumor cells and tumor-associated stromal cells (TASCs)⁸¹ that plays a significant role in tumor progression.⁸² MSCs have capability to differentiate into various mesenchymal lineage cell lines (Figure 1).⁸³⁻⁸⁵ For instance, MSCs are one of the sources of CAFs and it has been estimated that approximately less than 20 percent of CAFs may be originated from differentiation of MSCs.⁸⁶ In addition, CAFs are able to support tumor growth and angiogenesis by producing stromal cell-derived factor-1 (SDF-1) and increasing the recruitment of endothelial precursor cells into the tumor site.^{87,88} After differentiation of MSCs into CAFs, the CAFs can enhance tumor progression and metastasis by contributing to remodeling of extracellular matrix (ECM) and inducing epithelial-to-mesenchymal transition (EMT) (Figure 1).⁸⁹

Moreover, MSCs have also been shown to differentiate into other stromal cell lines such as pericytes and endothelial cells. They can rarely undergo neoplastic transformation which in turn may induce angiogenesis and tumor progression.⁹⁰

Induction of epithelial-to-mesenchymal transition

EMT process is a biological phenomenon that plays a crucial role in invasion, metastasis as well as acquisition of chemotherapy and apoptosis resistance in tumor cells.⁹¹ There are highly sophisticated networks of biological signaling pathways involved in EMT process including Notch, Hedgehog, nuclear factor κ -light-chain enhancer of activated B lymphocytes (NF- κ B), TGF- β , and Wnt/Wingless (Wg) signaling pathway.⁹²⁻⁹⁵ Moreover, EMT process can be facilitated by the presence of inflammatory mediators and cells such as pro-inflammatory and inflammatory cytokines or the presence of reactive oxygen species (ROS) that are induced under hypoxic conditions in tumor tissues. In this regard, the existence of hypoxia provides an opportunity to induce the formation

of ROS.⁹⁶ MSCs which are recruited into tumor-associated stroma (TAS) can also stimulate ROS formation and have a significant effect on EMT process.⁹⁷ MSCs can facilitate EMT process in tumors through their direct and indirect interaction with tumor cells.^{98,99} For instance, an *in vitro* direct co-culture experiment between colon cancer cells and MSCs has indicated that the crosstalk between MSCs and tumor cells via direct contact results in the overexpression of EMT-related genes such as fibronectin (FN), secreted protein, acidic and rich in cysteine, galectin-1, but these results are not obtained from indirect co-culture conditions.¹⁰⁰

MSCs as well as TASCs can secrete a variety of paracrine factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and TGF- β that can significantly enhance or stimulate the EMT process (Figure 1).^{90,101-103} One of the most significant signaling pathways that is classically associated with EMT process includes the TGF- β / mothers against decapentaplegic (SMAD)/ lymphoid enhancer-binding factor (LEF)/ PDGF axis.¹⁰⁴

The tumor-associated fibroblast (TAFs)/CAFs as well as myofibroblasts can originate from MSCs and play an important role in inducing and maintaining the inflammatory responses through releasing of pro-inflammatory mediators leading to the activation of EMT process (Figure 1).^{81,105} In addition, CAFs have been shown markedly to exert higher expression of fibroblast growth factor receptor 4 (FGFR4) by which induce EMT process in colorectal cancer cell lines.^{106,107}

Interestingly, another possible mechanism which may be involved in EMT process is the spontaneous hybridization between MSCs and tumor cells (Figure 1). Recent investigations have suggested that non-small-cell lung carcinoma (NSCLC) cells after co-culturing with human bone marrow-derived MSCs (hBM-MSCs) are capable of producing hybrid cells *in vitro*. The hybrid cells derived from hybridization between NSCLC and MSCs, exhibit similar biological properties of both EMT and stem cell-like cells.^{108,109}

Effects of MSCs on cancer stem cells

Various studies have found strong evidence for the existence of cancer stem cells (CSCs).¹¹⁰ According to this view, it is widely accepted that CSCs can be isolated from various hematological malignancies and solid tumors.^{111,112} CSCs are rare cells and share many characteristics with MSCs including self-renewal, stemness-related gene expression profiles, the capability of differentiation, the use of common signaling pathways, and the creation of stem cell niches.^{113,114} CSCs are able to differentiate and transdifferentiate into endothelial cells, other types of TASCs, and probably respective tumor types. They also exhibit high metastatic potential and are associated with the chemoradiation resistance. It is suggested that

CSCs may be responsible for an increased rate of tumor recurrence.^{113,115}

MSCs have a potent effect on the promotion of expansion and modification of CSCs and by which can enhance their biological functions. In this regard, it has demonstrated that co-culturing MSCs with gastric cancer cells led to an increase in the percentage of CD133-positive cells in the cultures.^{99,116-118} Similarly, it has concluded that after co-culturing MSCs with breast cancer cells, the ALDEFLUOR-positive cells (aldehyde dehydrogenases, ALDHs are markers for cancer stem-like cells in multiple tumor types) increased significantly in culture. They suggested that malignant cell-derived IL-1 resulted in a marked increase in PGE2 secreted by MSCs. The PGE2 and IL-1 were able to secrete synergistically several cytokines by MSCs. The secreted cytokines that was accompanied with PGE2 could promote the activation of beta-catenin (β -catenin) in tumor cells that finally led to CSCs generation.^{116,118} Both TA-MSCs and N-MSCs could create new CSCs by applying the above mentioned procedures.¹¹⁹ In addition, MSCs could secrete a wide array of regulatory molecules such as CXCL1, 5, 6, 7, and 8 which are ligands for the chemokine receptor CXCR2. It is noteworthy that, the CXCR2/CXCR2 ligand biological axis plays an important role in supporting the CSCs generation.¹¹⁶ Moreover, IL-6, CCL5, bone morphogenetic proteins, and also the expression of chemokine receptors CXCR4 and CXCR7 have also been implicated in the creation of CSCs in various types of cancer.^{120,121} MSCs also express several microRNA (miRNA) profiles which can be involved in the expansion of CSCs¹²² including MiR-302, MiR-21, MiR-106b-25, MiR-181, MiR-495, MiR9/9*, MiR-22, MiR-328-3p, MiR-214, MiR-130b, and MiR-199a-3p (Figure 2).^{123,124}

Stimulation of tumor metastasis

MSCs can promote tumor growth, dormancy, invasion, and their metastatic process through indirect and direct connections.¹²⁵⁻¹²⁷ with tumor cells and stromal components of the tumor. The reciprocal interaction between tumor cells and MSCs may induce MSCs to express ligands of CCR2 and CXCR2, and also CCL5.¹²⁸ Among the chemokine/ chemokine receptors that are stimulated by MSCs, the CCL2/CCR2 axis has a crucial role in acquisition of metastatic properties by tumor cells. MSC-derived CCL2 is an important chemokine receptor-ligand that mediates the recruitment of CCR2+ neutrophils into the tumor stroma.¹²⁸ After initial recruitment the interaction between CCR2+ neutrophils and tumor cells leads to a significant increase in metastasis-related gene expression such as CXCR4, CXCR7, matrix metalloproteinase (MMP)-13, MMP-12, IL-6, and TGF- β in tumor cells.^{128,129}

Interestingly, tumor cells cannot orient themselves toward metastatic sites.¹²⁸ Indeed, during the metastatic process tumor fragments which consist of the bulk tumor cells, TASCs, and MSCs are held together to form the

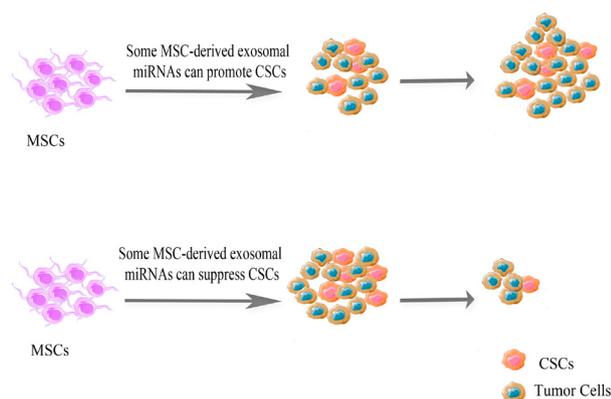


Figure 2. Mesenchymal stem cells play a pivotal role both directly or indirectly in tumor growth and progression, via regulation of cancer stem cell generation and their properties. For instance, MSCs indirectly regulate cancer stem cell niches via mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) and also the release of cytokines such as IL-6, IL-8, IL-12, and gremlin. CSCs, cancer stem cells; MSCs, mesenchymal stem cells.

pre-metastatic clusters. Moreover, the MSCs which are retrieved from the metastatic sites express CAF marker genes including alpha-smooth muscle actin, SDF-1- α , tenascin-C, MMP-9, and MMP-2.^{130,131}

Induction of anti-apoptotic effects in tumor cells

Emerging evidence indicates that tumor progression is a process that is accompanied by adaptation to anaerobic conditions. Indeed, chronic inflammatory status, hypoxia, acidic pH conditions, and nutrient deprivation have been observed during the tumor development.¹³²⁻¹³⁴ Under stress conditions MSCs are capable to maintain their primitive characters and functions such as self-renewal capacity and differentiation potentials by the activation of autophagy pathways. MSCs are able to secrete a number of pro-survival and anti-apoptotic factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-2, insulin like growth factor (IGF)-1, PDGF, SDF-1- α , basic fibroblast growth factor (bFGF), HGF, IGF binding protein-2 (IGFBP) -2, stanniocalcin-1 (STC-1), and NO (Figure 1).¹³⁵⁻¹⁴⁰ Among them the VEGF family which is known as a survival factor can act by increasing the B-cell lymphoma 2 (BCL-2)/BCL-2 associated X protein (BAX) ratio in tumor cells.¹⁴¹ In a similar manner, bFGF can also enhance BCL-2 expression.¹⁴² Hypoxia induce MSCs to secrete various factors including VEGF, IGF-1, HGF, and bFGF which may enhance tumor cell survival by the activation of angiogenesis and exerting anti-apoptotic effects.^{143,144} On the other hand, an increase in PDGF and TGF- β expression is usually associated with upregulation of VEGF and bFGF genes in tumor cells.¹³⁷ Furthermore, MSC-derived IL-6 exerts chiefly an anti-apoptotic effect on cancer cells and also may enhance tumor resistance to chemotherapy through activation of signal transducers and activators of transcription 3, and upregulation of BCL-2.¹⁴⁵ In this regard, the evidence

obtained from earlier studies that have been carried out on lung cancers (originating from epithelial tissues) suggests that STC-1 can inhibit apoptosis in tumor cells and promote tumor cell survival. The presence of STC-1 in tumor stroma is both necessary and sufficient for the inhibition of apoptosis in tumor cells. MSCs can also prevent apoptosis through the release of NO in a dose-related manner. Therefore, NO can inhibit the apoptosis in tumor cells at a relatively low concentration. Conversely, a high concentration of NO induces apoptosis in tumor cells.¹⁴⁶ Furthermore, exosomes generated by MSCs can induce tumor progression by inhibiting tumor cell death. It has been established that apoptosis-related miRNAs, which are transferred from MSCs, are critical regulators of tumor cell apoptosis (Figure 1). In this respect, several studies have revealed that miRNAs produced by MSCs are capable of predicting the clinical outcomes in several tumor types such as colorectal cancers, breast cancers, and gastric cancers through inhibition of apoptosis in tumor cells.¹⁴⁷

Induction of angiogenesis and neovascularization in tumors

Tumor angiogenesis and neovascularization are complex multistep processes which occur during tumor progression and can facilitate tumor growth and metastasis.¹⁴⁸ MSCs because of their potential to secrete wide variety of growth factors, cytokines and chemokines can effectively promote/support angiogenesis through several mechanisms include:

1. MSCs are capable to differentiate into CAFs, smooth muscle cells (SMCs), endothelial cells, and pericytes (nevertheless, transition of MSCs to endothelial cells remains controversial).^{149,150}
2. MSCs are able to release a large number of secretory factors to stimulate the tumor angiogenesis in a paracrine manner have been shown markedly to exert higher.
3. MSCs could induce angiogenesis through MSC-derived miRNAs.^{152,153}
4. MSCs interact with multiple cell types in TME which can potentially contribute to tumor angiogenesis (Figure 1).^{151,154-162}

The new studies have emphasized that MSCs which are located in perivascular niches share several phenotypic and functional characteristics with pericytes.¹⁶¹ Besides, accumulating evidence suggests that MSCs can also increase angiogenesis and contribute to vascular remodeling during the formation of tumor vasculature.^{163,164} The other emerging role of MSCs that facilitate tumor angiogenesis and malignant progression is the secretion of cytokines, chemokines, and growth factors by MSCs which are involved in angiogenesis process such as VEGF, FGF-2, HGF, interleukin (IL)-8, TGF- β , MMPs, CXCL8, CXCL2.^{161,165,166}

Furthermore, MSCs can also enhance tumor neovascularization through differentiation into CAFs,

recruitment of macrophages, and production of extracellular vesicles (Figure 1).^{165,167}

Interestingly, empirical evidence has revealed that a particular vessel region which exists in human blood vessels. This vascular mural zone, also referred to as vasculogenic zone, is located at the outer elastic membrane just at the border between tunica adventitia and tunica media which contains a population of vascular wall-resident CD44+ multipotent stem cells of mesenchymal origin (VW-MPSCs). The VW-MPSCs seem to represent the “first line” cells that migrate from their niches to tumor stroma. Besides, the VW-MPSCs are able to differentiate into vascular smooth muscle cells as well as pericytes.¹⁶⁷⁻¹⁶⁹

The findings indicate that MSCs express a primary receptor also known as the vascular endothelial growth factor receptor 1 (VEGFR1 or Flt-1) on their surface, which is involved in promoting tumor angiogenesis.¹⁷⁰ Implantation of BM derived MSCs and AT derived MSCs presented controversial outcome in which AT-MSCs stimulate tumor growth and metastatic aggression of cancer while BM-MSCs transplantation presented different effects. Indigenous MSCs may act as supporter of tumor growth after surgical resection through regeneration effect of cells and relapse the tumor.¹⁷¹

Inhibitory effects of mesenchymal stromal/stem cells on tumor growth

Although a large number of results have shown that MSCs can significantly support tumor growth, progression, and metastasis some of the observations suggest that these cells can exert multiple suppressive effects on tumor development (Figure 3; Table 1 and 2).^{23,172}

The suppressive effects of MSCs have been reported in several human tumor types such as liver cancers, leukaemia, Kaposi's sarcoma, pancreatic cancer, and melanoma. Anti-tumor property of MSCs function through exosomes which is derived from cells and also these cells could be used as an anti-tumor reagent carrier through the ability of migration to tumor site and integrate into tumor (Table 1).^{26,28,120,173-177}

The induction of apoptosis in tumor cells

MSCs can induce apoptosis in different tumor cells through direct or indirect pathways (Figure 3).^{173,203} For instance, MSC-conditioned media (MSC-CM) can induce both apoptosis and autophagy in tumor cells²⁰⁷ (Tables 1 and 2). Sandra et al²⁰⁸ provided compelling evidence that MSC-derived secretome could reduce cell proliferation of the human cervical cancer HeLa cell line in a time and concentration-dependent manner by the induction of tumor cell apoptosis.²⁰⁸ Moreover, human umbilical cord-derived mesenchymal stromal/stem cells (hUC-MSCs) display pro-apoptotic and anti-proliferative effects on human prostatic carcinoma cell line PC3 through direct and indirect communication in an in vitro co-culture system that accompanied by activation of c-Jun N-terminal

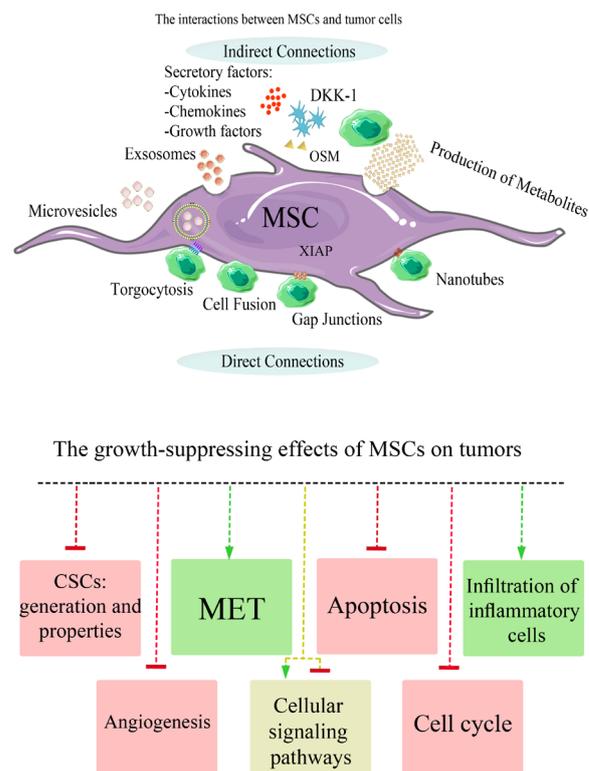


Figure 3. Different types of communication between MSCs and tumor cells and several different mechanisms adopted by MSCs to suppress tumor growth and progression through direct and indirect pathways. Some secreted factors such as MiR-122, IL-15, MiR-16, and OSM released by MSCs are capable of indirectly suppressing tumor progression through varying mechanisms. MET, mesenchymal-to-epithelial transition; XIAP, X chromosome-linked Inhibitor of Apoptosis Protein; DKK-1, Dickkopf-related protein 1; MSCs, mesenchymal stem cells.

kinase (JNK) and inhibition of phosphoinositide 3-kinase/protein kinase B, also known as Akt signaling pathways.²⁰⁹ It has reported that the modification of MSCs with IFN- γ causes a high-level production of functional IFN- γ that can result in a high-level expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/Apo-2 ligand (Apo2L) and through which MSCs can exhibit pro-apoptotic effects on tumor cells.²¹⁰ Furthermore, human umbilical cord blood-derived stromal/stem cells (hUCB-MSCs) induce apoptosis in U257 glioblastoma cell line through depletion of X-chromosome linked inhibitor of apoptosis protein (XIAP) which in turn lead to the activation of caspase-9/caspase-3 pathway in tumor cell lines.²¹¹

Inhibition of cell cycle progression

The previous studies have elucidated that MSCs isolated from various sources including breast tissue, human palatine tonsils, and adipose tissue exert the inhibitory effects on tumor cell proliferation by inducing cell-cycle arrest in G0/G1 phase (Figure 3; Table 1 and 2).^{175,212} In addition, *ex vivo* expansion of human amniotic mesenchymal tissue cells (hAMTCs) through co-

Table 1. Anticancer activities of the miRNAs which are detected in mesenchymal stem cell-derived extra cellular vesicles

Types of cancer	Donors of extracellular vesicles-derived miRNAs	MicroRNAs	Target cells	Pathways which are involved in suppressive effects	Therapeutic effects	References
Mouse breast cancer	MSC-derived exosomes	MiR- 16	Mouse mammary tumor cell line 4T1	Inhibition of angiogenesis through downregulation of VEGF	Inhibition of tumor growth	178
HCC	hAT -MSC-derived exosomes	MiR-122	HepG2 ^a	-Reduction in ADAM1 ^b , IGF-1R ^c , and CCNG1 ^d expression levels -Apoptosis induction -Cell cycle blocking	Sensitization of malignant cells to chemotherapy	179
-HCC -lymphoma -Glioblastoma	- HLSCs ^e - MicroRNAs	MiR-31, MiR-451, MiR-223, MiR-122, MiR-125b, MiR-24, MiR-214	HepG2	-Reduction of tumor cells proliferation -Proapoptotic activities of: MiR-451, MiR-31, MiR-125b, MiR-24, MiR-223 which induces resistance to chemotherapy mediated by MDR1/P-gp ^f	-Inhibition of tumor growth -Reduction in survival of tumor cells	180
Breast cancer	hBM-MSC-EVs ^g	MiR-23b	Bone marrow –derived metastatic human breast cancer cell line BM2	-Inhibition of MARCKS ^h promoter which is involved in cell-cycle progression -The prevention of cancer cell motility -The inhibition of cancer cell proliferation	-Inhibition of tumor growth -A decrease in stem cell-like surface markers -Inhibition of invasion -An increase in resistance to chemotherapy	181
Glioma	MSCs	MiR-145 and MiR-124	-Human glioma cell lines A172 and U87 - GSCs ⁱ	Downregulation of SCP-1 ^m and SOX2 ⁿ	A decrease in glioma cell migration and self-renewal of GSLCs ^o	182
Osteosarcoma	hBM-MSCs	MiR-143	Human osteosarcoma cell line 143B	-The delivery of MiR-143 to target tumor cells - The reduction of osteosarcoma cell migration	Reduction of metastasis	183
Glioma	MSC-EVs: MiR-146	MiR-146b	Human glioma cells	The binding of MiR-146b to EGFR ^p mRNA and the inhibition of EGFR expression	Reduction of human glioma xenograft growth, invasion, and migration	184
MM ^q	BM-MSCs	micro RNA	Human multiple myeloma cell lines U266 and ARP-1	Inhibition of eIF1 ^r and eIF4G1 ^s (Involvement of transcription factors such as: NF-kB ^t , c-Myc ^u , CCND1 ^v , HIF1α ^w , and Smad5 ^x) -Inhibition of autophagy and tumor cell proliferation	Inhibition of tumor cells	185
-HCC -Kaposi's sarcoma -ovarian cancer	MSCs	MSC-EVs	-HepG2 -Kaposi's sarcoma cell lines -Human ovarian carcinoma cell line SKOV-3	-Go/G1 cell cycle arrest -Apoptosis induction -Necrosis in SKOV3 cells	Inhibition of tumor growth	186

Table 1. Continued

Types of cancer	Donors of extracellular vesicles-derived miRNAs	MicroRNAs	Target cells	Pathways which are involved in suppressive effects	Therapeutic effects	References
B-CLL ^y	MSCs	MiR-15/-16 family (MiR 15a/MiR-16-1)	Targeting of BCL-2, MCL1 ^z , CCND1 gene -Anti-angiogenesis activities through Targeting VEGF-A ^{aa} and Akt3 ^{bb}	-Inhibition of tumor growth and progression	Under investigation	187-191
-pancreatic cancer -Breast cancer -Prostate cancer -Melanoma	MSCs	MiR-34	-Human melanoma cell line UACC-62 - p53 mutant pancreatic cancer cell line MIA PaCa-2 -Mutant p53 derived from metastasis of pancreatic cancer via cell-autonomous PDGFR Beta ^{cc} signaling pathway - Human pancreatic cancer cell line BxPC3 -Human breast carcinoma cell line MDA-MB-231	-Re-expression of CD44+ in prostate cancer -Inhibition of clonogenic tumor cell growth and invasion -Apoptosis induction -Blockage of cell cycle in G1 and G2/M phases - Silencing NOTCH signaling pathway causes the downregulation of BCL-2 -Suppression of cell proliferation	-Reduction of tumor growth -Sensitivity to chemotherapy and radiation -Reduction in survival of CSCs ^{dd} - There is probably no effect on melanoma	192
Prostate cancer	hBMMSCs	Let-7 MicroRNA	Cancer-associated MSCs which is co-cultured with human prostate cancer cell line PC3	Regulation of IL-6 expression and NF-kB in MSCs	There is probably an increase in Let-7 expression that cause the inhibition of tumor growth	193

^aHepG2, hepatocellular carcinoma cell line; ^bADAM1, A disintegrin and A metalloprotease domain 1; ^cIGF-1R, the human type 1 insulin-like growth factor receptor; ^dCCNG1, cyclin G1; ^eHLSCs, human liver stem cells; ^fMDR1, multidrug resistance protein 1 or P-glycoprotein; ^ghBMMSC-EVs, human bone marrow mesenchymal stemstromal cells derived extracellular vesicles ^hMARCKS, the myristoylated alanine-rich C-kinase substrate; ⁱGSCs, human glioma stem cells; ^jSCP-1, the human small c-terminal domain phosphatase 1; ^kSOX2, SRY (sex determining region Y)-box 2; ^lGSLCs, human glioma stem-like cells; ^mEGFR, the epidermal growth factor receptor; ⁿMM, multiple myeloma; ^oeIF1, eukaryotic translation initiation factor 1; ^peIF4G1, eukaryotic translation initiation factor 4G1; ^qNF-kB, nuclear factor kappa beta; ^rc-Myc, cellular myelocytomatosis oncogene; ^sCCND1, Cyclin D1 gene; ^tHIF1 α , hypoxia-inducible factor 1-alpha; ^uSmad5, mothers against decapentaplegic homolog 5 of the Drosophila gene; ^vB-CLL, B-cell chronic lymphocytic leukemia; ^wMCL1, myeloid cell leukemia sequence 1; ^xVEGF-A, vascular endothelial growth factor A; ^yAkt3, Akt serine/threonine kinase 3; ^zPDGFR Beta, platelet derived growth factor receptor beta; ^{aa}CSCs, cancer stem cells.

Table 2. Anti-tumor or anti-metastatic activity of MSC-secreted factors

Types of cancer	MSC donors and MSC products	The effective mediators	The target cells	The pathways and inflammatory mediators involved in the exertion of suppressive effects	The therapeutic effects	References
HCC	hf MSC-CM ^a	IGF ^b	HCC cell lines	A decrease in IGF-1R ^c activation and involvement of PI3K/Akt pathway; Cell cycle arrest	Inhibition of tumor growth and progression	194
Rat breast cancer	PMSCs ^d BMMSC-CM	DKK-1 ^e	Rat mammary tumor cell line	The blockage of Wnt/ β -catenin signaling pathway	Inhibition of tumor cell growth, migration and invasion	195
Pancreatic tumor	hUCB-MSCs ^f	IL-15	Murine pancreatic adenocarcinoma cell line Pan02 or Panc02	Tumor cell apoptosis; Immunomodulatory activity affected by accumulation of NK, and T- cell, the promotion of T-cell immune memory responses	Inhibition of tumor growth	196
LAC ^g , Melanoma	MSCs or MSC-CM	OSM ^h	LAC cell line	Down regulation of STAT1 ⁱ through inhibition of Nanog and Slug expressions; Cell- cycle inhibition; Enhancement of MET ^j process	Inhibition of tumor cell growth, invasion, and migration	197
Bladder tumor	hWJ-MSCs ^k	Unclear	Human bladder cancer cell line T24	Down regulation of Akt protein kinase; Phosphorylation and upregulation of cleaved caspase-3; Anti-proliferative and proapoptotic effect; Cell cycle arrest	Inhibition of tumor growth	198
Breast cancer	hUC-MSCs ^l	IL-18	Human breast carcinoma cell line MCF-7	Alteration in cell cycle	Inhibition of tumor cell growth, invasion and migration	199
HCC	hBM-MSCs ^m	IFN- β ⁿ	HepG2- and Huh7-based human hepatoma cell lines	An increase in p21 and p27 expression; The decrease in cyclin D1 expression lead to cell cycle modification; A decrease in RB ^o phosphorylation, suppression of Akt expression; Stimulation of FOXO3 ^p activity	Inhibition of tumor growth	200
Breast cancer	hAT-MSCs ^q , hATMSC-CM	IFN- β	Human breast carcinoma cell line MCF-7	The exertion of cytotoxic effects on breast cancer cells via STAT1 activation	Inhibition of tumor growth	201
Fibrosarcoma	MSCs	iNOS ^r	Fibrosarcoma cell line	Generation of NO or other cytotoxic agents and intermediate molecules	Inhibition of tumor growth or a significant tumor growth delay	202
Human mesothelioma, lung cancer, breast cancer, sarcomas, renal cancer, osteosarcoma, rhabdomyo sarcoma, ewing's sarcoma etc	MSCs	TRAIL ^s	-Human mesothelioma cell lines NCI-H2052,H2795, H2804, H2731, H2810,H2452, and H2869; Non small cell lung cancer cell lines NCI-H727, NCI-H460, A549, NCI-H23,and PC-9; Colon cancer cell lines COLO-205, RKO, and HT-29; Renal carcinoma cell lines RCC10 and HA7-RCC; Human oral squamous carcinomacell line H357	Apoptosis induction; The attenuation of inflammatory TME; Inhibition of angiogenesis	-Inhibition of tumor growth and progression	203-206

^a hfMSC-CM, human fetal mesenchymal stem cell-derived conditioned media; ^bIGFs, insulin like growth factors; ^cIGF1R, insulin like growth factor 1 receptor; ^dPMSCs, rib perichondrium mesenchymal stem stromal cells; ^eDKK-1 Dickkopf-related protein 1; ^fhUCB-MSCs, human umbilical cord blood-derived mesenchymal stem stromal cells; Nk, natural killer; ^gLAC, Lung adenocarcinoma; ^hOSM, oncostatin M; ⁱSTAT1, signal transducer and activator of transcription 1; ^jMET, mesenchymal-epithelial transition; ^khWJ-MSCs, Human Wharton's Jelly Derived Mesenchymal StemStromal cells; ^lhUC-MSCs, Human Umbilical Cord Blood-Derived Mesenchymal StemStromal cells; ^mhBM-MSCs, Human Bone Marrow-Derived Mesenchymal Stem Cells; ⁿIFN- β , interferon beta; ^oRB, retinoblastoma; ^pFOXO3, Human forkhead box protein O3; ^qhAT-MSCs, human adipose tissue-derived mesenchymal stem stromal cells; ^riNOS, inducible nitric oxide synthase; ^s trail, tumor necrosis factor-related apoptosis-inducing ligand

culturing with different types of human tumor cell lines have shown anti-proliferative effects on tumor cells. The microarray data have exhibited a significant decrease in expression of cyclin D1, cyclin E1, cyclin H, cyclin-dependent kinase (CDK) inhibitor p15^{INK4b}, and CDK inhibitor p21^{Waf1/Cip1} which is along with an increase in expression of retinoblastoma (RB) gene that finally leads to G0/G1 cell cycle arrest in tumor cells. Previous studies have also revealed that RB1 (p107) which normally acts as a transcriptional repressor markedly downregulates during G0/G1 cell cycle arrest.²¹³

Inhibition of specific cell signaling pathways

Multiple signal transduction pathways have been expected to be involved in tumor suppressive effects adopted by MSCs. The signaling pathways can be affected either directly or indirectly by MSCs. For instance, the PI3K/Akt signaling pathway has an important role in biological functions of tumor cells such as proliferation, apoptosis, differentiation, and oncogenic activities.^{90,214} Experiments have been shown that hUC-MSCs exert apoptotic and anti-proliferative effects on human prostatic carcinoma cell line PC3 via activation of JNK and inhibition of PI3K/Akt signaling pathways, in indirect and direct co-culture system.²⁰⁹ Strikingly, the NF- κ B family which is well known as a critical transcription factor related to the inflammation plays a critical role in tumor progression. It has already been shown that MSCs have also the ability to inhibit NF- κ B in tumor cells (Table 1).²¹⁴ Furthermore, MSCs can inhibit the proliferation-related signaling pathways through paracrine actions (Figure 3). For instance, MSCs can produce and release Dickkopf-related protein 1 (Dkk-1) which in turn inhibit the expression of Wnt downstream targets and/or effectors such as BCL-2, cellular myelocytomatosis oncogene (c-Myc), β -catenin, BAX, and survivin in tumor cells (Table 2).^{177,215}

Inhibition of tumor angiogenesis

There is considerable observational evidence that suggests MSCs have the ability to inhibit tumor angiogenesis and development. The anti-angiogenic effects of MSCs can be induced in a concentration-dependent manner in several tumor types.²¹⁵ An *in vitro* co-culture of BM-MSCs with melanoma cell lines has been shown that MSCs seem to produce locally cytotoxic molecules which are responsible for the blockage of capillary network formation, inhibition of tumor angiogenesis, and finally suppression of tumor growth and progression (Figure 3 and Table 1).^{215,216} It has also revealed that ROS generated by MSCs act like cytotoxic agents. Similarly, the oxidative stress directly affects gene expression profiles of vascular endothelial cells (VECs) that are accompanied by down-regulation of angiogenic cascade such as PDGF, platelet derived growth factor receptor (PDGFR), vascular endothelial-cadherin (VEC/VE-cadherin), and β -catenin. The process ultimately leads to the suppression of VEGF

expression in a concentration-dependent fashion. It is also noteworthy that the process happens through direct communication between MSCs and VECs that finally leads to the co-location of VE-cadherin/ β -catenin in the plasma membrane of endothelial cells.²¹⁵⁻²¹⁷

MSCs can also prevent formation of new blood vessels and tumor angiogenesis by the induction of apoptosis in vascular endothelial cells.²¹⁷

Induction of mesenchymal-epithelial transition

Emerging evidences suggest that the EMT is a critical and complex phenomenon that determines tumor invasiveness and the metastatic potentials of different types of tumors. The highly conserved molecular machinery which is responsible for controlling EMT can shift the process in the direction previously intended known as mesenchymal-epithelial transition (MET) (Figure 3).²¹⁸⁻²²⁰ Previous studies have been revealed that co-culture of lung adenocarcinoma (LAC) cell lines with MSCs leads to the suppression of tumor development, invasion, and tumor cell migration. Both MSCs and MSC-CM exert suppressive effects on several cancer cell lines through down-regulation of EMT-related markers and enhancement of MET pathway (Table 2). Moreover, it has been suggested that oncostatin M (OSM) as a paracrine factor has a decisive role in stimulating of MET process through the activation of signal transducer and activator of transcription 1 (STAT1) pathway.²¹⁹

Polarization of MSCs into a pro-inflammatory MSC1 or anti-tumor phenotype

Over the past decade the number of clinical trials involving MSCs has steadily increased, resulting in MSCs being the most commonly used cell type in tissue engineering, regenerative medicine and damage repair. These adult multipotent stem cells are massively proliferative and hold abilities to differentiate into wide variety of cell types. MSCs have been derived from various organs of healthy human subjects comprise a heterogeneous mixture of progenitor cells which are considered as suitable candidates for cell-based cancer therapies with different abilities. Substantial clinical trials confirmed that MSCs are frequently utilized cell types for regenerative medicine and tissue engineering. These cells express a diverse array of TLRs including TLRs1, 2, 3, 4, 5, 6, and 9.²²¹⁻²²³ TLRs can recognize exogenous and endogenous danger signals and have profound effects on proliferation, differentiation, migration, and survival of MSCs.²²¹ TLRs have been identified in different MSCs include BM-MSCs, human adipose-derived mesenchymal stromal/stem cells (hA-MSCs), human umbilical cord blood Wharton's jelly-derived mesenchymal stromal/stem cells (hUCBWJ-MSCs), hUC-MSCs, human dental follicle-derived mesenchymal stem/stromal cells (hDF-MSCs), and human dental pulp-derived mesenchymal stem/stromal cells (hDP-MSCs).²²⁴⁻²³¹

Toll-like receptors may also significantly affect the interaction between immune cells and MSCs.^{226-227,230} It is essential to note that the expression and function of TLRs in MSCs can be modulated under certain physiological conditions. For instance, an inflammatory milieu or exposure to bacterial components may determine the expression and function of TLRs in MSCs that lead to priming of specific TLRs and the alteration of immunomodulatory effects of MSCs.²³²⁻²³⁴ The expression pattern of TLRs in MSCs always coordinates with their origins.²³³

According to a new paradigm MSCs can be deeply polarized into two distinct phenotypes of MSCs named MSC1 and MSC2 (MSC2) which the resulting phenotypes are based on their TLR-priming that exhibit opposite effects on tumor development.^{39,235,236} The new paradigm suggests that TLR4-primed MSCs or MSC1 exert mainly pro-inflammatory or anti-tumor activities.^{235,237} While TLR3-primed MSCs or MSC2 display mostly anti-inflammatory and pro-tumor properties.²³⁵ Experimental evidence suggests that co-culture of MSC1 with different types of various cancer cell lines leads to a decrease in the number of colony-forming units derived from tumor cells and the reduction of three-dimensional (3D) tumor spheroid invasion assay. Meanwhile, a paradoxical result obtained using the conventionally prepared MSCs or MSC2 when co-cultured with various cancer cell lines.²³⁵

Romieu-Mourez et al²²⁸ have demonstrated that the stimulation of distinct TLRs in mouse-derived MSCs caused pro-inflammatory cytokines production including IL-8, IL-1, IL-6, and CCL5 by MSCs. They also argued that co-administration of TLR-primed MSCs (which are activated by IFN- γ) and extracellular matrix components (for instance, Matrigel Matrix) led to the generation of a local inflammatory site. Then the created site of local inflammation could attract and regulate the immune cells. Briefly, main changes occurred in this phenomenon including recruitment of neutrophils, secretion of different profiles of cytokines, alterations in the differentiation capability of MSCs, deposition of ECM; and also expression of the TGF- β , IDO, PGE2, and jagged-2 by MSCs.^{228,236}

More studies on MSC polarization may provide a convenient way to prevent the adverse effects of unmodified MSCs on tumor progression.

Conclusion

In the recent decade, there exists an increasing trend in the use of MSCs as an attractive therapeutic option in case of cancer therapy, regenerative medicine, and various human diseases. MSCs have unique characteristics such as the ability to migrate toward the primary tumor and metastatic sites, anti-tumor properties, and homing to be crucial determinants of tumor cell fate. For instance, MSCs in its unmodified or native form are being extensively studied and hold great promise for utilization in stem cell-

based therapies for cancer because of long time survival of exogenous MSCs in tumor mass. However, more findings imply that MSCs when confronted with tumors could exert dual and opposite effects on tumor growth and progression which depend on different conditions and factors. These divergent effects of MSCs in tumors can be considered as a major obstacle to successful stem cell-based therapies for cancer. It is also apparent that MSCs exert their contradictory effects on tumor growth and progression through different mechanisms. Hence, expanding the knowledge of these mechanisms involved in the control of tumor growth and their activation/deactivation process can result in more effective clinical outcomes. Prevention of the adverse effects of stem cell transplantation and the evolution of phenotypes which have anti-tumor effects can be one of the main goals of the research on the application of intact MSCs for the treatment of cancer. As the ability of homing phenomena and extended survival in tumor site, these cells could be genetically engineered for anti-cancer drug and reagent vehicle for therapeutic purposes. It should be noted that supportive effects of MSCs are predominant compared with their inhibitory effects on tumor development. Also, various conditions and factors can play a significant role in exhibiting of bidirectional effects of MSCs on tumor development.

Ethical Issues

Not applicable.

Conflict of Interest

Authors declare no conflict of interest in this study.

Acknowledgments

The authors would like to express their deepest gratitude and appreciation to the Department of Molecular Medicine, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, and the Drug Applied Research Center at Tabriz University of Medical Sciences, Tabriz-Iran whose assistance proved to be a milestone in the accomplishment of this paper.

References

1. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006;8(4):315-7. doi: 10.1080/14653240600855905
2. Gholizadeh-Ghalehaziz S, Farahzadi R, Fathi E, Pashaiasl M. A Mini Overview of Isolation, Characterization and Application of Amniotic Fluid Stem Cells. *Int J Stem Cells* 2015;8(2):115-20. doi: 10.15283/ijsc.2015.8.2.115
3. Ramkisoensing AA, Pijnappels DA, Askar SF, Passier R, Swildens J, Goumans MJ, et al. Human embryonic and fetal mesenchymal stem cells differentiate toward three different cardiac lineages in contrast to their adult counterparts. *PLoS One* 2011;6(9):e24164. doi: 10.1371/journal.pone.0024164
4. Schmelzer E, McKeel DT, Gerlach JC. Characterization of Human Mesenchymal Stem Cells from Different Tissues and Their Membrane Encasement for Prospective Transplantation Therapies. *Biomed Res Int*

- 2019;2019:6376271. doi: 10.1155/2019/6376271
5. Gholizadeh-Ghaleh Aziz S, Fardiyazar Z, Pashaei-Asl F, Rahmati-Yamchi M, Khodadadi K, Pashaiasl M. Human amniotic fluid stem cells (hAFSCs) expressing p21 and cyclin D1 genes retain excellent viability after freezing with (dimethyl sulfoxide) DMSO. *Bosn J Basic Med Sci* 2019;19(1):43-51. doi: 10.17305/bjbm.2018.2912
 6. Liu R, Chang W, Wei H, Zhang K. Comparison of the Biological Characteristics of Mesenchymal Stem Cells Derived from Bone Marrow and Skin. *Stem Cells Int* 2016;2016:3658798. doi: 10.1155/2016/3658798
 7. Gholizadeh-Ghaleh Aziz S, Pashaei-Asl F, Fardiyazar Z, Pashaiasl M. Isolation, Characterization, Cryopreservation of Human Amniotic Stem Cells and Differentiation to Osteogenic and Adipogenic Cells. *PLoS One* 2016;11(7):e0158281. doi: 10.1371/journal.pone.0158281
 8. Grégoire C, Ritacco C, Hannon M, Seidel L, Delens L, Belle L, et al. Comparison of Mesenchymal Stromal Cells From Different Origins for the Treatment of Graft-vs.-Host-Disease in a Humanized Mouse Model. *Front Immunol* 2019;10:619. doi: 10.3389/fimmu.2019.00619
 9. Wu M, Zhang R, Zou Q, Chen Y, Zhou M, Li X, et al. Comparison of the Biological Characteristics of Mesenchymal Stem Cells Derived from the Human Placenta and Umbilical Cord. *Sci Rep* 2018;8(1):5014. doi: 10.1038/s41598-018-23396-1
 10. Tsukamoto S, Honoki K, Fujii H, Tohma Y, Kido A, Mori T, et al. Mesenchymal stem cells promote tumor engraftment and metastatic colonization in rat osteosarcoma model. *Int J Oncol* 2012;40(1):163-9. doi: 10.3892/ijo.2011.1220
 11. Gholizadeh-Ghaleh Aziz S, Fathi E, Rahmati-Yamchi M, Akbarzadeh A, Fardiyazar Z, Pashaiasl M. An update clinical application of amniotic fluid-derived stem cells (AFSCs) in cancer cell therapy and tissue engineering. *Artif Cells Nanomed Biotechnol* 2017;45(4):765-74. doi: 10.1080/21691401.2016.1216857
 12. Brennen WN, Chen S, Denmeade SR, Isaacs JT. Quantification of Mesenchymal Stem Cells (MSCs) at sites of human prostate cancer. *Oncotarget* 2013;4(1):106-17. doi: 10.18632/oncotarget.805
 13. Bieback K, Schallmoser K, Klüter H, Strunk D. Clinical Protocols for the Isolation and Expansion of Mesenchymal Stromal Cells. *Transfus Med Hemother* 2008;35(4):286-94. doi: 10.1159/000141567
 14. Jiang Y, Wells A, Sylakowski K, Clark AM, Ma B. Adult Stem Cell Functioning in the Tumor Micro-Environment. *Int J Mol Sci* 2019;20(10). doi: 10.3390/ijms20102566
 15. Sun Z, Wang S, Zhao RC. The roles of mesenchymal stem cells in tumor inflammatory microenvironment. *J Hematol Oncol* 2014;7:14. doi: 10.1186/1756-8722-7-14
 16. LeBleu VS, Kalluri R. A peek into cancer-associated fibroblasts: origins, functions and translational impact. *Dis Model Mech* 2018;11(4). doi: 10.1242/dmm.029447
 17. Pashaei-Asl R, Pashaei-Asl F, Mostafa Gharabaghi P, Khodadadi K, Ebrahimi M, Ebrahimie E, et al. The Inhibitory Effect of Ginger Extract on Ovarian Cancer Cell Line; Application of Systems Biology. *Adv Pharm Bull* 2017;7(2):241-9. doi: 10.15171/apb.2017.029
 18. Junttila MR, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature* 2013;501(7467):346-54. doi: 10.1038/nature12626
 19. Ramamonjisoa N, Ackerstaff E. Characterization of the Tumor Microenvironment and Tumor-Stroma Interaction by Non-invasive Preclinical Imaging. *Front Oncol* 2017;7:3. doi: 10.3389/fonc.2017.00003
 20. Prasetyanti PR, Medema JP. Intra-tumor heterogeneity from a cancer stem cell perspective. *Mol Cancer* 2017;16(1):41. doi: 10.1186/s12943-017-0600-4
 21. Melzer C, Yang Y, Hass R. Interaction of MSC with tumor cells. *Cell Commun Signal* 2016;14(1):20. doi: 10.1186/s12964-016-0143-0
 22. Kazimirsky G, Jiang W, Slavin S, Ziv-Av A, Brodie C. Mesenchymal stem cells enhance the oncolytic effect of Newcastle disease virus in glioma cells and glioma stem cells via the secretion of TRAIL. *Stem Cell Res Ther* 2016;7(1):149. doi: 10.1186/s13287-016-0414-0
 23. Ridge SM, Sullivan FJ, Glynn SA. Mesenchymal stem cells: key players in cancer progression. *Mol Cancer* 2017;16(1):31. doi: 10.1186/s12943-017-0597-8
 24. Grisendi G, Bussolari R, Veronesi E, Piccinno S, Burns JS, De Santis G, et al. Understanding tumor-stroma interplays for targeted therapies by armed mesenchymal stromal progenitors: the Mesenkillers. *Am J Cancer Res* 2011;1(6):787-805.
 25. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 2007;449(7162):557-63. doi: 10.1038/nature06188
 26. Khakoo AY, Pati S, Anderson SA, Reid W, Elshal MF, Rovira, II, et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma. *J Exp Med* 2006;203(5):1235-47. doi: 10.1084/jem.20051921
 27. Serhal R, Saliba N, Hilal G, Moussa M, Hassan GS, El Atat O, et al. Effect of adipose-derived mesenchymal stem cells on hepatocellular carcinoma: In vitro inhibition of carcinogenesis. *World J Gastroenterol* 2019;25(5):567-83. doi: 10.3748/wjg.v25.i5.567
 28. Lee MW, Ryu S, Kim DS, Lee JW, Sung KW, Koo HH, et al. Mesenchymal stem cells in suppression or progression of hematologic malignancy: current status and challenges. *Leukemia* 2019;33(3):597-611. doi: 10.1038/s41375-018-0373-9
 29. Gholizadeh-Ghaleh Aziz S, Fardiyazar Z, Pashaiasl M. The human amniotic fluid mesenchymal stem cells therapy on, SKOV3, ovarian cancer cell line. *Mol Genet Genomic Med* 2019;7(7):e00726. doi: 10.1002/mgg3.726
 30. Pashaei-Asl F, Pashaei-Asl R, Khodadadi K, Akbarzadeh A, Ebrahimie E, Pashaiasl M. Enhancement of anticancer activity by silibinin and paclitaxel combination on the ovarian cancer. *Artif Cells Nanomed Biotechnol* 2018;46(7):1483-7. doi: 10.1080/21691401.2017.1374281
 31. Kéramidas M, de Fraipont F, Karageorgis A, Moisan A, Persoons V, Richard MJ, et al. The dual effect of mesenchymal stem cells on tumour growth and tumour angiogenesis. *Stem Cell Res Ther* 2013;4(2):41. doi: 10.1186/scrt195
 32. Qiao L, Xu Z, Zhao T, Zhao Z, Shi M, Zhao RC, et al. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. *Cell Res* 2008;18(4):500-7. doi: 10.1038/cr.2008.40
 33. Yagi H, Kitagawa Y. The role of mesenchymal stem cells in cancer development. *Front Genet* 2013;4:261. doi: 10.3389/fgene.2013.00261
 34. Kang I, Lee BC, Choi SW, Lee JY, Kim JJ, Kim BE, et al. Donor-dependent variation of human umbilical cord blood mesenchymal stem cells in response to hypoxic

- preconditioning and amelioration of limb ischemia. *Exp Mol Med* 2018;50(4):35. doi: 10.1038/s12276-017-0014-9
35. Liu J, Han G, Liu H, Qin C. Suppression of cholangiocarcinoma cell growth by human umbilical cord mesenchymal stem cells: a possible role of Wnt and Akt signaling. *PLoS One* 2013;8(4):e62844. doi: 10.1371/journal.pone.0062844
36. Kean TJ, Lin P, Caplan AI, Dennis JE. MSCs: Delivery Routes and Engraftment, Cell-Targeting Strategies, and Immune Modulation. *Stem Cells Int* 2013;2013:732742. doi: 10.1155/2013/732742
37. Raicevic G, Najar M, Stamatopoulos B, De Bruyn C, Meuleman N, Bron D, et al. The source of human mesenchymal stromal cells influences their TLR profile as well as their functional properties. *Cell Immunol* 2011;270(2):207-16. doi: 10.1016/j.cellimm.2011.05.010
38. Wong RS. Mesenchymal stem cells: angels or demons? *J Biomed Biotechnol* 2011;2011:459510. doi: 10.1155/2011/459510
39. Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an immunosuppressive MSC2 phenotype. *PLoS One* 2010;5(4):e10088. doi: 10.1371/journal.pone.0010088
40. Suzuki K, Sun R, Origuchi M, Kanehira M, Takahata T, Itoh J, et al. Mesenchymal stromal cells promote tumor growth through the enhancement of neovascularization. *Mol Med* 2011;17(7-8):579-87. doi: 10.2119/molmed.2010.00157
41. Wei HJ, Zeng R, Lu JH, Lai WF, Chen WH, Liu HY, et al. Adipose-derived stem cells promote tumor initiation and accelerate tumor growth by interleukin-6 production. *Oncotarget* 2015;6(10):7713-26. doi: 10.18632/oncotarget.3481
42. Liu C, Feng X, Wang B, Wang X, Wang C, Yu M, et al. Bone marrow mesenchymal stem cells promote head and neck cancer progression through Periostin-mediated phosphoinositide 3-kinase/Akt/mammalian target of rapamycin. *Cancer Sci* 2018;109(3):688-98. doi: 10.1111/cas.13479
43. Hossain A, Gumin J, Gao F, Figueroa J, Shinojima N, Takezaki T, et al. Mesenchymal Stem Cells Isolated From Human Gliomas Increase Proliferation and Maintain Stemness of Glioma Stem Cells Through the IL-6/gp130/STAT3 Pathway. *Stem Cells* 2015;33(8):2400-15. doi: 10.1002/stem.2053
44. Prantl L, Muehlberg F, Navone NM, Song YH, Vykoukal J, Logothetis CJ, et al. Adipose tissue-derived stem cells promote prostate tumor growth. *Prostate* 2010;70(15):1709-15. doi: 10.1002/pros.21206
45. Li W, Zhou Y, Yang J, Zhang X, Zhang H, Zhang T, et al. Gastric cancer-derived mesenchymal stem cells prompt gastric cancer progression through secretion of interleukin-8. *J Exp Clin Cancer Res* 2015;34:52. doi: 10.1186/s13046-015-0172-3
46. Zhu W, Xu W, Jiang R, Qian H, Chen M, Hu J, et al. Mesenchymal stem cells derived from bone marrow favor tumor cell growth in vivo. *Exp Mol Pathol* 2006;80(3):267-74. doi: 10.1016/j.yexmp.2005.07.004
47. Gao T, Yu Y, Cong Q, Wang Y, Sun M, Yao L, et al. Human mesenchymal stem cells in the tumour microenvironment promote ovarian cancer progression: the role of platelet-activating factor. *BMC Cancer* 2018;18(1):999. doi: 10.1186/s12885-018-4918-0
48. Zhao M, Sachs PC, Wang X, Dumur CI, Idowu MO, Robila V, et al. Mesenchymal stem cells in mammary adipose tissue stimulate progression of breast cancer resembling the basal-type. *Cancer Biol Ther* 2012;13(9):782-92. doi: 10.4161/cbt.20561
49. Lin JT, Wang JY, Chen MK, Chen HC, Chang TH, Su BW, et al. Colon cancer mesenchymal stem cells modulate the tumorigenicity of colon cancer through interleukin 6. *Exp Cell Res* 2013;319(14):2216-29. doi: 10.1016/j.yexcr.2013.06.003
50. Rivera-Cruz CM, Shearer JJ, Figueiredo Neto M, Figueiredo ML. The Immunomodulatory Effects of Mesenchymal Stem Cell Polarization within the Tumor Microenvironment Niche. *Stem Cells Int* 2017;2017:4015039. doi: 10.1155/2017/4015039
51. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005;105(4):1815-22. doi: 10.1182/blood-2004-04-1559
52. Luz-Crawford P, Kurte M, Bravo-Alegria J, Contreras R, Nova-Lamperti E, Tejedor G, et al. Mesenchymal stem cells generate a CD4+CD25+Foxp3+ regulatory T cell population during the differentiation process of Th1 and Th17 cells. *Stem Cell Res Ther* 2013;4(3):65. doi: 10.1186/scrt216
53. Luz-Crawford P, Djouad F, Toupet K, Bony C, Franquesa M, Hoogduijn MJ, et al. Mesenchymal Stem Cell-Derived Interleukin 1 Receptor Antagonist Promotes Macrophage Polarization and Inhibits B Cell Differentiation. *Stem Cells* 2016;34(2):483-92. doi: 10.1002/stem.2254
54. Sharma RR, Pollock K, Hubel A, McKenna D. Mesenchymal stem or stromal cells: a review of clinical applications and manufacturing practices. *Transfusion* 2014;54(5):1418-37. doi: 10.1111/trf.12421
55. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. *Blood* 2008;111(3):1327-33. doi: 10.1182/blood-2007-02-074997
56. Weiss ARR, Dahlke MH. Immunomodulation by Mesenchymal Stem Cells (MSCs): Mechanisms of Action of Living, Apoptotic, and Dead MSCs. *Front Immunol* 2019;10:1191. doi: 10.3389/fimmu.2019.01191
57. Zhang R, Qi F, Zhao F, Li G, Shao X, Zhang X, et al. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress NK cells function in colorectal cancer. *Cell Death Dis* 2019;10(4):273. doi: 10.1038/s41419-019-1435-2
58. van Dalen FJ, van Stevendaal M, Fennemann FL, Verdoes M, Iliina O. Molecular Repolarisation of Tumour-Associated Macrophages. *Molecules* 2018;24(1). doi: 10.3390/molecules24010009
59. Cho DI, Kim MR, Jeong HY, Jeong HC, Jeong MH, Yoon SH, et al. Mesenchymal stem cells reciprocally regulate the M1/M2 balance in mouse bone marrow-derived macrophages. *Exp Mol Med* 2014;46:e70. doi: 10.1038/emm.2013.135
60. Cagliani J, Grande D, Molmenti EP, Miller EJ, Rilo HLR. Immunomodulation by Mesenchymal Stromal Cells and Their Clinical Applications. *J Stem Cell Regen Biol* 2017;3(2). doi: 10.15436/2471-0598.17.022
61. Di Nicola M, Carlo-Stella C, Magni M, Milanese M, Longoni PD, Matteucci P, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or

- nonspecific mitogenic stimuli. *Blood* 2002;99(10):3838-43. doi: 10.1182/blood.v99.10.3838
62. Meisel R, Zibert A, Laryea M, Göbel U, Däubener W, Dilloo D. Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. *Blood* 2004;103(12):4619-21. doi: 10.1182/blood-2003-11-3909
 63. Kim HS, Yun JW, Shin TH, Lee SH, Lee BC, Yu KR, et al. Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-beta1 alleviate atopic dermatitis by reducing mast cell degranulation. *Stem Cells* 2015;33(4):1254-66. doi: 10.1002/stem.1913
 64. Klopp AH, Gupta A, Spaeth E, Andreeff M, Marini F, 3rd. Concise review: Dissecting a discrepancy in the literature: do mesenchymal stem cells support or suppress tumor growth? *Stem Cells* 2011;29(1):11-9. doi: 10.1002/stem.559
 65. Batten P, Sarathchandra P, Antoniw JW, Tay SS, Lowdell MW, Taylor PM, et al. Human mesenchymal stem cells induce T cell anergy and downregulate T cell allo-responses via the TH2 pathway: relevance to tissue engineering human heart valves. *Tissue Eng* 2006;12(8):2263-73. doi: 10.1089/ten.2006.12.2263
 66. Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. *Blood* 2005;105(7):2821-7. doi: 10.1182/blood-2004-09-3696
 67. Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringden O. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. *Scand J Immunol* 2003;57(1):11-20. doi: 10.1046/j.1365-3083.2003.01176.x
 68. Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. *Stem Cells* 2006;24(2):386-98. doi: 10.1634/stemcells.2005-0008
 69. Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. *Blood* 2005;106(5):1755-61. doi: 10.1182/blood-2005-04-1496
 70. Wang M, Yuan Q, Xie L. Mesenchymal Stem Cell-Based Immunomodulation: Properties and Clinical Application. *Stem Cells Int* 2018;2018:3057624. doi: 10.1155/2018/3057624
 71. Laranjeira P, Pedrosa M, Pedreiro S, Gomes J, Martinho A, Antunes B, et al. Effect of human bone marrow mesenchymal stromal cells on cytokine production by peripheral blood naive, memory, and effector T cells. *Stem Cell Res Ther* 2015;6:3. doi: 10.1186/scrt537
 72. Davies LC, Heldring N, Kadri N, Le Blanc K. Mesenchymal Stromal Cell Secretion of Programmed Death-1 Ligands Regulates T Cell Mediated Immunosuppression. *Stem Cells* 2017;35(3):766-76. doi: 10.1002/stem.2509
 73. Akiyama K, Chen C, Wang D, Xu X, Qu C, Yamaza T, et al. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/FAS-mediated T cell apoptosis. *Cell Stem Cell* 2012;10(5):544-55. doi: 10.1016/j.stem.2012.03.007
 74. Ljujic B, Milovanovic M, Volarevic V, Murray B, Bugarski D, Przyborski S, et al. Human mesenchymal stem cells creating an immunosuppressive environment and promote breast cancer in mice. *Sci Rep* 2013;3:2298. doi: 10.1038/srep02298
 75. Wang L, Zhao Y, Shi S. Interplay between mesenchymal stem cells and lymphocytes: implications for immunotherapy and tissue regeneration. *J Dent Res* 2012;91(11):1003-10. doi: 10.1177/0022034512460404
 76. Lee HJ, Kim SN, Jeon MS, Yi T, Song SU. ICOSL expression in human bone marrow-derived mesenchymal stem cells promotes induction of regulatory T cells. *Sci Rep* 2017;7:44486. doi: 10.1038/srep44486
 77. Duffy MM, Ritter T, Ceredig R, Griffin MD. Mesenchymal stem cell effects on T-cell effector pathways. *Stem Cell Res Ther* 2011;2(4):34. doi: 10.1186/scrt75
 78. Bai L, Lennon DP, Eaton V, Maier K, Caplan AI, Miller SD, et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. *Glia* 2009;57(11):1192-203. doi: 10.1002/glia.20841
 79. Zhao E, Xu H, Wang L, Kryczek I, Wu K, Hu Y, et al. Bone marrow and the control of immunity. *Cell Mol Immunol* 2012;9(1):11-9. doi: 10.1038/cmi.2011.47
 80. Fan L, Hu C, Chen J, Cen P, Wang J, Li L. Interaction between Mesenchymal Stem Cells and B-Cells. *Int J Mol Sci* 2016;17(5). doi: 10.3390/ijms17050650
 81. Bussard KM, Mutkus L, Stumpf K, Gomez-Manzano C, Marini FC. Tumor-associated stromal cells as key contributors to the tumor microenvironment. *Breast Cancer Res* 2016;18(1):84. doi: 10.1186/s13058-016-0740-2
 82. Bremnes RM, Donnem T, Al-Saad S, Al-Shibli K, Andersen S, Sirera R, et al. The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. *J Thorac Oncol* 2011;6(1):209-17. doi: 10.1097/JTO.0b013e3181f8a1bd
 83. Guan J, Chen J. Mesenchymal stem cells in the tumor microenvironment. *Biomed Rep* 2013;1(4):517-21. doi: 10.3892/br.2013.103
 84. CuiFFo BG, Karnoub AE. Mesenchymal stem cells in tumor development: emerging roles and concepts. *Cell Adh Migr* 2012;6(3):220-30. doi: 10.4161/cam.20875
 85. Li P, Gong Z, Shultz LD, Ren G. Mesenchymal stem cells: From regeneration to cancer. *Pharmacol Ther* 2019;200:42-54. doi: 10.1016/j.pharmthera.2019.04.005
 86. Castro-Manreza ME. Participation of mesenchymal stem cells in the regulation of immune response and cancer development. *Bol Med Hosp Infant Mex* 2016;73(6):380-7. doi: 10.1016/j.bmhmx.2016.10.003
 87. Shiga K, Hara M, Nagasaki T, Sato T, Takahashi H, Takeyama H. Cancer-Associated Fibroblasts: Their Characteristics and Their Roles in Tumor Growth. *Cancers (Basel)* 2015;7(4):2443-58. doi: 10.3390/cancers7040902
 88. Rajaram M, Li J, Egeblad M, Powers RS. System-wide analysis reveals a complex network of tumor-fibroblast interactions involved in tumorigenicity. *PLoS Genet* 2013;9(9):e1003789. doi: 10.1371/journal.pgen.1003789
 89. Perentes JY, McKee TD, Ley CD, Mathiew H, Dawson M, Padera TP, et al. In vivo imaging of extracellular matrix remodeling by tumor-associated fibroblasts. *Nat Methods* 2009;6(2):143-5. doi: 10.1038/nmeth.1295
 90. Rhee KJ, Lee JI, Eom YW. Mesenchymal Stem Cell-Mediated Effects of Tumor Support or Suppression. *Int J Mol Sci* 2015;16(12):30015-33. doi: 10.3390/ijms161226215
 91. Son H, Moon A. Epithelial-mesenchymal Transition and Cell Invasion. *Toxicol Res* 2010;26(4):245-52. doi: 10.5487/

- tr.2010.26.4.245
92. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2014;15(3):178-96. doi: 10.1038/nrm3758
 93. Sader F, Denis JF, Laref H, Roy S. Epithelial to mesenchymal transition is mediated by both TGF-beta canonical and non-canonical signaling during axolotl limb regeneration. *Sci Rep* 2019;9(1):1144. doi: 10.1038/s41598-018-38171-5
 94. Chen J, Ji T, Wu D, Jiang S, Zhao J, Lin H, et al. Human mesenchymal stem cells promote tumor growth via MAPK pathway and metastasis by epithelial mesenchymal transition and integrin alpha5 in hepatocellular carcinoma. *Cell Death Dis* 2019;10(6):425. doi: 10.1038/s41419-019-1622-1
 95. Nurwidya F, Takahashi F, Murakami A, Takahashi K. Epithelial mesenchymal transition in drug resistance and metastasis of lung cancer. *Cancer Res Treat* 2012;44(3):151-6. doi: 10.4143/crt.2012.44.3.151
 96. Tan J, Xu X, Tong Z, Lin J, Yu Q, Lin Y, et al. Decreased osteogenesis of adult mesenchymal stem cells by reactive oxygen species under cyclic stretch: a possible mechanism of age related osteoporosis. *Bone Res* 2015;3:15003. doi: 10.1038/boneres.2015.3
 97. Jing Y, Han Z, Zhang S, Liu Y, Wei L. Epithelial-Mesenchymal Transition in tumor microenvironment. *Cell Biosci* 2011;1:29. doi: 10.1186/2045-3701-1-29
 98. Takigawa H, Kitadai Y, Shinagawa K, Yuge R, Higashi Y, Tanaka S, et al. Mesenchymal Stem Cells Induce Epithelial to Mesenchymal Transition in Colon Cancer Cells through Direct Cell-to-Cell Contact. *Neoplasia* 2017;19(5):429-38. doi: 10.1016/j.neo.2017.02.010
 99. Plaks V, Kong N, Werb Z. The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? *Cell Stem Cell* 2015;16(3):225-38. doi: 10.1016/j.stem.2015.02.015
 100. Takigawa H, Kitadai Y, Kuwai T, Yuge R, Tanaka S, Chayama K. Abstract 4341: Mesenchymal stem cells promote epithelial-mesenchymal transition of colon cancer cells via direct cell-to-cell contact. *Cancer Res* 2017;77(13 Suppl):4341. doi: 10.1158/1538-7445.am.2017-4341
 101. Cannito S, Novo E, di Bonzo LV, Busletta C, Colombatto S, Parola M. Epithelial-mesenchymal transition: from molecular mechanisms, redox regulation to implications in human health and disease. *Antioxid Redox Signal* 2010;12(12):1383-430. doi: 10.1089/ars.2009.2737
 102. Thompson EW, Newgreen DF, Tarin D. Carcinoma invasion and metastasis: a role for epithelial-mesenchymal transition? *Cancer Res* 2005;65(14):5991-5; discussion 5. doi: 10.1158/0008-5472.can-05-0616
 103. Wu S, Wang Y, Yuan Z, Wang S, Du H, Liu X, et al. Human adiposederived mesenchymal stem cells promote breast cancer MCF7 cell epithelialmesenchymal transition by cross interacting with the TGFbeta/Smad and PI3K/AKT signaling pathways. *Mol Med Rep* 2019;19(1):177-86. doi: 10.3892/mmr.2018.9664
 104. Heldin CH, Vanlandewijck M, Moustakas A. Regulation of EMT by TGFbeta in cancer. *FEBS Lett* 2012;586(14):1959-70. doi: 10.1016/j.febslet.2012.02.037
 105. Trivanović D, Krstić J, Djordjević IO, Mojsilović S, Santibanez JF, Bugarški D, et al. The Roles of Mesenchymal Stromal/Stem Cells in Tumor Microenvironment Associated with Inflammation. *Mediators Inflamm* 2016;2016:7314016. doi: 10.1155/2016/7314016
 106. Bai YP, Shang K, Chen H, Ding F, Wang Z, Liang C, et al. FGF-1/-3/FGFR4 signaling in cancer-associated fibroblasts promotes tumor progression in colon cancer through Erk and MMP-7. *Cancer Sci* 2015;106(10):1278-87. doi: 10.1111/cas.12745
 107. Liu R, Li J, Xie K, Zhang T, Lei Y, Chen Y, et al. FGFR4 promotes stroma-induced epithelial-to-mesenchymal transition in colorectal cancer. *Cancer Res* 2013;73(19):5926-35. doi: 10.1158/0008-5472.can-12-4718
 108. Xu MH, Gao X, Luo D, Zhou XD, Xiong W, Liu GX. EMT and acquisition of stem cell-like properties are involved in spontaneous formation of tumorigenic hybrids between lung cancer and bone marrow-derived mesenchymal stem cells. *PLoS One* 2014;9(2):e87893. doi: 10.1371/journal.pone.0087893
 109. Xue J, Zhu Y, Sun Z, Ji R, Zhang X, Xu W, et al. Tumorigenic hybrids between mesenchymal stem cells and gastric cancer cells enhanced cancer proliferation, migration and stemness. *BMC Cancer* 2015;15:793. doi: 10.1186/s12885-015-1780-1
 110. Kirk R. Tumour evolution: Evidence points to the existence of cancer stem cells. *Nat Rev Clin Oncol* 2012;9(10):552. doi: 10.1038/nrclinonc.2012.149
 111. Albers AE, Chen C, Köberle B, Qian X, Klussmann JP, Wollenberg B, et al. Stem cells in squamous head and neck cancer. *Crit Rev Oncol Hematol* 2012;81(3):224-40. doi: 10.1016/j.critrevonc.2011.03.004
 112. Taniguchi H, Suzuki Y, Natori Y. The Evolving Landscape of Cancer Stem Cells and Ways to Overcome Cancer Heterogeneity. *Cancers (Basel)* 2019;11(4). doi: 10.3390/cancers11040532
 113. Huang Z, Wu T, Liu AY, Ouyang G. Differentiation and transdifferentiation potentials of cancer stem cells. *Oncotarget* 2015;6(37):39550-63. doi: 10.18632/oncotarget.6098
 114. Lobo NA, Shimono Y, Qian D, Clarke MF. The biology of cancer stem cells. *Annu Rev Cell Dev Biol* 2007;23:675-99. doi: 10.1146/annurev.cellbio.22.010305.104154
 115. Flemming A. Cancer stem cells: Targeting the root of cancer relapse. *Nat Rev Drug Discov* 2015;14(3):165. doi: 10.1038/nrd4560
 116. Liu S, Ginestier C, Ou SJ, Clouthier SG, Patel SH, Monville F, et al. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. *Cancer Res* 2011;71(2):614-24. doi: 10.1158/0008-5472.can-10-0538
 117. Nishimura K, Semba S, Aoyagi K, Sasaki H, Yokozaki H. Mesenchymal stem cells provide an advantageous tumor microenvironment for the restoration of cancer stem cells. *Pathobiology* 2012;79(6):290-306. doi: 10.1159/000337296
 118. Li Z. CD133: a stem cell biomarker and beyond. *Exp Hematol Oncol* 2013;2(1):17. doi: 10.1186/2162-3619-2-17
 119. Li HJ, Reinhardt F, Herschman HR, Weinberg RA. Cancer-stimulated mesenchymal stem cells create a carcinoma stem cell niche via prostaglandin E2 signaling. *Cancer Discov* 2012;2(9):840-55. doi: 10.1158/2159-8290.cd-12-0101
 120. Lazennec G, Lam PY. Recent discoveries concerning the tumor - mesenchymal stem cell interactions. *Biochim Biophys Acta* 2016;1866(2):290-9. doi: 10.1016/j.bbcan.2016.10.004
 121. Varas-Godoy M, Rice G, Illanes SE. The Crosstalk between Ovarian Cancer Stem Cell Niche and the Tumor Microenvironment. *Stem Cells Int* 2017;2017:5263974. doi: 10.1155/2017/5263974

122. Sinha G, Sherman LS, Sandiford OA, Williams LM, Ayer S, Walker ND, et al. Mesenchymal Stem Cell-Breast Cancer Stem Cell: Relevance to Dormancy. *J Cancer Stem Cell Res* 2016;4(1):1. doi: 10.14343/jcscr.2016.4e1001
123. Ji J, Yamashita T, Budhu A, Forgues M, Jia HL, Li C, et al. Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM-positive hepatic cancer stem cells. *Hepatology* 2009;50(2):472-80. doi: 10.1002/hep.22989
124. Tran N, McLean T, Zhang X, Zhao CJ, Thomson JM, O'Brien C, et al. MicroRNA expression profiles in head and neck cancer cell lines. *Biochem Biophys Res Commun* 2007;358(1):12-7. doi: 10.1016/j.bbrc.2007.03.201
125. Cammarota F, Laukkanen MO. Mesenchymal Stem/Stromal Cells in Stromal Evolution and Cancer Progression. *Stem Cells Int* 2016;2016:4824573. doi: 10.1155/2016/4824573
126. Räsänen K, Herlyn M. Paracrine signaling between carcinoma cells and mesenchymal stem cells generates cancer stem cell niche via epithelial-mesenchymal transition. *Cancer Discov* 2012;2(9):775-7. doi: 10.1158/2159-8290.cd-12-0312
127. Norozi F, Ahmadzadeh A, Shahrabi S, Vosoughi T, Saki N. Mesenchymal stem cells as a double-edged sword in suppression or progression of solid tumor cells. *Tumour Biol* 2016;37(9):11679-89. doi: 10.1007/s13277-016-5187-7
128. Yu PF, Huang Y, Han YY, Lin LY, Sun WH, Rabson AB, et al. TNF α -activated mesenchymal stromal cells promote breast cancer metastasis by recruiting CXCR2(+) neutrophils. *Oncogene* 2017;36(4):482-90. doi: 10.1038/onc.2016.217
129. Ren G, Zhao X, Wang Y, Zhang X, Chen X, Xu C, et al. CCR2-dependent recruitment of macrophages by tumor-educated mesenchymal stromal cells promotes tumor development and is mimicked by TNF α . *Cell Stem Cell* 2012;11(6):812-24. doi: 10.1016/j.stem.2012.08.013
130. Lim SY, Yuzhalin AE, Gordon-Weeks AN, Muschel RJ. Targeting the CCL2-CCR2 signaling axis in cancer metastasis. *Oncotarget* 2016;7(19):28697-710. doi: 10.18632/oncotarget.7376
131. Mi Z, Bhattacharya SD, Kim VM, Guo H, Talbot LJ, Kuo PC. Osteopontin promotes CCL5-mesenchymal stromal cell-mediated breast cancer metastasis. *Carcinogenesis* 2011;32(4):477-87. doi: 10.1093/carcin/bgr009
132. Kato Y, Ozawa S, Miyamoto C, Maehata Y, Suzuki A, Maeda T, et al. Acidic extracellular microenvironment and cancer. *Cancer Cell Int* 2013;13(1):89. doi: 10.1186/1475-2867-13-89
133. Akakura N, Kobayashi M, Horiuchi I, Suzuki A, Wang J, Chen J, et al. Constitutive expression of hypoxia-inducible factor-1 α renders pancreatic cancer cells resistant to apoptosis induced by hypoxia and nutrient deprivation. *Cancer Res* 2001;61(17):6548-54.
134. Reiser-Erkan C, Erkan M, Pan Z, Bekasi S, Giese NA, Streit S, et al. Hypoxia-inducible proto-oncogene Pim-1 is a prognostic marker in pancreatic ductal adenocarcinoma. *Cancer Biol Ther* 2008;7(9):1352-9. doi: 10.4161/cbt.7.9.6418
135. Chang CP, Chio CC, Cheong CU, Chao CM, Cheng BC, Lin MT. Hypoxic preconditioning enhances the therapeutic potential of the secretome from cultured human mesenchymal stem cells in experimental traumatic brain injury. *Clin Sci (Lond)* 2013;124(3):165-76. doi: 10.1042/cs20120226
136. Sanchez C, Oskowitz A, Pochampally RR. Epigenetic reprogramming of IGF1 and leptin genes by serum deprivation in multipotential mesenchymal stromal cells. *Stem Cells* 2009;27(2):375-82. doi: 10.1634/stemcells.2008-0546
137. Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. *Circulation* 1994;90(2):649-52. doi: 10.1161/01.cir.90.2.649
138. Semenza GL. HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *J Clin Invest* 2013;123(9):3664-71. doi: 10.1172/jci67230
139. Hung SC, Pochampally RR, Chen SC, Hsu SC, Prockop DJ. Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. *Stem Cells* 2007;25(9):2363-70. doi: 10.1634/stemcells.2006-0686
140. Block GJ, Ohkouchi S, Fung F, Frenkel J, Gregory C, Pochampally R, et al. Multipotent stromal cells are activated to reduce apoptosis in part by upregulation and secretion of stanniocalcin-1. *Stem Cells* 2009;27(3):670-81. doi: 10.1002/stem.20080742
141. Dias S, Shmelkov SV, Lam G, Rafii S. VEGF(165) promotes survival of leukemic cells by Hsp90-mediated induction of Bcl-2 expression and apoptosis inhibition. *Blood* 2002;99(7):2532-40. doi: 10.1182/blood.v99.7.2532
142. König A, Menzel T, Lynen S, Wrazel L, Rosén A, Al-Katib A, et al. Basic fibroblast growth factor (bFGF) upregulates the expression of bcl-2 in B cell chronic lymphocytic leukemia cell lines resulting in delaying apoptosis. *Leukemia* 1997;11(2):258-65. doi: 10.1038/sj.leu.2400556
143. Crisostomo PR, Wang Y, Markel TA, Wang M, Lahm T, Meldrum DR. Human mesenchymal stem cells stimulated by TNF- α , LPS, or hypoxia produce growth factors by an NF kappa B- but not JNK-dependent mechanism. *Am J Physiol Cell Physiol* 2008;294(3):C675-82. doi: 10.1152/ajpcell.00437.2007
144. Efimenko A, Starostina E, Kalinina N, Stolzinger A. Angiogenic properties of aged adipose derived mesenchymal stem cells after hypoxic conditioning. *J Transl Med* 2011;9:10. doi: 10.1186/1479-5876-9-10
145. Catlett-Falcone R, Landowski TH, Oshiro MM, Turkson J, Levitzki A, Savino R, et al. Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity* 1999;10(1):105-15. doi: 10.1016/s1074-7613(00)80011-4
146. Stamler JS. Redox signaling: nitrosylation and related target interactions of nitric oxide. *Cell* 1994;78(6):931-6. doi: 10.1016/0092-8674(94)90269-0
147. Boisen MK, Dehlendorff C, Linnemann D, Nielsen BS, Larsen JS, Osterlind K, et al. Tissue microRNAs as predictors of outcome in patients with metastatic colorectal cancer treated with first line Capecitabine and Oxaliplatin with or without Bevacizumab. *PLoS One* 2014;9(10):e109430. doi: 10.1371/journal.pone.0109430
148. Zhao C, Wang X, Zhao Y, Li Z, Lin S, Wei Y, et al. A novel xenograft model in zebrafish for high-resolution investigating dynamics of neovascularization in tumors.

- PLoS One* 2011;6(7):e21768. doi: 10.1371/journal.pone.0021768
149. Kéramidas M, de Fraipont F, Karageorgis A, Moisan A, Persoons V, Richard MJ, et al. The dual effect of mesenchymal stem cells on tumour growth and tumour angiogenesis. *Stem Cell Res Ther* 2013;4(2):41. doi: 10.1186/scrt195
 150. Lin W, Huang L, Li Y, Fang B, Li G, Chen L, et al. Mesenchymal Stem Cells and Cancer: Clinical Challenges and Opportunities. *Biomed Res Int* 2019;2019:2820853. doi: 10.1155/2019/2820853
 151. Beckermann BM, Kallifatidis G, Groth A, Frommhold D, Apel A, Mattern J, et al. VEGF expression by mesenchymal stem cells contributes to angiogenesis in pancreatic carcinoma. *Br J Cancer* 2008;99(4):622-31. doi: 10.1038/sj.bjc.6604508
 152. Wang Y, Wang L, Chen C, Chu X. New insights into the regulatory role of microRNA in tumor angiogenesis and clinical implications. *Mol Cancer* 2018;17(1):22. doi: 10.1186/s12943-018-0766-4
 153. Wang X, Wang H, Cao J, Ye C. Exosomes from Adipose-Derived Stem Cells Promotes VEGF-C-Dependent Lymphangiogenesis by Regulating miRNA-132/TGF-beta Pathway. *Cell Physiol Biochem* 2018;49(1):160-71. doi: 10.1159/000492851
 154. Au P, Tam J, Fukumura D, Jain RK. Bone marrow-derived mesenchymal stem cells facilitate engineering of long-lasting functional vasculature. *Blood* 2008;111(9):4551-8. doi: 10.1182/blood-2007-10-118273
 155. Zhang T, Lee YW, Rui YF, Cheng TY, Jiang XH, Li G. Bone marrow-derived mesenchymal stem cells promote growth and angiogenesis of breast and prostate tumors. *Stem Cell Res Ther* 2013;4(3):70. doi: 10.1186/scrt221
 156. Corcoran KE, Trzaska KA, Fernandes H, Bryan M, Taborga M, Srinivas V, et al. Mesenchymal stem cells in early entry of breast cancer into bone marrow. *PLoS One* 2008;3(6):e2563. doi: 10.1371/journal.pone.0002563
 157. Quante M, Tu SP, Tomita H, Gonda T, Wang SS, Takashi S, et al. Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth. *Cancer Cell* 2011;19(2):257-72. doi: 10.1016/j.ccr.2011.01.020
 158. Keung EZ, Nelson PJ, Conrad C. Concise review: genetically engineered stem cell therapy targeting angiogenesis and tumor stroma in gastrointestinal malignancy. *Stem Cells* 2013;31(2):227-35. doi: 10.1002/stem.1269
 159. Zhu W, Huang L, Li Y, Zhang X, Gu J, Yan Y, et al. Exosomes derived from human bone marrow mesenchymal stem cells promote tumor growth in vivo. *Cancer Lett* 2012;315(1):28-37. doi: 10.1016/j.canlet.2011.10.002
 160. Seke Etet PF, Vecchio L, Nwabo Kamdje AH. Signaling pathways in chronic myeloid leukemia and leukemic stem cell maintenance: key role of stromal microenvironment. *Cell Signal* 2012;24(9):1883-8. doi: 10.1016/j.cellsig.2012.05.015
 161. Caplan AI. All MSCs are pericytes? *Cell Stem Cell* 2008;3(3):229-30. doi: 10.1016/j.stem.2008.08.008
 162. Kitadai Y. Cancer-stromal cell interaction and tumor angiogenesis in gastric cancer. *Cancer Microenviron* 2010;3(1):109-16. doi: 10.1007/s12307-009-0032-9
 163. Klein D, Meissner N, Kleff V, Jastrow H, Yamaguchi M, Ergun S, et al. Nestin(+) tissue-resident multipotent stem cells contribute to tumor progression by differentiating into pericytes and smooth muscle cells resulting in blood vessel remodeling. *Front Oncol* 2014;4:169. doi: 10.3389/fonc.2014.00169
 164. Steens J, Zuk M, Benchellal M, Bornemann L, Teichweyde N, Hess J, et al. In Vitro Generation of Vascular Wall-Resident Multipotent Stem Cells of Mesenchymal Nature from Murine Induced Pluripotent Stem Cells. *Stem Cell Reports* 2017;8(4):919-32. doi: 10.1016/j.stemcr.2017.03.001
 165. Rani S, Ryan AE, Griffin MD, Ritter T. Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. *Mol Ther* 2015;23(5):812-23. doi: 10.1038/mt.2015.44
 166. Yang X, Hou J, Han Z, Wang Y, Hao C, Wei L, et al. One cell, multiple roles: contribution of mesenchymal stem cells to tumor development in tumor microenvironment. *Cell Biosci* 2013;3(1):5. doi: 10.1186/2045-3701-3-5
 167. Klein D, Weisshardt P, Kleff V, Jastrow H, Jakob HG, Ergun S. Vascular wall-resident CD44+ multipotent stem cells give rise to pericytes and smooth muscle cells and contribute to new vessel maturation. *PLoS One* 2011;6(5):e20540. doi: 10.1371/journal.pone.0020540
 168. Klein D. Vascular Wall-Resident Multipotent Stem Cells of Mesenchymal Nature within the Process of Vascular Remodeling: Cellular Basis, Clinical Relevance, and Implications for Stem Cell Therapy. *Stem Cells Int* 2016;2016:1905846. doi: 10.1155/2016/1905846
 169. de Souza LE, Malta TM, Kashima Haddad S, Covas DT. Mesenchymal Stem Cells and Pericytes: To What Extent Are They Related? *Stem Cells Dev* 2016;25(24):1843-52. doi: 10.1089/scd.2016.0109
 170. Okuyama H, Krishnamachary B, Zhou YF, Nagasawa H, Bosch-Marce M, Semenza GL. Expression of vascular endothelial growth factor receptor 1 in bone marrow-derived mesenchymal cells is dependent on hypoxia-inducible factor 1. *J Biol Chem* 2006;281(22):15554-63. doi: 10.1074/jbc.M602003200
 171. Moskaleva EY, Semochkina YP, Shuvatova VG, Rodina AV, Krasheninnikova AA. Mesenchymal Stem Cells from Mouse Adipose Tissue Stimulate Tumor Growth. *Bull Exp Biol Med* 2019;167(1):145-9. doi: 10.1007/s10517-019-04479-z
 172. Gomes CM. The dual role of mesenchymal stem cells in tumor progression. *Stem Cell Res Ther* 2013;4(2):42. doi: 10.1186/scrt189
 173. Hou L, Wang X, Zhou Y, Ma H, Wang Z, He J, et al. Inhibitory effect and mechanism of mesenchymal stem cells on liver cancer cells. *Tumour Biol* 2014;35(2):1239-50. doi: 10.1007/s13277-013-1165-5
 174. Song N, Gao L, Qiu H, Huang C, Cheng H, Zhou H, et al. Mouse bone marrow-derived mesenchymal stem cells inhibit leukemia/lymphoma cell proliferation in vitro and in a mouse model of allogeneic bone marrow transplant. *Int J Mol Med* 2015;36(1):139-49. doi: 10.3892/ijmm.2015.2191
 175. Cousin B, Ravet E, Poglio S, De Toni F, Bertuzzi M, Lulka H, et al. Adult stromal cells derived from human adipose tissue provoke pancreatic cancer cell death both in vitro and in vivo. *PLoS One* 2009;4(7):e6278. doi: 10.1371/journal.pone.0006278
 176. Ahn JO, Coh YR, Lee HW, Shin IS, Kang SK, Youn HY. Human adipose tissue-derived mesenchymal stem cells inhibit melanoma growth in vitro and in vivo. *Anticancer Res* 2015;35(1):159-68.
 177. Zhu Y, Sun Z, Han Q, Liao L, Wang J, Bian C, et al. Human mesenchymal stem cells inhibit cancer cell proliferation

- by secreting DKK-1. *Leukemia* 2009;23(5):925-33. doi: 10.1038/leu.2008.384
178. Lee JK, Park SR, Jung BK, Jeon YK, Lee YS, Kim MK, et al. Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. *PLoS One* 2013;8(12):e84256. doi: 10.1371/journal.pone.0084256
179. Lou G, Song X, Yang F, Wu S, Wang J, Chen Z, et al. Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. *J Hematol Oncol* 2015;8:122. doi: 10.1186/s13045-015-0220-7
180. Fonsato V, Collino F, Herrera MB, Cavallari C, Deregis MC, Cisterna B, et al. Human liver stem cell-derived microvesicles inhibit hepatoma growth in SCID mice by delivering antitumor microRNAs. *Stem Cells* 2012;30(9):1985-98. doi: 10.1002/stem.1161
181. Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi RU, et al. Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. *Sci Signal* 2014;7(332):ra63. doi: 10.1126/scisignal.2005231
182. Lee HK, Finnis S, Cazacu S, Bucris E, Ziv-Av A, Xiang C, et al. Mesenchymal stem cells deliver synthetic microRNA mimics to glioma cells and glioma stem cells and inhibit their cell migration and self-renewal. *Oncotarget* 2013;4(2):346-61. doi: 10.18632/oncotarget.868
183. Shimbo K, Miyaki S, Ishitobi H, Kato Y, Kubo T, Shimose S, et al. Exosome-formed synthetic microRNA-143 is transferred to osteosarcoma cells and inhibits their migration. *Biochem Biophys Res Commun* 2014;445(2):381-7. doi: 10.1016/j.bbrc.2014.02.007
184. Katakowski M, Buller B, Zheng X, Lu Y, Rogers T, Osobamiro O, et al. Exosomes from marrow stromal cells expressing miR-146b inhibit glioma growth. *Cancer Lett* 2013;335(1):201-4. doi: 10.1016/j.canlet.2013.02.019
185. Marcus H, Attar-Schneider O, Dabbah M, Zismanov V, Tartakover-Matalon S, Lishner M, et al. Mesenchymal stem cells secretomes' affect multiple myeloma translation initiation. *Cell Signal* 2016;28(6):620-30. doi: 10.1016/j.cellsig.2016.03.003
186. Bruno S, Collino F, Deregis MC, Grange C, Tetta C, Camussi G. Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. *Stem Cells Dev* 2013;22(5):758-71. doi: 10.1089/scd.2012.0304
187. Lee JK, Park SR, Jung BK, Jeon YK, Lee YS, Kim MK, et al. Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. *PLoS One* 2013;8(12):e84256. doi: 10.1371/journal.pone.0084256
188. Pekarsky Y, Croce CM. Role of miR-15/16 in CLL. *Cell Death Differ* 2015;22(1):6-11. doi: 10.1038/cdd.2014.87
189. Fernandez-Mercado M, Manterola L, Larrea E, Goicoechea I, Arestin M, Armesto M, et al. The circulating transcriptome as a source of non-invasive cancer biomarkers: concepts and controversies of non-coding and coding RNA in body fluids. *J Cell Mol Med* 2015;19(10):2307-23. doi: 10.1111/jcmm.12625
190. Musumeci M, Coppola V, Addario A, Patrizii M, Maugeri-Sacca M, Memeo L, et al. Control of tumor and microenvironment cross-talk by miR-15a and miR-16 in prostate cancer. *Oncogene* 2011;30(41):4231-42. doi: 10.1038/onc.2011.140
191. Spinetti G, Fortunato O, Caporali A, Shantikumar S, Marchetti M, Meloni M, et al. MicroRNA-15a and microRNA-16 impair human circulating proangiogenic cell functions and are increased in the proangiogenic cells and serum of patients with critical limb ischemia. *Circ Res* 2013;112(2):335-46. doi: 10.1161/circresaha.111.300418
192. Jones E, Mazirka P, McNurlan MA, Brink P, Caso G. Mir-16 and Mir-34a Suppress Growth of a Variety of Human Cancer Cells. *FASEB J* 2017;31(1_Suppl):lb178.
193. Sung SY, Liao CH, Wu HP, Hsiao WC, Wu IH, Jinpu, et al. Loss of let-7 microRNA upregulates IL-6 in bone marrow-derived mesenchymal stem cells triggering a reactive stromal response to prostate cancer. *PLoS One* 2013;8(8):e71637. doi: 10.1371/journal.pone.0071637
194. Yulyana Y, Ho IA, Sia KC, Newman JP, Toh XY, Endaya BB, et al. Paracrine factors of human fetal MSCs inhibit liver cancer growth through reduced activation of IGF-1R/PI3K/Akt signaling. *Mol Ther* 2015;23(4):746-56. doi: 10.1038/mt.2015.13
195. Li M, Cai H, Yang Y, Zhang J, Sun K, Yan Y, et al. Perichondrium mesenchymal stem cells inhibit the growth of breast cancer cells via the DKK-1/Wnt/beta-catenin signaling pathway. *Oncol Rep* 2016;36(2):936-44. doi: 10.3892/or.2016.4853
196. Jing W, Chen Y, Lu L, Hu X, Shao C, Zhang Y, et al. Human umbilical cord blood-derived mesenchymal stem cells producing IL15 eradicate established pancreatic tumor in syngeneic mice. *Mol Cancer Ther* 2014;13(8):2127-37. doi: 10.1158/1535-7163.mct-14-0175
197. Wang ML, Pan CM, Chiou SH, Chen WH, Chang HY, Lee OK, et al. Oncostatin m modulates the mesenchymal-epithelial transition of lung adenocarcinoma cells by a mesenchymal stem cell-mediated paracrine effect. *Cancer Res* 2012;72(22):6051-64. doi: 10.1158/0008-5472.can-12-1568
198. Wu S, Ju GQ, Du T, Zhu YJ, Liu GH. Microvesicles derived from human umbilical cord Wharton's jelly mesenchymal stem cells attenuate bladder tumor cell growth in vitro and in vivo. *PLoS One* 2013;8(4):e61366. doi: 10.1371/journal.pone.0061366
199. Liu X, Hu J, Sun S, Li F, Cao W, Wang YU, et al. Mesenchymal stem cells expressing interleukin-18 suppress breast cancer cells in vitro. *Exp Ther Med* 2015;9(4):1192-200. doi: 10.3892/etm.2015.2286
200. Xie C, Xie DY, Lin BL, Zhang GL, Wang PP, Peng L, et al. Interferon-beta gene-modified human bone marrow mesenchymal stem cells attenuate hepatocellular carcinoma through inhibiting AKT/FOXO3a pathway. *Br J Cancer* 2013;109(5):1198-205. doi: 10.1038/bjc.2013.422
201. Ryu H, Oh JE, Rhee KJ, Baik SK, Kim J, Kang SJ, et al. Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-beta and suppress the growth of MCF-7 human breast cancer cells. *Cancer Lett* 2014;352(2):220-7. doi: 10.1016/j.canlet.2014.06.018
202. Xiang J, Tang J, Song C, Yang Z, Hirst DG, Zheng QJ, et al. Mesenchymal stem cells as a gene therapy carrier for treatment of fibrosarcoma. *Cytotherapy* 2009;11(5):516-26. doi: 10.1080/14653240902960429
203. Yuan Z, Kolluri KK, Sage EK, Gowers KH, Janes SM. Mesenchymal stromal cell delivery of full-length tumor necrosis factor-related apoptosis-inducing ligand is superior to soluble type for cancer therapy. *Cytotherapy* 2015;17(7):885-96. doi: 10.1016/j.jcyt.2015.03.603

204. Lathrop MJ, Sage EK, Macura SL, Brooks EM, Cruz F, Bonenfant NR, et al. Antitumor effects of TRAIL-expressing mesenchymal stromal cells in a mouse xenograft model of human mesothelioma. *Cancer Gene Ther* 2015;22(1):44-54. doi: 10.1038/cgt.2014.68
205. Grisendi G, Spano C, D'Souza N, Rasini V, Veronesi E, Prapa M, et al. Mesenchymal progenitors expressing TRAIL induce apoptosis in sarcomas. *Stem Cells* 2015;33(3):859-69. doi: 10.1002/stem.1903
206. Grisendi G, Bussolari R, Cafarelli L, Petak I, Rasini V, Veronesi E, et al. Adipose-derived mesenchymal stem cells as stable source of tumor necrosis factor-related apoptosis-inducing ligand delivery for cancer therapy. *Cancer Res* 2010;70(9):3718-29. doi: 10.1158/0008-5472.can-09-1865
207. Özcan S, Alessio N, Acar MB, Toprak G, Gönen ZB, Peluso G, et al. Myeloma cells can corrupt senescent mesenchymal stromal cells and impair their anti-tumor activity. *Oncotarget* 2015;6(37):39482-92. doi: 10.18632/oncotarget.5430
208. Sandra F, Sudiono J, Ardiani Sidharta E, Pricilia Sunata E, Jane Sungkono D, Dirgantara Y, et al. Conditioned media of human umbilical cord blood mesenchymal stem cell-derived secretome induced apoptosis and inhibited growth of HeLa cells. *Indones Biomed J* 2014;6(1):57-62. doi: 10.18585/inabj.v6i1.44
209. Han I, Yun M, Kim EO, Kim B, Jung MH, Kim SH. Umbilical cord tissue-derived mesenchymal stem cells induce apoptosis in PC-3 prostate cancer cells through activation of JNK and downregulation of PI3K/AKT signaling. *Stem Cell Res Ther* 2014;5(2):54. doi: 10.1186/scrt443
210. Yang X, Du J, Xu X, Xu C, Song W. IFN-gamma-secreting-mesenchymal stem cells exert an antitumor effect in vivo via the TRAIL pathway. *J Immunol Res* 2014;2014:318098. doi: 10.1155/2014/318098
211. Dasari VR, Velpula KK, Kaur K, Fassett D, Klopfenstein JD, Dinh DH, et al. Cord blood stem cell-mediated induction of apoptosis in glioma downregulates X-linked inhibitor of apoptosis protein (XIAP). *PLoS One* 2010;5(7):e11813. doi: 10.1371/journal.pone.0011813
212. Bruno S, Collino F, Iavello A, Camussi G. Effects of mesenchymal stromal cell-derived extracellular vesicles on tumor growth. *Front Immunol* 2014;5:382. doi: 10.3389/fimmu.2014.00382
213. Magatti M, De Munari S, Vertua E, Parolini O. Amniotic membrane-derived cells inhibit proliferation of cancer cell lines by inducing cell cycle arrest. *J Cell Mol Med* 2012;16(9):2208-18. doi: 10.1111/j.1582-4934.2012.01531.x
214. Qiao L, Zhao TJ, Wang FZ, Shan CL, Ye LH, Zhang XD. NF-kappaB downregulation may be involved the depression of tumor cell proliferation mediated by human mesenchymal stem cells. *Acta Pharmacol Sin* 2008;29(3):333-40. doi: 10.1111/j.1745-7254.2008.00751.x
215. Otsu K, Das S, Houser SD, Quadri SK, Bhattacharya S, Bhattacharya J. Concentration-dependent inhibition of angiogenesis by mesenchymal stem cells. *Blood* 2009;113(18):4197-205. doi: 10.1182/blood-2008-09-176198
216. Menge T, Gerber M, Wataha K, Reid W, Guha S, Cox CS Jr, et al. Human mesenchymal stem cells inhibit endothelial proliferation and angiogenesis via cell-cell contact through modulation of the VE-Cadherin/beta-catenin signaling pathway. *Stem Cells Dev* 2013;22(1):148-57. doi: 10.1089/scd.2012.0165
217. Matthay MA. Mesenchymally "stemming" angiogenesis. *Blood* 2009;113(18):4131-2. doi: 10.1182/blood-2009-01-195396
218. Savagner P. The epithelial-mesenchymal transition (EMT) phenomenon. *Ann Oncol* 2010;21 Suppl 7:vii89-92. doi: 10.1093/annonc/mdq292
219. Wang ML, Pan CM, Chiou SH, Chen WH, Chang HY, Lee OK, et al. Oncostatin m modulates the mesenchymal-epithelial transition of lung adenocarcinoma cells by a mesenchymal stem cell-mediated paracrine effect. *Cancer Res* 2012;72(22):6051-64. doi: 10.1158/0008-5472.can-12-1568
220. Banyard J, Bielenberg DR. The role of EMT and MET in cancer dissemination. *Connect Tissue Res* 2015;56(5):403-13. doi: 10.3109/03008207.2015.1060970
221. Tomchuck SL, Zvezdaryk KJ, Coffelt SB, Waterman RS, Danka ES, Scandurro AB. Toll-like receptors on human mesenchymal stem cells drive their migration and immunomodulating responses. *Stem Cells* 2008;26(1):99-107. doi: 10.1634/stemcells.2007-0563
222. Pevsner-Fischer M, Morad V, Cohen-Sfady M, Rouso-Noori L, Zanin-Zhorov A, Cohen S, et al. Toll-like receptors and their ligands control mesenchymal stem cell functions. *Blood* 2007;109(4):1422-32. doi: 10.1182/blood-2006-06-028704
223. Hwa Cho H, Bae YC, Jung JS. Role of toll-like receptors on human adipose-derived stromal cells. *Stem Cells* 2006;24(12):2744-52. doi: 10.1634/stemcells.2006-0189
224. van den Berk LC, Jansen BJ, Siebers-Vermeulen KG, Netea MG, Latuhihin T, Bergevoet S, et al. Toll-like receptor triggering in cord blood mesenchymal stem cells. *J Cell Mol Med* 2009;13(9b):3415-26. doi: 10.1111/j.1582-4934.2009.00653.x
225. Tomic S, Djokic J, Vasilijic S, Vucevic D, Todorovic V, Supic G, et al. Immunomodulatory properties of mesenchymal stem cells derived from dental pulp and dental follicle are susceptible to activation by toll-like receptor agonists. *Stem Cells Dev* 2011;20(4):695-708. doi: 10.1089/scd.2010.0145
226. Opitz CA, Litzemberger UM, Lutz C, Lanz TV, Tritschler I, Köppel A, et al. Toll-like receptor engagement enhances the immunosuppressive properties of human bone marrow-derived mesenchymal stem cells by inducing indoleamine-2,3-dioxygenase-1 via interferon-beta and protein kinase R. *Stem Cells* 2009;27(4):909-19. doi: 10.1002/stem.7
227. Krampera M, Sartoris S, Liotta F, Pasini A, Angeli R, Cosmi L, et al. Immune regulation by mesenchymal stem cells derived from adult spleen and thymus. *Stem Cells Dev* 2007;16(5):797-810. doi: 10.1089/scd.2007.0024
228. Romieu-Mourez R, Francois M, Boivin MN, Bouchentouf M, Spaner DE, Galipeau J. Cytokine modulation of TLR expression and activation in mesenchymal stromal cells leads to a proinflammatory phenotype. *J Immunol* 2009;182(12):7963-73. doi: 10.4049/jimmunol.0803864
229. Wang X, Zhu Y, Xu B, Wang J, Liu X. Identification of TLR2 and TLR4-induced microRNAs in human mesenchymal stem cells and their possible roles in regulating TLR signals. *Mol Med Rep* 2016;13(6):4969-80. doi: 10.3892/mmr.2016.5197
230. Shirjang S, Mansoori B, Solali S, Farshdousti Hagh M, Shamsasenjan K. Toll-like receptors as a key regulator of mesenchymal stem cell function: An up-to-date review. *Cell Immunol* 2017;315:1-10. doi: 10.1016/j.cellimm.2016.12.005
231. Fawzy El-Sayed KM, Klingebiel P, Dörfer CE. Toll-like

- Receptor Expression Profile of Human Dental Pulp Stem/Progenitor Cells. *J Endod* 2016;42(3):413-7. doi: 10.1016/j.joen.2015.11.014
232. Chen GY, Shiah HC, Su HJ, Chen CY, Chuang YJ, Lo WH, et al. Baculovirus transduction of mesenchymal stem cells triggers the toll-like receptor 3 pathway. *J Virol* 2009;83(20):10548-56. doi: 10.1128/jvi.01250-09
233. Sallustio F, Curci C, Stasi A, De Palma G, Divella C, Gramignoli R, et al. Role of Toll-Like Receptors in Actuating Stem/Progenitor Cell Repair Mechanisms: Different Functions in Different Cells. *Stem Cells Int* 2019;2019:6795845. doi: 10.1155/2019/6795845
234. Bernardo ME, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell* 2013;13(4):392-402. doi: 10.1016/j.stem.2013.09.006
235. Waterman RS, Henkle SL, Betancourt AM. Mesenchymal stem cell 1 (MSC1)-based therapy attenuates tumor growth whereas MSC2-treatment promotes tumor growth and metastasis. *PLoS One* 2012;7(9):e45590. doi: 10.1371/journal.pone.0045590
236. Bunnell BA, Betancourt AM, Sullivan DE. New concepts on the immune modulation mediated by mesenchymal stem cells. *Stem Cell Res Ther* 2010;1(5):34. doi: 10.1186/scrt34
237. Yan XL, Fu CJ, Chen L, Qin JH, Zeng Q, Yuan HF, et al. Mesenchymal stem cells from primary breast cancer tissue promote cancer proliferation and enhance mammosphere formation partially via EGF/EGFR/Akt pathway. *Breast Cancer Res Treat* 2012;132(1):153-64. doi: 10.1007/s10549-011-1577-0