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REVIEW

Mesenchymal stromal cells' role in tumor microenvironment: involvement of signaling pathways

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ABSTRACT Mesenchymal stromal cells (MSCs) are adult multipotent stem cells residing as pericytes in various tissues and organs where they can differentiate into specialized cells to replace dying cells and damaged tissues. These cells are commonly found at injury sites and in tumors that are known to behave like "wounds that do not heal." In this article, we discuss the mechanisms of MSCs in migrating, homing, and repairing injured tissues. We also review a number of reports showing that tumor microenvironment triggers plasticity mechanisms in MSCs to induce malignant neoplastic tissue formation, maintenance, and chemoresistance, as well as tumor growth. The antitumor properties and therapeutic potential of MSCs are also discussed.

KEYWORDS Mesenchymal stromal cells; systemic circulation; migration; homing; tumor modulation; signaling pathways; chemoresistance

Introduction

Mesenchymal stromal cells (MSCs) are immature, adherent stromal cells residing in various tissues and organs, including bone marrow (BM-MSCs), adipose tissue (AT-MSCs), umbilical cord blood, and placenta. The presence of circulating MSCs in the peripheral blood is still debated[1,2]. MSCs divide into daughter cells that share the same properties of their mother cell (self-renewal) or differentiate into specialized cells to replace dying cells and repair damaged tissues (multilineage differentiation). Notably, these adult stem cells can differentiate into various cell types of the mesodermal lineage, including chondrocytes, osteoblasts, adipocytes, endothelial cells, and myocytes[3]; moreover, non-mesodermal differentiation into neural, liver, pancreatic, and gastric cells has been reported *in vitro*, but this phenomenon occurring *in vivo* has not been proven[4-7]. MSCs express membrane CD90, CD73, and CD105, and are negative for CD45, CD34, CD31, CD14, CD19, and HLA-DR[3,8].

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Emerging data suggest that MSCs can promote tumorigenic processes, including malignant transformation, establishment and maintenance of cancer cells, promotion of angiogenesis and neovascularization-sustaining neoplastic tissues, metastasis formation, and chemoresistance to anticancer drugs[9-11]. MSCs have the capability to contribute to the formation of cancer stem cell niche and support stemness[9-11]. In this article, we provide an overview on the MSC properties that drive their tissue repair capability, such as migration, adhesion, differentiation, growth factor production, and immune regulation. Then, we discuss how the same features may boost tumor development and favor chemoresistance mediated by the tumor microenvironment.

MSCs, regenerative medicine, and cell therapy

Therapeutic potential of embryonic and adult stem cells

Tissue or organ transplantation is still associated with various issues, including inadequate donor availability, compatibility between donors and recipients, and risk of developing graft-related complications. Stem cell transplantation has emerged

as a promising strategy to replace or improve organ transplantation[12,13]. The premise is that stem cells, once administered to the recipient with organ failure, migrate to the damaged sites and differentiate into the specific affected cell types to restore/replace damaged tissues and rescue organ functions. Stem cells can be classified as embryonic stem cells, which give rise to all tissue types, and adult stem cells, which are involved in the tissue homeostasis by replacing senescent or damaged cells based on their differentiation potency and developmental hierarchy. The high proliferation rate and pluripotency of embryonic stem cells, that is, the ability to differentiate into virtually all cell types of the three germinal layers (ectoderm, mesoderm, and endoderm), would make them the optimal model for tissue engineering, regardless of their potential immunogenicity. However, their therapeutic use is entangled with critical ethical issues and uncontrolled proliferation, leading to teratoma formation *in vivo*; moreover, the latter issue remains unsolved even with the use of alternative technologies aimed at achieving embryonic stem cell-like cells, such as induced pluripotent stem cells[14,15]. Consequently, adult stem cells have rapidly become the main tool in regenerative medicine and tissue engineering because of their high proliferative and differentiation properties, easy collection, and weak immunogenicity[16-20].

MSC therapeutic potential

MSC use is a first attempt in adult stem cells-based therapy. A body of evidence from *in vivo* and *in vitro* studies shows that MSCs possess regenerative potential associated to their adhesion, migration, proliferation, differentiation, and immunosuppression properties[21-24]. This adult stem cell type is highly used in preclinical studies and phase 2 and 3 clinical trials aimed at mitigating graft-versus-host disease (GvHD) and at regenerating damaged tissues in many diseases and conditions that are thought to originate from deleterious damages to tissues[16,25]. Examples include the attempts to regenerate bone, heart, muscle, and nervous tissues following tissue injury from inflammation- and oxidative stress-associated pathogenic processes[26,27]. Tissue repair and attenuation of chronic or acute inflammation were observed after local or systemic infusion of MSC in patients[16,25]. However, the real clinical impact of this cell therapy approach remains unknown and requires further multicenter studies based on standardized methods to assess safety and efficacy.

MSCs have been well characterized with respect to their ability to produce a range of growth factors and cytokines, which inspired the designation of these cells as an "injury drugstore"[28]. Notably, MSC secretome screening revealed numerous growth factors that potentially contribute to tissue repair, such as (*i*) vascular endothelial growth factor (VEGF), which has angiogenic abilities and triggers endothelial differentiation in MSCs through VEGFR-2/Sox18[29] and Rho/myocardin-related transcription factor-dependent mechanisms, thereby promoting blood vessel repair[30,31]; (*ii*) hepatocyte growth factor (HGF) that may play a role in MSC regenerative effects on the liver, as it promotes the differentiation and proliferation of hepatic-like cells and induces MSC-associated cytoprotective effects on hepatocytes *in vivo*[32-34]; (*iii*) transforming growth factor-beta (TGF-β), whose involvement was reported in MSC-mediated heart repair, where it stimulated the differentiation of cardiomyocytes and promoted angiogenesis[35]; (*iv*) angiopoietin-1, another pro-angiogenic factor involved in MSC-mediated improvement of cardiac function (36) and skin damage[37]; (*v*) epidermal growth factor (EGF) that mediates MSC-associated protection of podocytes from high glucose-induced apoptosis[38]; (*vi*) platelet-derived growth factor (PDGF), whose release by MSCs was reported to play a role in cardiac healing after myocardial injury by exerting a pro-migratory effect on resident cardiac stem cells[39]; (*vii*) granulocyte-colony stimulating factor (G-CSF), whose release by MSCs is triggered by co-cultures with counter-inflammatory or tissue repair macrophages, enhanced by the MSC cartilage-forming capacity[40]; and (*viii*) fibroblast growth factor (FGF), and cytoprotective factors that partly account for the therapeutic effects of MSCs in lung diseases[41]. Numerous other soluble factors are released by MSCs and contribute to the properties of these cells, including stem cell factor, MCP-3, CXCL8, CXCL9, CXCL16, CCL20, CCL25, IL-6, and IL-12[42-45].

MSC properties contributing to tissue repair ability

Migration and homing

Determinant factors of cell therapeutic potential include migration, homing, and survival when administered through a specific route. Labeling and tracking of MSCs have been employed to understand the MSC distribution in the body following local or systemic injection. Reported labeling approaches include intracellular magnetic contrast materials, radioactive compound, and fluorescent dyes[46-48]; and expression systems, such as luciferase, green fluorescent protein (GFP), and Alu sequences[48-52]. Studies addressing the final location of MSCs after systemic infusion in disease-free

laboratory animals revealed that injected MSCs could localize in diverse sites of organs, such as the lung, liver, and spleen[53,54]. Interestingly, comparable studies in animals with damaged organs revealed a tropism of injected MSCs for damaged sites, particularly following administration at neighboring areas. For instance, Barbash and colleagues[54] reported that ^{99}mTc-exametazime-labeled MSCs infused in the left ventricle cavity, instead of intravenously, resulted in a drastically reduced lung uptake and increased infarcted myocardium uptake in a rat model. Comparably, after palatine tonsil MSCs (T-MSCs) were intravenously administered to carbon tetrachloride-induced mouse model of liver fibrosis, the T-MSCs were only found in the liver[55]. Intravenously injected MSCs migrated, distributed to the colon, and effectively mitigated disease severity indicators in a rat model of ulcerative colitis via an anti-inflammatory effect partly mediated by G-CSF[56]. Moreover, nasal mucosa ecto-mesenchymal stromal cells injected in the tail vein migrated to the inflammation sites and suppressed eosinophils and sneezing in a mouse model of allergic rhinitis via downregulation of Th-2 cell secretory activity, that is, decreases in IgE, IL-4, IL-5, and IL-10 secretions; and upregulation of Th-1 cell secretion, including the release of IgG2 and IFN-γ[57]. Interestingly, MSC delivery into the arterial system via injection into the aortic arch or tail vein supports the "first-pass" cell delivery hypothesis. Indeed, MSCs showed significant entrapment in the lungs when delivered intravenously into the tail vein. However, when delivered intra-arterially through the aortic arch, the cells were highly and evenly distributed in the entire animal[45]. MSCs were reported to home at the sites of ischemia, hypoxia, inflammation, and other injuries[54,55,58]. Overall, such sites have high concentrations of pro-inflammatory cytokines, chemokines, and soluble factors that may attract MSCs and favor their homing[21,22].

The migration and homing of infused MSCs to damaged tissues are important parameters to consider for clinical purposes. Failure or poor results following attempts of MSC-based therapy observed in a significant number of patients raised at least three concerns. First is their overall viability following infusion via the route used (local versus systemic[43]); moreover, despite clinical evidence and reports from experimental models supporting the assumption that MSC homing may be governed by damaged tissues, MSCs can still be found in unwanted sites, thereby raising safety concerns for the long-term effects of MSC-based therapy[59,60], particularly in pediatric patients[61-63]. Second is the engraftment degree of MSCs in targeted tissues, and the third, as a consequence, is the fate of these cells if improperly engrafted. Improving the MSC viability and therapeutic potency is currently a challenge. A remarkable example is provided by MSC-based therapy in lung diseases, where MSC grafting and homing to affected tissues are successful. This therapeutic approach has been held back by the difficulty of engrafted MSCs to survive more than one week after-transplantation in hostile microenvironments[41]. Similar observations have been reported in other injuries, including renal ischemia/reperfusion injury, where hypoxia preconditioning of MSCs appeared as a possible solution[64]. Hypoxia induces the secretion of anti-inflammatory, antiapoptotic, and anti-fibrotic factors, as well as the expression of cytoprotective genes, thereby enhancing the therapeutic potential and survival duration of the engrafted MSCs[41,64]. Recently, a study in human umbilical cord MSCs suggested the three-dimensional spheroid culture of these stem cells as a strategy to promote cell yield and stemness maintenance[65].

Moreover, functional differences were reported in MSCs from human dental pulp and periodontal ligaments[66], indicating that MSCs from topographically related tissues do not necessarily share identical properties, thereby emphasizing the need for comparing the multipotency, immunosuppression properties, response to pro-inflammatory cytokines, and eventually the secretome of MSCs from diverse sources before clinical use. Reports in various human studies[21,22] and animal models[23,24] corroborated these observations.

Differentiation and transdifferentiation

The differentiation ability of MSCs accounts for their positive effects in diseases wherein pathogenic processes include severe tissue damage, such as in cardiac lesions. For instance, a promising observation in MSC-mediated therapy was the finding that injecting MSCs in an infarcted heart generates a new tissue made up of proliferating myocyte and vascular structures[67]. In a study with enhanced-GFP-labeled MSC, the regenerated cardiomyocytes, vascular smooth muscle, and endothelial cells were EGFP+, suggesting that the new heart tissue was mainly derived from MSC differentiation[68]. In a study where the injection of GFP-labeled AT-MSC in spinal cord of a canine model of acute spinal injury was associated with a functional recovery, GFP-positive cells at the injury site included cells positive for GFAP (astrocyte marker), Tuj-1, and NF160 (markers of immature post-mitotic neurons), suggesting that functional improvement was mediated by the differentiation of AT-MSCs into functional astrocytes and neurons[69].

The plasticity of MSCs does not derive only from their

ability to differentiate into other cell types (cell replacement), but includes fusion with resident cells, thereby resulting in the emergence of new cells capable of tissue-specific functions. This fusion is termed as lineage reprogramming or transdifferentiation. MSC transdifferentiation results in phenotypes that are highly related to resident cells[70,71]. Many studies report MSC ability to fuse with various cell types. Examples of such cell types include cardiomyocytes[72,73], hepatocytes[74,75], neurons, and corneal cells[76,77]. The increasing number of reports suggests that cell fusion is an alternate and a common and probably pivotal pathway in MSC plasticity.

Immune modulation

Besides the classic cell replacement (differentiation) and reprogramming (transdifferentiation) paradigms, immune modulatory properties contribute to the benefits of MSC therapy. MSCs may modulate immune responses using paracrine mechanisms and cell-cell interaction. Studies suggesting that the activating properties in MSCs are scarce include reports of the ability of MSC to activate allogeneic T-cells in mixed leukocyte reaction[78], stimulate the activation and proliferation of resting T-cells in co-cultures[79], the MSC behavior as conditional antigen presenting cells (APCs) in syngeneic immune responses[80], the TLR-activated MSC ability to recruit and activate immune inflammatory cells[81], and the secretion of pro-inflammatory cytokines and chemokines by MSCs[42,44,45]. However, the clinical implications of these observations are still unclear.

The immunosuppressive properties of MSCs are well documented. These effects may emerge from cell-cell interactions with both innate and adaptive immune system cells[82-85], partly mediated by Toll-like receptor (TLR) pathways, as revealed by the immunosuppression effects of TLR4 activation (via mechanisms involving VCAM-1- and ICAM-1-mediated binding of immune cells) and TLR3 activation (via mechanisms that induce the formation of cable-like hyaluronic acid structures)[86,87]. The immunosuppressive abilities of MSC can be mediated by the release of soluble factors with anti-inflammatory effects, like indoleamine 2, 3-dioxygenase (IDO), inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), G-CSF, and TGF-β[40,56,88-90]. Such immunosuppressive effects account for the ability of MSC to inhibit inflammatory responses that are induced by the presence of transplanted tissues, thereby decreasing the probability of rejection[91-95]. MSCs prevents autoimmunity via CCL2-dependent recruitment of myeloid-derived suppressor cells, in a mouse model of experimental autoimmune uveitis[96].

Clinical application of MSCs requires a relatively long-term *ex vivo* culture that results in cellular senescence and reduced therapeutic activity of transplanted cells[97]. Experimental evidence shows that the therapeutic potency of MSCs may be enhanced and even restored by improving the immunosuppressive properties of these cells. For instance, in a recent study, these properties were improved by using vitamin D receptor agonists as additives in a mouse model of sterile kidney inflammation[98]. This approach resulted in the suppression of Th17 and related inflammatory responses in the kidney. In another study, the MSC-activating neuropeptide, termed as substance P, potentiated the ability to secrete TGF-β1 in long-term culture MSCs, indicating a recovery of their immunosuppressive function[97]. Moreover, these cells recovered their ability to inactivate CD4+ cells in co-cultures (cell-cell contact). Adenoviral transduction of MSCs was proposed as a strategy for increasing the immunosuppressive properties of engrafted MSCs after cell transplantation[66]. Overall, because of their immune modulatory features, MSC are being tested to treat immune disorders, such as GvHD, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease, and to enhance transplant tolerance[45].

MSCs and tumor microenvironment

MSC plasticity and tumorigenesis

A major role for MSCs in cancer development emerged from the fact that MSCs are commonly found in stromal niches of various tissues undergoing tumorigenesis, including bone marrow in hematological malignancies[9-11], and in the affected ducts and lobules of breast cancer[99-101]. Moreover, MSC research insights raised concerns about the possibility of their role in all the developmental and maintenance steps of malignant tumors from initiation until the metastatic spread. Growing evidence supports the idea that MSCs may exploit the properties related to tissue repair to promote tumorigenesis and protect transforming cells from chemotherapy[10,83,102-109]. Therefore, events and mechanisms accounting for MSC-mediated tissue regeneration and repair, such as MSC activation, mobilization, migration, and homing to stromal microenvironment, differentiation and transdifferentiation, as well as the secretion of cytokines, growth factors, and other soluble factors modulating the local immune responses and improving stromal cell survival, may support the pro-oncogenic role of MSCs. Thus, MSCs may eventually facilitate cancer cell growth, partly by favoring the angiogenic and neovascularization processes that

allow the survival of malignant neoplastic tissues[107-109] and by modulating anticancer immunity and hijacking immune cells to favor tumor invasion and, subsequently, metastatic processes[99,103-105,110]. These findings have tempered the enthusiasm over the clinical application of stem cells and further raised safety concerns of the long-term use of these cells and which categories of patients may be suitable for MSC-based therapies.

Tumor stroma recapitulates damaged tissue microenvironment

MSC plastic properties generate pro-tumoral stroma

Tumor stroma mainly include immune, endothelial, and immune cells, such as lymphocytes, macrophages, neutrophils, and natural killer cells, as well as adipocytes, myofibroblasts, and carcinoma associated fibroblasts (CAFs)[111]. Among the most abundant tumor stroma components, CAFs considerably boost tumor growth, induce epithelial-mesenchymal transition, promote the acquisition of invasive phenotypes, and support angiogenesis[112-115]. Moreover, CAFs could induce epithelial-mesenchymal transition through paracrine TGF-β signaling[115].

Besides, early *in vitro* studies revealed that, following long treatments with tumor cell-conditioned medium *in vitro*, MSCs can differentiate into CAFs[116] via a TGFβ1/Smad3-dependent mechanism[117,118]. Growing evidence supports the ability of the MSC to differentiate into CAFs *in vivo*. For instance, MSCs differentiate into CAFs to promote metastatic tumors in advanced solid cancers[118-124]. Moreover, MSCs in tumors may display transdifferentiation, wherein fusion occurs with resident cells, such as malignant cells and other components of the tumor stroma, thereby resulting in the remodeling of the tissue stroma of the affected organ into a pro-tumoral stroma[103,107,125-127]. Examples of MSC transdifferentiation include MSC fusion-induced reprogramming in lung cancer[127], human melanoma[107], breast cancer, and ovarian adenocarcinoma cells[126]. These reports further suggested that the plastic role of MSCs is a major pathogenic step because it drives the generation of a pro-tumoral stroma.

Homing: MSCs exhibit tropism for tumors

Tumors behave like "wounds that do not heal", and recapitulate most of the characteristic events of damaged tissue (wounding) microenvironment, such as hypoxia, mechanical stress, sustained inflammation, and increased oxidative/nitrosative stress[50,111]. Numerous studies reported tumor microenvironment tropisms of both endogenous and exogenous MSCs. For instance, in a study where MSCs labeled with firefly luciferase-enhanced GFP (fLuc-eGFP) reporter gene were intravenously injected to subcutaneous and lung metastasis mouse models, the injected MSCs survived, proliferated, and differentiated in tumor sites but not anywhere else[50], thereby suggesting that exogenous MSCs are disease responsive.

Various soluble molecules have been reported to play a role in the mobilization or recruitment of MSCs to tumor sites; however, the major players are the immunoregulatory cytokine TGF-β[40,56,88-90], stromal cell-derived factor 1, also known as C-X-C motif chemokine 12 (CXCL12), and CXCR4, its receptor that is abundantly secreted by tumor cells[118,121-124,128]. Specifically, experimental evidence has established the CXCL12/CXCR4 pathway as a pivotal pathway for MSC and malignant cell migration and homing. Examples include reports suggesting the following: (*i*) MSC tumor tropism is mediated by matrix metalloproteinase-1 via a mechanism dependent on cross-talk with CXCL12/CXCR4 axis[129] (129); (*ii*) CXCL12 is abundantly released by BM-MSCs and drives the homing of leukemic cells in the bone marrow stroma in pediatric precursor B-cell acute lymphoblastic leukemia[130]; and (*iii*) CXCL12/CXCR4 signals the silencing results in the inhibition of MSC migration to the primary tumor and metastasis sites in solid cancers, such as breast carcinoma[119,120].

MSC paracrine activity controls stromal component production and immune response

MSCs and derived tumorigenesis-favoring cells, such as CAFs, control the production of stromal components and may sustain the maintenance of cancer cells[10,11,99]. For instance, MSCs regulate chemotaxis, activation, function, and survival of neutrophils via an IL-6-STAT3-ERK1/2 signaling cascade in gastric cancer and related solid cancers[99,131]. These MSC-primed neutrophils promote the differentiation of normal MSCs into CAFs[131]. Furthermore, MSCs promote angiogenic processes that result in blood vessels sustaining neoplastic tissue through its paracrine activity. The proangiogenic molecules released include IL-6, endotheline-1, VEGF, and FGF4[132,133].

Unlike injured sites where tissue repair is promoted[84-87,133] and in organ transplant settings where the probability of rejection of transplant tissues is decreased[94,95,103], the immunosuppressive action of MSCs may result in the suppression of cancer immunity in tumors, enabling cancer cells to escape immune surveillance. As observed in tissue repair processes, MSCs can influence almost all the

components of the immune system to attenuate inflammation and control immune response by interfering with various immune phenomena, such as cytokine secretion and the cytotoxicity of T- and NK cells, B-cell maturation and antibody secretion, and APC maturation, activation, and function[102,134,135]. Moreover, the MSC-mediated immunosuppression in the tumor stroma is partly triggered via paracrine activity. Immunosuppressive properties appear when MSCs and CAFS are involved in cell-cell interaction with immune cells, released by the anti-inflammatory cytokine TGF-β, or are stimulated by proinflammatory cytokines, such as TNF-α and IFN-γ[40,56,88-90]. For example, the *in vitro* immunosuppressive properties of MSCs towards NK, T, and B cells are triggered by the stimulation of MSCs in TNF-α and IFN-γ treatments. Such stimulation enables MSCs to produce molecules, such as PGE2, iNOS (mouse), or IDO (human)[96-98]. Notably, some of these products (that is, chemokines and PGE2) can attract immune cells[136-138], whereas others (that is, iNOS and IDO) induce immunosuppression[40,56,88-90].

Moreover, damaged tissues and tumor microenvironments are rich in soluble factors belonging to the secretome of MSCs that can favor tumorigenic processes, such as IL-1, IL-17, IL6, IFN-γ, TNF-α, Wnt, and Jagged[135,36,39-41,139]. These factors can induce profound changes in the capacity for MSC, drive its differentiation into CAFs[111,114,115], and produce growth factors[29,35,39] and angiogenic[112,115] and metastatic cytokines[118-121]. These findings suggest that MSCs may participate in the pathogenic vicious cycle wherein tumor cells modify stromal cells, and in turn, MSCs promote malignant cell maintenance and tumor growth via plastic and biochemical changes in the tumor microenvironment (**Figure1**).

MSC homing to tumors: pro- or antitumor action?

Discrepancies in antitumor and tumor-promoting roles of homing MSCs

Conflicting data and concepts about antitumor and tumor-promoting roles of MSCs have been reported. Most reports suggest the tumor-promoting roles of MSCs. Gastric cancer-derived MSCs can prompt gastric cancer progression through secretion of CXCL8[140] and PDGF[141]. In another recent report, BM-MSCs protected primary B cell precursor acute lymphoblastic leukemia cells from p53 accumulation and subsequent apoptotic cell death via a PGE2-dependent mechanism[142], suggesting that MSCs protect cancer cells from external aggression and confer chemoresistance[10,83,102]. Cross-talk between MSCs and tumor cells allows the latter to escape from apoptosis induced by chemotherapy drugs, suggesting that an enhanced understanding of such cross-talk could reveal improved targets for progressing classical therapies. Evidence-based reported mechanisms accounting for the protective interaction between MSCs and tumor cells include the activation of developmental pathways, such as Wnt, notch, sonic hedgehog, TGF-β, and MAPK[83,102-105], as well as cell adhesion and growth factors[10,107-109,143]. Inhibiting these factors improves treatments using classical chemotherapy agents. When MSCs were cultured with B-ALL and CLL cells in presence of notch-blocking antibodies or pan notch inhibitors, like gamma-secretase inhibitors, the resistant leukemic cells were sensitized to drug-induced apoptosis, even in the presence of MSCs[83,102]. Similarly, the inhibition of hedgehog[144] or Wnt[103] signaling on MSCs enhanced the sensibility of tumors to classical chemotherapies.

The anticancer properties of MSCs have been reported, particularly the attractive MSC potential for gene or drug delivery in cancer therapy that has emerged from the cancer tropism of these cells[145,146]. For instance, targeted inhibition of osteosarcoma tumor growth by BM-MSCs expressing the suicide gene therapy system cytosine deaminase/5-fluorocytosine was reported in tumor-bearing mice[145]. Human AT-MSCs inhibited human melanoma cell growth in a conditioned medium, and a reduction in tumor size was observed in athymic mice when MSCs were injected in the tissues surrounding the tumor[147]. The antitumor role of MSCs was suggested by studies aimed at developing a traceable therapeutic strategy for treating breast cancer using MSCs[148,149].

MSCs can induce cancer cell survival, stemness, and chemoresistance by differentiating into cancer-associated fibroblasts (CAFs) using a tumor growth factor β type 1 (TGFβ1)-dependent mechanism, and by releasing soluble factors that favor angiogenesis and immunosuppression in the tumor microenvironment, such as prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF). MSCs can mediate anti-cancer effects by releasing anti-cancer factors, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), via mechanisms that are not well understood.

Factors accounting for MSC ability to play both tumorigenic and anti-tumorigenic roles

Factors accounting for the ability of MSCs to play both pro- and anti-tumorigenic roles in tumor microenvironment are

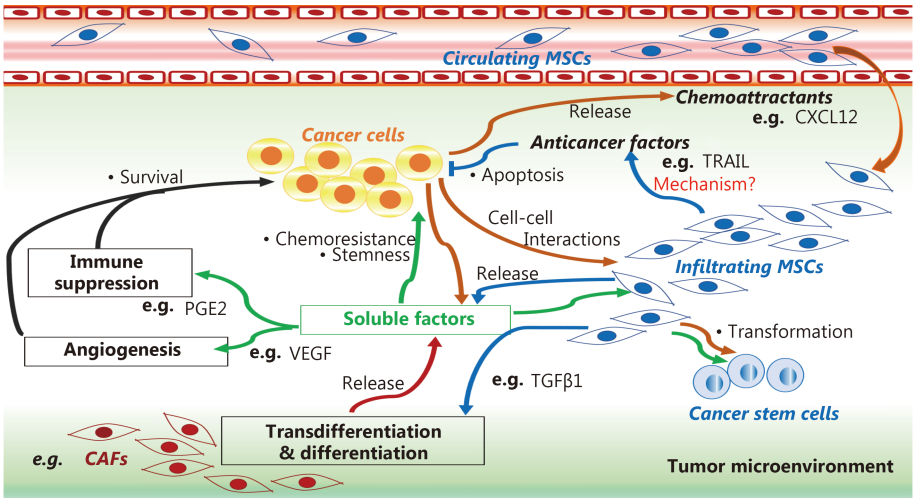

Figure 1 MSC role in tumor microenvironment. MSCs can induce cancer cell survival, stemness, and chemoresistance by differentiating into cancer-associated fibroblasts (CAFs) using a tumor growth factor β type 1 (TGFβ1)-dependent mechanism, and by releasing soluble factors that favor angiogenesis and immunosuppression in the tumor microenvironment, such as prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF). MSCs can mediate anti-cancer effects by releasing anti-cancer factors, such as tumor necrosis factor-related apoptosis inducing ligand (TRAIL), via mechanisms that are not well understood.

complex. These factors include MSC source, secretome, nature of interactions with cancer and host immune cells, type of cancer and cancer cell lines, and specific *in vivo* or *in vitro* condition[7,146,150,151]. Notably, MSC-secreted tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was reported as a major promoter of MSC pro-apoptotic properties on tumor cells[150,151], but its expression patterns in MSCs and cancer models has not been extensively investigated[146]. Consequently, data on the precise conditions of release of TRAIL and, thus, on the therapeutic relevance of the release induction by MSCs in tumors, are poorly understood, despite recent reports suggesting that MSC-released TRAIL promotes apoptosis even in resistant solid cancer cells[150,151].

Moreover, concerning the origin of MSCs, several studies have been designed involving MSCs originating from healthy donors and are functionally different from cancer patients' MSCs that have undergone deep cellular and molecular changes in the tumor stroma, following direct interaction with tumor cells[111,114,115] or exposure to soluble molecules secreted by the microenvironment[112-115,121]. Consequently, MSCs from tumors could promote cancer progression mainly by secreting soluble factors and increasing the number of cancer-promoting stem cells in the tumor microenvironment[152-154]. Moreover, short-term memory of environmental stimuli and danger signals were recently reported in MSCs[7], thereby increasing the complexity for predicting MSC responses in a specific environment.

Finally, discrepancies in available data emerged from changes in MSC properties when moving from *in vitro* to *in vivo* contexts[155]. Moreover, in a number of studies, cellular events that are considered as unequivocal indicators of antitumor or tumor promoting effect are insufficient for such conclusion. For instance, co-culture of leukemic cells with MSCs can induce growth arrest of leukemic cells; however, this cannot be always considered as an anticancer effect because cell quiescence is a well-known strategy of leukemic stem cells that allow them to escape from chemotherapeutic agents that target rapidly dividing cells[156].

Conclusions

The multipotency and the ability of MSCs to secrete soluble factors that induce immunosuppression and favoring angiogenesis confer to these stem cells the ability to repair injured tissues. The specific tropism of these cells allows them to migrate and home into injured tissues to repair them and induce immunosuppression, resulting in the prevention of transplant-related immunity. These properties are the basis for the large use of MSCs in regenerative medicine, tissue engineering, and organ transplantation. However, clinical and experimental bodies of evidence show that MSCs are chemically attracted by tumors. In this context, the plastic properties of MSCs favor tumorigenesis; as soluble factors,

they favor cancer cell maintenance, proliferation, chemoresistance, and suppress anticancer immunity. Moreover, MSC fusion with cancer cells and the tumor microenvironment drive MSC differentiation into CAFs, thereby favoring tumorigenesis and soluble factor release. Nevertheless, many studies showed that MSCs release potent anticancer molecules in the tumor microenvironment. Characterization of the mechanisms that drive the release of such molecules may give the cue for anticancer strategies to re-sensitize and induce apoptosis in previously chemoresistant cancer cells.

Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. Cell Commun Signal. 2011; 9: 12
2. Jin HJ, Bae YK, Kim M, Kwon SJ, Jeon HB, Choi SJ, et al. Comparative analysis of human mesenchymal stem cells from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. Int J Mol Sci. 2013; 14: 17986-8001.
3. Phinney DG, Sensebé L. Mesenchymal stromal cells: misconceptions and evolving concepts. Cytotherapy. 2013; 15: 140-5.
4. Oswald J, Boxberger S, Jørgensen B, Feldmann S, Ehninger G, Bornhäuser M, et al. Mesenchymal stem cells can be differentiated into endothelial cells in vitro. Stem Cells. 2004; 22: 377-84.
5. Portalska KJ, Groen N, Krenning G, Georgi N, Mentink A, Harmsen MC, et al. The effect of donor variation and senescence on endothelial differentiation of human mesenchymal stromal cells. Tissue Eng Part A. 2013; 19: 2318-29.
6. Rybachuk OA, Pivneva TA. Prospects of the use of mesenchymal and neuromesenchymal stem cells. Neurophysiology. 2013; 45: 477-94.
7. Liu GY, Liu Y, Lu Y, Qin YR, Di GH, Lei YH, et al. Short-term memory of danger signals or environmental stimuli in mesenchymal stem cells: implications for therapeutic potential. Cell Mol Immunol. 2016; 13: 369-78.
8. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006; 8: 315-7.
9. 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: 1883-8.
10. Seke Etet PF, Vecchio L, Bogne Kamga P, Nchiwan Nukenine E, Krampera M, Nwabo Kamdje AH. Normal hematopoiesis and hematologic malignancies: role of canonical Wnt signaling pathway and stromal microenvironment. Biochim Biophys Acta. 2013; 1835: 1-10.
11. Vecchio L, Seke Etet PF, Kipanyula MJ, Krampera M, Nwabo Kamdje AH. Importance of epigenetic changes in cancer etiology, pathogenesis, clinical profiling, and treatment: what can be learned from hematologic malignancies? Biochim Biophys Acta. 2013; 1836: 90-104.
12. Kuliev A, Rechitsky S, Tur-Kaspa I, Verlinsky Y. Preimplantation genetics: Improving access to stem cell therapy. Ann N Y Acad Sci. 2005; 1054: 223-7.
13. Brunstein CG, Wagner JE. Cord blood transplantation for adults. Vox Sang. 2006; 91: 195-205.
14. Ismail A. Stem cell research and ethics: an update. Oman Med J. 2015; 30: 1-2.
15. Lowenthal J, Sugarman J. Ethics and policy issues for stem cell research and pulmonary medicine. Chest. 2015; 147: 824-34.
16. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol. 2007; 213: 341-7.
17. Satija NK, Singh VK, Verma YK, Gupta P, Sharma S, Afrin F, et al. Mesenchymal stem cell-based therapy: a new paradigm in regenerative medicine. J Cell Mol Med. 2009; 13: 4385-402.
18. Tevlin R, Walmsley GG, Marecic O, Hu MS, Wan DC, Longaker MT. Stem and progenitor cells: advancing bone tissue engineering. Drug Deliv Transl Res. 2016; 6: 159-73.
19. Huyer LD, Montgomery M, Zhao YM, Xiao Y, Conant G, Korolj A, et al. Biomaterial based cardiac tissue engineering and its applications. Biomed Mater. 2015; 10: 034004
20. James R, Laurencin CT. Regenerative engineering and bionic limbs. Rare Metals. 2015; 34: 143-55.
21. Chi Y, Han ZB, Xu FY, Wang YW, Feng XM, Chen F, et al. Adipogenic potentials of mesenchymal stem cells from human bone marrow, umbilical cord and adipose tissue are different. J Exp Hematol. 2014; 22: 588-94.
22. Li CY, Wu XY, Tong JB, Yang XX, Zhao JL, Zheng QF, et al. Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. Stem Cell Res Ther. 2015; 6: 55
23. Barberini DJ, Freitas NP, Magnoni MS, Maia L, Listoni AJ, Heckler MC, et al. Equine mesenchymal stem cells from bone marrow, adipose tissue and umbilical cord: immunophenotypic characterization and differentiation potential. Stem Cell Res Ther. 2014; 5: 25
24. Huang L, Niu CG, Willard B, Zhao WM, Liu L, He W, et al. Proteomic analysis of porcine mesenchymal stem cells derived from bone marrow and umbilical cord: implication of the proteins involved in the higher migration capability of bone marrow mesenchymal stem cells. Stem Cell Res Ther. 2015; 6: 77
25. Saxena AK, Singh D, Gupta J. Role of stem cell research in therapeutic purpose—a hope for new horizon in medical biotechnology. J Exp Ther Oncol. 2010; 8: 223-33.

26. Alrefai MT, Murali D, Paul A, Ridwan KM, Connell JM, Shum-Tim D. Cardiac tissue engineering and regeneration using cell-based therapy. Stem Cells Cloning. 2015; 8: 81-101.
27. Chen S, Fu PL, Cong RJ, Wu HS, Pei M. Strategies to minimize hypertrophy in cartilage engineering and regeneration. Genes Dis. 2015; 2: 76-95.
28. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011; 9: 11-5.
29. Ikhapoh IA, Pelham CJ, Agrawal DK. Sry-type HMG box 18 contributes to the differentiation of bone marrow-derived mesenchymal stem cells to endothelial cells. Differentiation. 2015; 89: 87-96.
30. Wang N, Zhang R, Wang SJ, Zhang CL, Mao LB, Zhuang CY, et al. Vascular endothelial growth factor stimulates endothelial differentiation from mesenchymal stem cells via Rho/myocardin-related transcription factor—a signaling pathway. Int J Biochem Cell Biol. 2013; 45: 1447-56.
31. Zhang R, Wang N, Zhang M, Zhang LN, Guo ZX, Luo XG, et al. Rho/MRTF-A-induced integrin expression regulates angiogenesis in differentiated multipotent mesenchymal stem cells. Stem Cells Int. 2015;2015:Article ID 534758.
32. Roos F, Terrell TG, Godowski PJ, Chamow SM, Schwall RH. Reduction of alpha-naphthylisothiocyanate-induced hepatotoxicity by recombinant human hepatocyte growth factor. Endocrinology. 1992; 131: 2540-4.
33. Ishiki Y, Ohnishi H, Muto Y, Matsumoto K, Nakamura T. Direct evidence that hepatocyte growth factor is a hepatotrophic factor for liver regeneration and has a potent antihepatitis effect in vivo. Hepatology. 1992; 16: 1227-35.
34. Yao P, Zhan YQ, Xu WX, Li CY, Yue PB, Xu CW, et al. Hepatocyte growth factor-induced proliferation of hepatic stem-like cells depends on activation of NF-κB. J Hepatol. 2004; 40: 391-8.
35. Chablais F, Jaźwińska A. The regenerative capacity of the zebrafish heart is dependent on TGFβ signaling. Development. 2012; 139: 1921-30.
36. Liu XB, Chen HQ, Zhu W, Chen H, Hu XY, Jiang Z, et al. Transplantation of SIRT1-engineered aged mesenchymal stem cells improves cardiac function in a rat myocardial infarction model. J Heart Lung Transplant. 2014; 33: 1083-92.
37. Edwards SS, Zavala G, Prieto CP, Elliott M, Martínez S, Egaña JT, et al. Functional analysis reveals angiogenic potential of human mesenchymal stem cells from Wharton's jelly in dermal regeneration. Angiogenesis. 2014; 17: 851-66.
38. Li DG, Wang N, Zhang L, Zhu HY, Bai XY, Fu B, et al. Mesenchymal stem cells protect podocytes from apoptosis induced by high glucose via secretion of epithelial growth factor. Stem Cell Res Ther. 2013; 4: 103
39. Windmolders S, De Boeck A, Koninckx R, Daniëls A, De Wever O, Bracke M, et al. Mesenchymal stem cell secreted platelet derived growth factor exerts a pro-migratory effect on resident Cardiac Atrial appendage Stem Cells. J Mol Cell Cardiol. 2014; 66: 177-88.
40. Sesia SB, Duhr R, Medeiros da Cunha C, Todorov A, Schaeren S, Padovan E, et al. Anti-inflammatory/tissue repair macrophages enhance the cartilage-forming capacity of human bone marrow-derived mesenchymal stromal cells. J Cell Physiol. 2015; 230: 1258-69.
41. Lan YW, Choo KB, Chen CM, Hung TH, Chen YB, Hsieh CH, et al. Hypoxia-preconditioned mesenchymal stem cells attenuate bleomycin-induced pulmonary fibrosis. Stem Cell Res Ther. 2015; 6: 97
42. Kim DH, Yoo KH, Choi KS, Choi J, Choi SY, Yang SE, et al. Gene expression profile of cytokine and growth factor during differentiation of bone marrow-derived mesenchymal stem cell. Cytokine. 2005; 31: 119-26.
43. Kean TJ, Lin P, Caplan AI, Dennis JE. MSCs: delivery routes and engraftment, cell-targeting strategies, and immune modulation. Stem Cells Int. 2013;2013:Article ID 732742.
44. Li N, Wang C, Jia LX, Du J. Heart regeneration, stem cells, and cytokines. Regen Med Res. 2014; 2: 6
45. Ma S, Xie N, Li W, Yuan B, Shi Y, Wang Y. Immunobiology of mesenchymal stem cells. Cell Death Differ. 2014; 21: 216-25.
46. Bindslev L, Haack-Sorensen M, Bisgaard K, Kragh L, Mortensen S, Hesse B, et al. Labelling of human mesenchymal stem cells with indium-111 for SPECT imaging: effect on cell proliferation and differentiation. Eur J Nucl Med Mol Imaging. 2006; 33: 1171-7.
47. Amsalem Y, Mardor Y, Feinberg MS, Landa N, Miller L, Daniels D, et al. Iron-oxide labeling and outcome of transplanted mesenchymal stem cells in the infarcted myocardium. Circulation. 2007;116:I-38-45.
48. Toupet K, Maumus M, Peyrafitte JA, Bourin P, van Lent PLEM, Ferreira R, et al. Long-term detection of human adipose-derived mesenchymal stem cells after intraarticular injection in SCID mice. Arthritis Rheum. 2013; 65: 1786-94.
49. Niyibizi C, Wang SJ, Mi ZB, Robbins PD. The fate of mesenchymal stem cells transplanted into immunocompetent neonatal mice: implications for skeletal gene therapy via stem cells. Mol Ther. 2004; 9: 955-63.
50. Wang H, Cao F, De A, Cao Y, Contag C, Gambhir SS, et al. Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging. Stem Cells. 2009; 27: 1548-58.
51. Bexell D, Gunnarsson S, Tormin A, Darabi A, Gisselsson D, Roybon L, et al. Bone marrow multipotent mesenchymal stroma cells act as pericyte-like migratory vehicles in experimental gliomas. Mol Ther. 2009; 17: 183-90.
52. Liu X, Shen W, Yang Y, Liu G. Therapeutic implications of mesenchymal stem cells transfected with hepatocyte growth factor transplanted in rat kidney with unilateral ureteral obstruction. J Pediatr Surg. 2011; 46: 537-45.
53. Gao JZ, Dennis JE, Muzic RF, Lundberg M, Caplan AI. The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion. Cells Tissues Organs. 2001; 169: 12-20.
54. Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S,

Tessone A, et al. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. Circulation. 2003; 108: 863-8.

55. Park M, Kim YH, Woo SY, Lee HJ, Yu Y, Kim HS, et al. Tonsil-derived mesenchymal stem cells ameliorate CCl_4-induced liver fibrosis in mice via autophagy activation. Sci Rep. 2015; 5: 8616
56. Tang YH, Chen YY, Wang X, Song G, Li YG, Shi LJ. Combinatorial intervention with mesenchymal stem cells and granulocyte colony-stimulating factor in a rat model of ulcerative colitis. Dig Dis Sci. 2015; 60: 1948-57.
57. Yang C, Li J, Lin H, Zhao KQ, Zheng CQ. Nasal mucosa derived-mesenchymal stem cells from mice reduce inflammation via modulating immune responses. PLoS One. 2015; 10: e0118849
58. Rustad KC, Gurtner GC. Mesenchymal stem cells home to sites of injury and inflammation. Adv Wound Care (New Rochelle). 2012; 1: 147-52.
59. Min K, Song J, Kang JY, Ko J, Ryu JS, Kang MS, et al. Umbilical cord blood therapy potentiated with erythropoietin for children with cerebral palsy: a double-blind, randomized, placebo-controlled trial. Stem Cells. 2013; 31: 581-91.
60. Kang M, Min K, Jang J, Kim SC, Kang MS, Jang SJ, et al. Involvement of immune responses in the efficacy of cord blood cell therapy for cerebral palsy. Stem Cells Dev. 2015; 24: 2259-68.
61. Alvarez Palomo AB, McLenachan S, Chen FK, Da Cruz L, Dilley RJ, Requena J, et al. Prospects for clinical use of reprogrammed cells for autologous treatment of macular degeneration. Fibrogenesis Tissue Repair. 2015; 8: 9
62. Siler U, Paruzynski A, Holtgreve-Grez H, Kuzmenko E, Koehl U, Renner ED, et al. Successful combination of sequential gene therapy and rescue Allo-HSCT in two children with X-CGD-Importance of timing. Curr Gene Ther. 2015; 15: 416-27.
63. de Berranger E, Jubert C, Michel G. [Post-hematopietic stem cell transplant complications]. Bull Cancer. 2015; 102: 648-55.
64. Liu HB, Liu SB, Li Y, Wang XH, Xue WJ, Ge GQ, et al. The role of SDF-1-CXCR4/CXCR7 axis in the therapeutic effects of hypoxia-preconditioned mesenchymal stem cells for renal ischemia/reperfusion injury. PLoS One. 2012; 7: e34608
65. Li Y, Guo G, Li L, Chen F, Bao J, Shi YJ, et al. Three-dimensional spheroid culture of human umbilical cord mesenchymal stem cells promotes cell yield and stemness maintenance. Cell Tissue Res. 2015; 360: 297-307.
66. Treacy O, Ryan AE, Heinzl T, O'Flynn L, Cregg M, Wilk M, et al. Adenoviral transduction of mesenchymal stem cells: in vitro responses and in vivo immune responses after cell transplantation. PLoS One. 2012; 7: e42662
67. Orlic D, Kajstura J, Chimenti S, Bodine DM, Leri A, Anversa P. Bone marrow stem cells regenerate infarcted myocardium. Pediatr Transplant. 2003; 7: 86-8.
68. Duran JM, Makarewich CA, Sharp TE, Starosta T, Zhu F, Hoffman NE, et al. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. Circ Res. 2013; 113: 539-52.
69. Ryu HH, Lim JH, Byeon YE, Park JR, Seo MS, Lee YW, et al. Functional recovery and neural differentiation after transplantation of allogenic adipose-derived stem cells in a canine model of acute spinal cord injury. J Vet Sci. 2009; 10: 273-84.
70. Kouris NA, Schaefer JA, Hatta M, Freeman BT, Kamp TJ, Kawaoka Y, et al. Directed fusion of mesenchymal stem cells with cardiomyocytes via VSV-G facilitates stem cell programming. Stem Cells Int. 2012;2012:Article ID 414038.
71. He XH, Li BS, Shao Y, Zhao N, Hsu Y, Zhang ZX, et al. Cell fusion between gastric epithelial cells and mesenchymal stem cells results in epithelial-to-mesenchymal transition and malignant transformation. BMC Cancer. 2015; 15: 24
72. Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circ Res. 2011; 109: 923-40.
73. Zhang J, Ho JCY, Chan YC, Lian QZ, Siu CW, Tse HF. Overexpression of myocardin induces partial transdifferentiation of human-induced pluripotent stem cell-derived mesenchymal stem cells into cardiomyocytes. Physiol Rep. 2014; 2: e00237
74. Hao NB, Li CZ, Lü MH, Tang B, Wang SM, Wu YY, et al. SDF-1/CXCR4 axis promotes MSCs to repair liver injury partially through trans-differentiation and fusion with hepatocytes. Stem Cells Int. 2015;2015:Article ID 960387.
75. Liu WH, Song FQ, Ren LN, Guo WQ, Wang T, Feng YX, et al. The multiple functional roles of mesenchymal stem cells in participating in treating liver diseases. J Cell Mol Med. 2015; 19: 511-20.
76. Manochantr S, Marupanthorn K, Tantrawatpan C, Kheolamai P. The expression of neurogenic markers after neuronal induction of chorion-derived mesenchymal stromal cells. Neurol Res. 2015; 37: 545-52.
77. Harkin DG, Foyn L, Bray LJ, Sutherland AJ, Li FJ, Cronin BG. Concise reviews: can mesenchymal stromal cells differentiate into corneal cells? A systematic review of published data Stem Cells. 2015; 33: 785-91.
78. Klyushnenkova E, Mosca JD, Zernetkina V, Majumdar MK, Beggs KJ, Simonetti DW, et al. T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci. 2005; 12: 47-57.
79. Crop MJ, Baan CC, Korevaar SS, Ijzermans JNM, Weimar W, Hoogduijn MJ. Human adipose tissue-derived mesenchymal stem cells induce explosive T-cell proliferation. Stem Cells Dev. 2010; 19: 1843-53.
80. Stagg J, Pommey S, Eliopoulos N, Galipeau J. Interferon-γ-stimulated marrow stromal cells: a new type of nonhematopoietic antigen-presenting cell. Blood. 2006; 107: 2570-7.
81. Romieu-Mourez R, François 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: 7963-73.
82. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood. 2005; 105: 1815-22.

83. Nwabo Kamdje AH, Mosna F, Bifari F, Lisi V, Bassi G, Malpeli G, et al. Notch-3 and Notch-4 signaling rescue from apoptosis human B-ALL cells in contact with human bone marrow-derived mesenchymal stromal cells. Blood. 2011; 118: 380-9.
84. Reading JL, Sabbah S, Busch S, Tree TIM. Mesenchymal stromal cells as a means of controlling pathological T-cell responses in allogeneic islet transplantation. Curr Opin Organ Transplant. 2013; 18: 59-64.
85. Calkoen FGJ, Brinkman DMC, Vervat C, van Ostaijen-Ten Dam MM, Ten Cate R, van Tol MJD, et al. Mesenchymal stromal cells isolated from children with systemic juvenile idiopathic arthritis suppress innate and adaptive immune responses. Cytotherapy. 2013; 15: 280-91.
86. Cassatella MA, Mosna F, Micheletti A, Lisi V, Tamassia N, Cont C, et al. Toll-like receptor-3-activated human mesenchymal stromal cells significantly prolong the survival and function of neutrophils. Stem Cells. 2011; 29: 1001-11.
87. Kota DJ, DiCarlo B, Hetz RA, Smith P, Cox CS Jr, Olson SD. Differential MSC activation leads to distinct mononuclear leukocyte binding mechanisms. Sci Rep. 2014; 4: 4565
88. Molendijk I, Duijvestein M, van der Meulen-de Jong AE, van Deen WK, Swets M, Hommes DW, et al. Immunomodulatory effects of mesenchymal stromal cells in Crohn's disease. J Allergy (Cairo). 2012;2012: Article ID 187408.
89. Su J, Chen X, Huang Y, Li W, Li J, Cao K, et al. Phylogenetic distinction of iNOS and IDO function in mesenchymal stem cell-mediated immunosuppression in mammalian species. Cell Death Differ. 2014; 21: 388-96.
90. Jin YJ, Hong HS, Son Y. Substance P enhances mesenchymal stem cells-mediated immune modulation. Cytokine. 2015; 71: 145-53.
91. Oh JY, Lee RH, Yu JM, Ko JH, Lee HJ, Ko AY, et al. Intravenous mesenchymal stem cells prevented rejection of allogeneic corneal transplants by aborting the early inflammatory response. Mol Ther. 2012; 20: 2143-52.
92. Reading JL, Yang JH, Sabbah S, Skowera A, Knight RR, Pinxteren J, et al. Clinical-grade multipotent adult progenitor cells durably control pathogenic T cell responses in human models of transplantation and autoimmunity. J Immunol. 2013; 190: 4542-52.
93. Zhang R, Liu Y, Yan K, Chen L, Chen XR, Li P, et al. Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury. J Neuroinflammation. 2013; 10: 871
94. Lee HJ, Ko JH, Ko AY, Kim MK, Wee WR, Oh JY. Intravenous infusion of mesenchymal stem/stromal cells decreased $CCR7^{+}$ antigen presenting cells in mice with corneal allotransplantation. Curr Eye Res. 2014; 39: 780-9.
95. Omoto M, Katikireddy KR, Rezazadeh A, Dohlman TH, Chauhan SK. Mesenchymal stem cells home to inflamed ocular surface and suppress allosensitization in corneal transplantation. Invest Ophthalmol Vis Sci. 2014; 55: 6631-8.
96. Lee HJ, Ko JH, Jeong HJ, Ko AY, Kim MK, Wee WR, et al. Mesenchymal stem/stromal cells protect against autoimmunity via CCL2-dependent recruitment of myeloid-derived suppressor cells. J Immunol. 2015; 194: 3634-45.
97. Ricciardi M, Malpeli G, Bifari F, Bassi G, Pacelli L, Nwabo Kamdje AH, Chilosi M, Krampera M. Comparison of epithelial differentiation and immune regulatory properties of mesenchymal stromal cells derived from human lung and bone marrow. PLoS One. 2012; 7(5): e35639
98. Duffy MM, McNicholas BA, Monaghan DA, Hanley SA, McMahon JM, Pindjakova J, et al. Mesenchymal stem cells and a vitamin D receptor agonist additively suppress T helper 17 cells and the related inflammatory response in the kidney. Am J Physiol Renal Physiol. 2014; 307: F1412-26.
99. Krawiec JT, Liao HT, Kwan LL, D'Amore A, Weinbaum JS, Rubin JP, et al. Evaluation of the stromal vascular fraction of adipose tissue as the basis for a stem cell-based tissue-engineered vascular graft. J Vasc Surg. doi: 10.1016/j.jvs.2016.09.034.
100. Nwabo Kamdje AH, Seke Etet PF, Vecchio L, Muller JM, Krampera M, Lukong KE. Signaling pathways in breast cancer: therapeutic targeting of the microenvironment. Cell Signal. 2014; 26: 2843-56.
101. Nwabo Kamdje AH, Seke Etet PF, Vecchio L, Tagne RS, Amvene JM, Muller JM, et al. New targeted therapies for breast cancer: A focus on tumor microenvironmental signals and chemoresistant breast cancers. World J Clin Cases. 2014; 2: 769-86.
102. Nwabo Kamdje AH, Bassi G, Pacelli L, Malpeli G, Amati E, Nichele I, et al. Role of stromal cell-mediated Notch signaling in CLL resistance to chemotherapy. Blood Cancer J. 2012; 2: e73
103. Zhang B, Li M, McDonald T, Holyoake TL, Moon RT, Campana D, et al. Microenvironmental protection of CML stem and progenitor cells from tyrosine kinase inhibitors through N-cadherin and Wnt-β-catenin signaling. Blood. 2013; 121: 1824-38.
104. Han ZP, Jing YY, Xia Y, Zhang SS, Hou J, Meng Y, et al. Mesenchymal stem cells contribute to the chemoresistance of hepatocellular carcinoma cells in inflammatory environment by inducing autophagy. Cell Biosci. 2014; 4: 22
105. Donnelly JM, Engevik A, Feng R, Xiao C, Boivin GP, Li J, et al. Mesenchymal stem cells induce epithelial proliferation within the inflamed stomach. Am J Physiol Gastrointest Liver Physiol. 2014; 306: G1075-88.
106. Djiogue S, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, et al. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013; 20: R1-17.
107. Kucerova L, Skolekova S, Demkova L, Bohovic R, Matuskova M. Long-term efficiency of mesenchymal stromal cell-mediated CD-MSC/5FC therapy in human melanoma xenograft model. Gene Ther. 2014; 21: 874-87.
108. Takam Kamga P, Nwabo Kamdje AH. Signaling pathways in leukemia: any role for medicinal plants in leukemia therapy. J Dis Med Plants. 2015; 1: 76-9.
109. Richard TS, Nwabo Kamdje AH, Mukhtar F. Medicinal plants in breast cancer therapy. J Dis Med Plants. 2015; 1: 19-23.
110. Fodouop SPC, Simo RT, Amvene JM, Talla E, Etet PFS, Takam P, et al. Bioactivity and therapeutic potential of plant extracts in

cancer and infectious diseases. J Dis Med Plants. 2015; 1: 8-18.
111. Pattabiraman DR, Weinberg RA. Tackling the cancer stem cells - what challenges do they pose? Nat Rev Drug Discov. 2014; 13: 497-512.
112. Orimo A, Weinberg RA. Stromal fibroblasts in cancer: a novel tumor-promoting cell type. Cell Cycle. 2006; 5: 1597-601.
113. Erez N, Truitt M, Olson P, Hanahan D. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-κB-dependent manner. Cancer Cell. 2010; 17: 135-47.
114. Cirri P, Chiarugi P. Cancer associated fibroblasts: the dark side of the coin. Am J Cancer Res. 2011; 1: 482-97.
115. Yu Y, Xiao CH, Tan LD, Wang QS, Li XQ, Feng YM. Cancer-associated fibroblasts induce epithelial-mesenchymal transition of breast cancer cells through paracrine TGF-β signalling. Br J Cancer. 2014; 110: 724-32.
116. Mishra PJ, Mishra PJ, Humeniuk R, Medina DJ, Alexe G, Mesirov JP, et al. Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res. 2008; 68: 4331-9.
117. Jotzu C, Alt E, Welte G, Li J, Hennessy BT, Devarajan E, et al. Adipose tissue derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor derived factors. Cell Oncol. 2011; 34: 55-67.
118. Sugihara H, Ishimoto T, Yasuda T, Izumi D, Eto K, Sawayama H, et al. Cancer-associated fibroblast-derived CXCL12 causes tumor progression in adenocarcinoma of the esophagogastric junction. Med Oncol. 2015; 32: 618
119. Hong BX, Li HY, Zhang MJ, Xu JD, Lu Y, Zheng YH, et al. p38 MAPK inhibits breast cancer metastasis through regulation of stromal expansion. Int J Cancer. 2015; 136: 34-43.
120. Wobus M, List C, Dittrich T, Dhawan A, Duryagina R, Arabanian LS, et al. Breast carcinoma cells modulate the chemoattractive activity of human bone marrow-derived mesenchymal stromal cells by interfering with CXCL12. Int J Cancer. 2015; 136: 44-54.
121. Muhlethaler-Mottet A, Liberman J, Ascenção K, Flahaut M, Balmas BK, Yan P, et al. The CXCR4/CXCR7/CXCL12 axis is involved in a secondary but complex control of neuroblastoma metastatic cell homing. PLoS One. 2015; 10: e0125616
122. Müller N, Michen S, Tietze S, Töpfer K, Schulte A, Lamszus K, et al. Engineering NK cells modified with an EGFRvIII-specific chimeric antigen receptor to overexpress CXCR4 improves immunotherapy of CXCL12/SDF-1α-secreting glioblastoma. J Immunother. 2015; 38: 197-210.
123. Liao YX, Fu ZZ, Zhou CH, Shan LC, Wang ZY, Yin F, et al. AMD3100 reduces CXCR4-mediated survival and metastasis of osteosarcoma by inhibiting JNK and Akt, but not p38 or Erk1/2, pathways in *in vitro* and mouse experiments. Oncol Rep. 2015; 34: 33-42.
124. Margolin DA, Myers T, Zhang X, Bertoni DM, Reuter BA, Obokhare I, et al. The critical roles of tumor-initiating cells and the lymph node stromal microenvironment in human colorectal cancer extranodal metastasis using a unique humanized orthotopic mouse model. FASEB J. 2015; 29: 3571-81.
125. Aquino JB, Bolontrade MF, García MG, Podhajcer OL, Mazzolini G. Mesenchymal stem cells as therapeutic tools and gene carriers in liver fibrosis and hepatocellular carcinoma. Gene Ther. 2010; 17: 692-708.
126. Yang Y,Y Otte A, Hass R. Human mesenchymal stroma/stem cells exchange membrane proteins and alter functionality during interaction with different tumor cell lines. Stem Cells Dev. 2015; 24: 1205-22.
127. Wei HJ, Nickoloff JA, Chen WH, Liu HY, Lo WC, Chang YT, et al. FOXF1 mediates mesenchymal stem cell fusion-induced reprogramming of lung cancer cells. Oncotarget. 2014; 5: 9514-29.
128. Guo F, Wang Y, Liu J, Mok SC, Xue F, Zhang W. CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. Oncogene. 2016; 35: 816-26.
129. Ho IAW, Yulyana Y, Sia KC, Newman JP, Guo CM, Hui KM, et al. Matrix metalloproteinase-1-mediated mesenchymal stem cell tumor tropism is dependent on crosstalk with stromal derived growth factor 1/C-X-C chemokine receptor 4 axis. FASEB J. 2014; 28: 4359-68.
130. van den Berk LCJ, van der Veer A, Willemse ME, Theeuwes MJGA, Luijendijk MW, Tong WH, et al. Disturbed CXCR4/CXCL12 axis in paediatric precursor B-cell acute lymphoblastic leukaemia. Br J Haematol. 2014; 166: 240-9.
131. Zhu Q, Zhang X, Zhang L, Li W, Wu H, Yuan X, et al. The IL-6-STAT3 axis mediates a reciprocal crosstalk between cancer-derived mesenchymal stem cells and neutrophils to synergistically prompt gastric cancer progression. Cell Death Dis. 2014; 5: e1295
132. Watt SM, Gullo F, van der Garde M, Markeson D, Camicia R, Khoo CP, et al. The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. Br Med Bull. 2013; 108: 25-53.
133. Huang WH, Chang MC, Tsai KS, Hung MC, Chen HL, Hung SC. Mesenchymal stem cells promote growth and angiogenesis of tumors in mice. Oncogene. 2013; 32: 4343-54.
134. De Miguel MP, Fuentes-Julian S, Blazquez-Martinez A, Pascual CY, Aller MA, Arias J, et al. Immunosuppressive properties of mesenchymal stem cells: advances and applications. Curr Mol Med. 2012; 12: 574-91.
135. Haddad R, Saldanha-Araujo F. Mechanisms of T-cell immunosuppression by mesenchymal stromal cells: what do we know so far?. BioMed Res Int. 2014;2014:Article ID 216806.
136. Muthuswamy R, Mueller-Berghaus J, Haberkorn U, Reinhart TA, Schadendorf D, Kalinski P. PGE_2 transiently enhances DC expression of CCR7 but inhibits the ability of DCs to produce CCL19 and attract naive T cells. Blood. 2010; 116: 1454-9.
137. Obermajer N, Muthuswamy R, Odunsi K, Edwards RP, Kalinski P. PGE_2-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment. Cancer Res. 2011; 71: 7463-70.
138. Barrio L, Cuevas VD, Menta R, Mancheño-Corvo P, delaRosa O, Dalemans W, et al. Human adipose tissue-derived mesenchymal stromal cells promote B-cell motility and chemoattraction.

Cytotherapy. 2014; 16: 1692-9.

139. Korkaya H, Liu SL, Wicha MS. Breast cancer stem cells, cytokine networks, and the tumor microenvironment. J Clin Invest. 2011; 121: 3804-9.
140. Li W, Zhou Y, Yang J, Zhang X, Zhang HH, 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
141. Huang F, Wang M, Yang TT, Cai J, Zhang Q, Sun ZX, et al. Gastric cancer-derived MSC-secreted PDGF-DD promotes gastric cancer progression. J Cancer Res Clin Oncol. 2014; 140: 1835-48.
142. Naderi EH, Skah S, Ugland H, Myklebost O, Sandnes DL, Torgersen ML, et al. Bone marrow stroma-derived PGE2 protects BCP-ALL cells from DNA damage-induced p53 accumulation and cell death. Mol Cancer. 2015; 14: 14
143. Takam Kamga P, Bassi G, Cassaro A, Midolo M, Di Trapani M, Gatti A, Carusone R, Resci F, Perbellini O, Gottardi M, Bonifacio M, Nwabo Kamdje AH, Ambrosetti A, Krampera M. Notch signalling drives bone marrow stromal cell-mediated chemoresistance in acute myeloid leukemia. Oncotarget. 2016 Mar 7. doi: 10.18632/oncotarget.7964.
144. Liu ZQ, Xu JD, He J, Zheng YH, Li HY, Lu Y, et al. A critical role of autocrine sonic hedgehog signaling in human CD138+ myeloma cell survival and drug resistance. Blood. 2014; 124: 2061-71.
145. NguyenThai QA, Sharma N, Luong do H, Sodhi SS, Kim JH, Kim N, et al. Targeted inhibition of osteosarcoma tumor growth by bone marrow-derived mesenchymal stem cells expressing cytosine deaminase/5-fluorocytosine in tumor-bearing mice. J Gene Med. 2015; 17: 87-99.
146. Ramdasi S, Sarang S, Viswanathan C. Potential of Mesenchymal Stem Cell based application in Cancer. Int J Hematol Oncol Stem Cell Res. 2015; 9: 95-103.
147. 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: 159-68.
148. Wang YB, Li ZJ. Traceable therapeutic strategy for treatment of breast cancer with mesenchymal stem cells (MSCs). Cancer Cell & Microenvironment. 2014; 1: e198
149. Mohammadpour H, Majidzadeh-A K. Antitumor effect of conditioned media derived from murine MSCs and 5-aminolevulinic acid (5-ALA) mediated photodynamic therapy in breast cancer in vitro. Photodiagnosis Photodyn Ther. 2015; 12: 238-42.
150. Yuan ZQ, Kolluri KK, Sage EK, Gowers KHC, 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: 885-96.
151. Khorashadizadeh M, Soleimani M, Khanahmad H, Fallah A, Naderi M, Khorramizadeh M. Bypassing the need for pre-sensitization of cancer cells for anticancer TRAIL therapy with secretion of novel cell penetrable form of Smac from hA-MSCs as cellular delivery vehicle. Tumor Biol. 2015; 36: 4213-21.
152. Corre J, Mahtouk K, Attal M, Gadelorge M, Huynh A, Fleury-Cappellesso S, et al. Bone marrow mesenchymal stem cells are abnormal in multiple myeloma. Leukemia. 2007; 21: 1079-88.
153. McLean K, Gong YS, Choi Y, Deng N, Yang K, Bai SM, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. J Clin Invest. 2011; 121: 3206-19.
154. Guilloton F, Caron G, Ménard C, Pangault C, Amé-Thomas P, Dulong J. Mesenchymal stromal cells orchestrate follicular lymphoma cell niche through the CCL2-dependent recruitment and polarization of monocytes. Blood. 2012; 119: 2556-67.
155. Li L, Tian H, Yue WM, Zhu F, Li SH, Li WJ. Human mesenchymal stem cells play a dual role on tumor cell growth in vitro and in vivo. J Cell Physiol. 2011; 226: 1860-7.
156. Jin LH, Tabe Y, Konoplev S, Xu YY, Leysath CE, Lu HB, et al. CXCR4 up-regulation by imatinib induces chronic myelogenous leukemia (CML) cell migration to bone marrow stroma and promotes survival of quiescent CML cells. Mol Cancer Ther. 2008; 7: 48-58.

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