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Mesenchymal Stromal Cell Engagement in Cancer Cell Epithelial to Mesenchymal Transition

Drenka Trivanović,[1] Jelena Krstić,[1‡] Aleksandra Jauković,[1] Diana Bugarski,[1] and Juan F. Santibanez[2*]

[1]Laboratory for Experimental Hematology and Stem Cells, Institute for Medical Research, University of Belgrade, Belgrade, Republic of Serbia
[2]Group for Molecular Oncology, Institute for Medical Research, University of Belgrade, Belgrade, Republic of Serbia

Due to coexistence of stromal and epithelial tumor cells, their dynamic interactions have been widely recognized as significant cellular components to the tumor tissue integrity. Initiation and outcome of epithelial to mesenchymal transition (EMT) in tumor cells are dependent on their interaction with adjacent or recruited mesenchymal stromal cells (MSCs). A plethora of mechanisms are involved in MSCs-controlled employment of the developmental processes of EMT that contribute to loss of epithelial cell phenotype and acquisition of stemness, invasiveness and chemoresistance of tumor cells. Interplay of MSCs with tumor cells, including interchange of soluble biomolecules, plasma membrane structures, cytoplasmic content, and organelles, is established through cell–cell contact and/or by means of paracrine signaling. The main focus of this review is to summarize knowledge about involvement of MSCs in cancer cell EMT. Understanding the underlying cellular and molecular mechanism involved in the interplay between MSCs and cancer EMT is essential for development of effective therapy approaches, which in combination with current treatments may improve the control of tumor progression. *Developmental Dynamics 247:359–367, 2018*. © 2017 Wiley Periodicals, Inc.

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Introduction

It is now accepted that tumors are heterogeneous entities comprised by cells of multiple lineages, the extracellular matrix (ECM) and soluble molecules (Tlsty and Coussens, 2006). Furthermore, the tumor stroma or tumor microenvironment (TME), which includes several types of noncancerous cells and connective tissue, structurally and functionally supports cancer development (Eng et al., 2009). The tumor stroma is a complex mixture of cells, including local fibroblasts, smooth muscle cells, adipocytes, endothelium, pericytes, and various types of inflammatory cells, as well as extracellular matrix components (including structural proteins collagen, fibronectin, and proteoglycans, among others), whereas the interstitial fluid contains a variety of soluble inflammatory mediators and growth factors. TME has been recognized as a permissive or supporting feature for the tumor progression in epithelial cancers. Today, it is accepted that TME is not only an 'innocent bystander' actor, because it plays an important and active role in every step of epithelial cells tumorigenesis (Quail and Joyce, 2013). From some viewpoints, tumor development is dependent on physiologic response of tissue to aberrant TME (Barcellos-Hoff and Medina, 2005).

Stromal and epithelial cells may interact through direct cell–cell contac or by means of paracrine signaling as both cell populations produce a variety of matrix proteins, growth factors, proteases and their inhibitors, and cytokines (Hemmings, 2013). Importantly, stromal cells actively participate in the process of epithelial to mesenchymal transition (EMT). Due to their tumor-homing capacity and evident paracrine activity mesenchymal stromal cells (MSCs), also referred to as multipotent stromal cells or mesenchymal stem cells (Spees et al., 2016) are found also to be important players in tumor progression (Shi et al., 2016).

In this review, we use MSCs abbreviation for the mesenchymal stromal cells, as is proposed by the International Society for Cellular Therapy (Dominici et al., 2006). MSCs are recognized as heterogenic population tissue-specific stromal cells involved in homeostasis and repair of normal and injured tissues, with low frequency of "true" mesenchymal stem cells within (Lindner et al., 2010; Nombela-Arrieta et al., 2011; Robey, 2017). MSCs could be isolated from various adult connective tissues, while they are identified according to the Dominici et al. criteria (2006), considering surface marker expression (CD73, CD105, and CD90), in vitro tri-lineage differentiation (osteoblasts, adipocytes, and chondrocytes) and plastic adherence. Importantly, the in vivo functionality of MSCs is poorly understood and revealed, while

‡Author *Krstić*'s present address: Institute of Cell Biology, Histology and Embryology, Medical University of Graz, Graz, Austria
Grant sponsor: Ministry of Education Science and Technological Development of Serbia; Grant numbers: 175024, 175062.
*Correspondence to: Juan F. Santibanez, the Group for Molecular Oncology, Institute for Medical Research, University of Belgrade, Dr Subotica 4, POB 102, 11129 Belgrade, Serbia, E-mail: jfsantibanez@imi.bg.ac.rs

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most data obtained from in vitro studies are without rigorous assays for testing self-renewal and multipotency of their progeny.

In cancer, MSCs may have incidence to poorer outcomes, and they home within and support tumor progression, cell motility, and invasiveness that enhance cancer cell metastatic potential. Furthermore, they contribute to the colonization at secondary organs (Ridge et al., 2017; Melzer et al., 2017). In this review, we attempt to mainly describe the mechanism and capacity of MSCs to modulate cancer EMT program as well as their involvement in the reverse program mesenchymal to epithelial transition (MET), whose balance contributes to consolidate tumor malignancy and metastasis.

Mesenchymal Stromal Cells Within Tumor Microenvironment

Mesenchymal gene signature in tumors has been implicated in cancer transcriptome, recurrence, metastasis, and poor prognosis of patients (Ridge et al., 2017). The source of these mesenchymal signals has been mostly attributed to the EMT-like phenotype of epithelial tumor cells. In addition MSCs can be involved in development of mesenchymal tumors also, acquiring somatic mutations during the proliferative phase of wound healing process (Carothers et al., 2012; Mohseny and Hogendoorn, 2011). The presence of MSCs within the tumor has been corroborated by several studies that efficiently isolated them from tumor samples. It is described that noncancerous mesenchymal stromal cells can be isolated from human osteosarcoma specimens in high frequency (Brune et al., 2011). Also, MSCs were isolated from sarcoma tissues where they reside in perivascular regions (Morozov et al., 2010). Furthermore, infiltration of mouse Lin-Sca-1^{+}CD9^{+}CD44^{+}CD166$^{+/-}$ MSCs was described in GL261 murine glioma model, signed as brain tumor MSCs, which correlated to the brain tumor progression (Behnan et al., 2014). Similarly, MSCs are presented in breast cancer microenvironment, contributing to proliferation, migration, and tumor progression of MCF-7 tumor cell line in vitro (Zhang et al., 2013; Gonzalez et al., 2017). Similarly, efficient isolation of stromal cells with characteristics of MSCs from human gastric epithelial cancer, ovarian, and lung carcinoma was reported (Berger et al., 2016). More precisely, immunophenotyping analysis of human ovarian tumor ascites demonstrated that cells with the surface protein expression pattern of MSCs (CD44^{+}CD73^{+}CD90^{+}) were relatively abundant (approximately 6% of cells; ranging from 1% to 11%), while in prostate cancer MSCs represented approximately 0.01 to 1.1 % of the total cells of tumor sample mass (McLean et al., 2011; Brennen et al., 2013).

Although MSCs are widely distributed in TME, where they per se communicate with other cells and participate in the tumor development, bone marrow also contributes to the number of tumor-associated MSCs because these cells can also be mobilized and recruited into TME in response to the tumor inflammatory milieu (Quante et al., 2011). Moreover, MSCs also have capacity to transdifferentiate into cancer-associated fibroblasts (CAFs) by achieving "activated phenotype" and tumor-supporting feature (Shangguan et al., 2012; Jung et al., 2013). Due to heterogeneity within cells in the CAF population and their unresolved origin, many intermediate populations occurring during their context-specific lineage commitment, and cellular plasticity, there is still no consensus regarding defined phenotype and function of CAFs in TME (Kalluri, 2016; Trivanović et al., 2016a).

Nevertheless, the transition of MSCs toward CAFs has been described as crucial event for the development of EMT program of cancer cells (Jung et al., 2013). Moreover, MSCs or CAFs play an important role not only in primary tumor TME but also in metastatic niche. Specifically, metastatic breast mesenchymal stromal-type cancer cells can adjust feature of highly secretory lung mesenchymal fibroblasts, and alpha-smooth muscle actin and fibroblast activation protein to achieve CAF-properties. Furthermore, such activated stromal cells sustain MET of breast mesenchymal-type cancer cells, thus favoring survival of cancer cell in distant niches and consolidate metastasis.

During MET, breast cancer cells regained epithelial phenotype through an inhibition of transforming growth factor β (TGF-β) signaling and the stimulation bone morphogenetic protein signaling, allowing cancer cell metastatic outgrowth in lungs (del Pozo Martin et al., 2015). Importantly, MSCs are constituents of bone marrow stroma, which is often targeting place for metastatic breast, prostate, or lung cancer cells. MSCs participate in process of bone remodeling, involving osteoclast-mediated bone resorption resulting in the release of a multitude of growth factors, cytokines, and cell adhesion molecules from the bone matrix, and then create the bone as an attractive site for metastatic tumor cells.

Once in the bone microenvironment, tumor-derived growth factors prime the bone for subsequent colonization of tumor cells (Ottewell et al., 2015). Collectively, these data suggest that MSCs, either resident or recruited to the tissue, can achieve "activated secretory phenotype" by displaying CAF-associated properties and by their contribution in critical steps of cancer EMT (Fig. 1). Moreover, MSCs may play a role in the balance of EMT and MET in cancer cells, which is closely linked to stemness in development and cancer (Lamouille et al., 2014).

Cancer Cell EMT

EMT is a reversible embryonic genetic program, during which motile cells can be generated from polarized sessile epithelial cells. In addition, EMT is naturally occurring transdifferentiation program. The reprogramming of the terminally differentiated adult cells into induced pluripotent stem cells makes almost any type of dedifferentiation or transdifferentiation a possible event (Ye and Weinberg, 2015). EMT is a complex multistep process in which phenotype switches are mediated by a network of transcription factors (TFs). Systematic characterization of all dynamic TFs controlling EMT state transitions, especially for the intermediate partial-EMT state, represents a highly relevant yet mostly unrevealed issue (Chang et al., 2016). Currently, EMT is divided into three subtypes, which are associated with distinct biological functions: (1) embryogenesis and organ development, (2) tissue regeneration, organ fibrosis and wound healing process, (3) cancer progression and metastasis. EMT (3) plays a central role during tumor metastasis and frequently imparts a stem cell-like phenotype and therapeutic resistance to tumor cells (Kalluri and Weinberg, 2009; Ottewell et al., 2015).

Cancers of epithelial origin (carcinomas) have been mostly described at the invasive point of the primary tumor mass, simultaneously indicating an important role of microenvironmental cues generated by the surrounding stroma in the transdifferentiation process. It is accepted that most human cancers arise either from epithelial cells or their progenitors (Macara and McCaffrey, 2013). During EMT, epithelial cells undergo a change in cytoarchitecture,

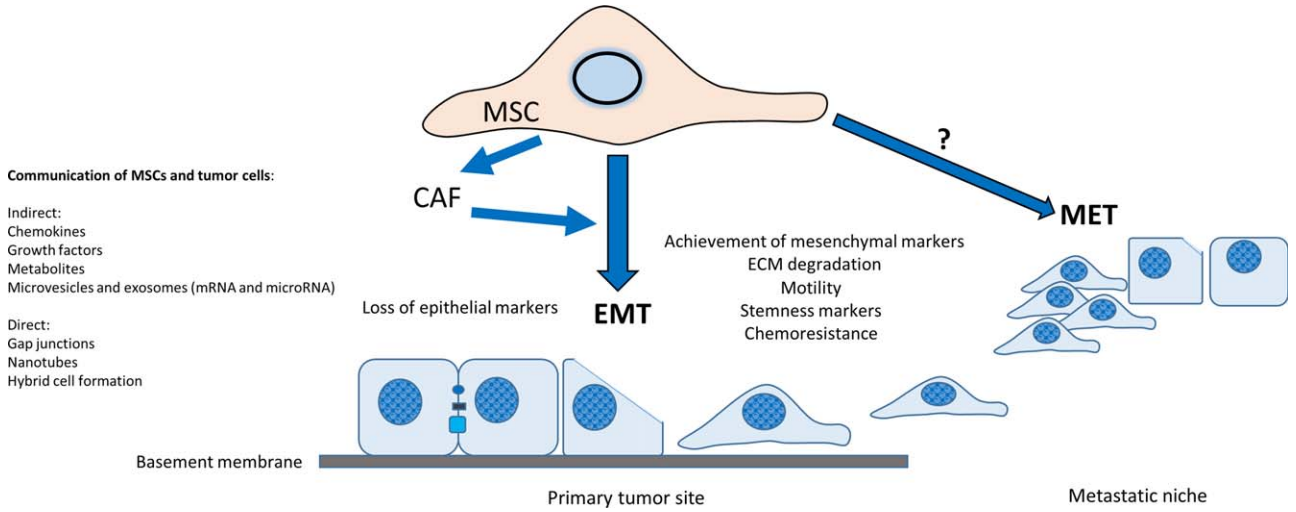

Fig. 1. Involvement of MSCs in tumor cell EMT. Schematic illustration of modification of tumor cell phenotype and activity in presence of MSCs. MSCs can be regulators of mesenchymal properties achievement (left, primary tumor site) and epithelial properties regress in tumor cells (right, metastatic niche).

associated with the loss of cell–cell adhesions in favor of cell–ECM interactions and cell motility (Thiery et al., 2009). Adherent junctions are organized by N- and P-cadherin which mediate weak and transient connections and are associated with motility cells. P-cadherin is expressed in progenitor cells in myoepithelium of the differentiated breast tissue, but is up-regulated in breast cancers.

N-cadherin is associated with mesenchymal state, and the switch from E- to N-cadherin is a major hallmark of EMT (Lamouille et al., 2014). Moreover, the repression of the apical tight junctions' protein expressions, such as occluding, claudins, desmoplakin and plakophilin, during EMT contribute to the establishment of the loss of cell–cell interaction and epithelial barrier function by preventing de novo formation of epithelial cell–cell junctions (Huang et al., 2012; Lamouille et al., 2014; Yu and Elble, 2016).

The EMT process is initiated by the activation of EMT-associated TFs, including Snail, zinc-finger E-box-binding (ZEB), and Twist1, which drive the loose epithelial phenotype of cancer cells by reducing the expression of the adherens junction proteins, such as E-cadherin, and stimulate the expression of mesenchymal markers (Donnenberg and Donnenberg, 2015). As the loss of E-cadherin expression is considered as a crucial event in EMT, the EMT-associated TFs can be classified on the basis of their ability to repress E-cadherin directly or indirectly. For instance, direct repressors include: zinc finger proteins of the SNAIL superfamily, such as SNAI1 (also known as Snail), SNAI2 (SLUG), and SNAI3 (SMUC); ZEB1 (TCF8), and ZEB2 (SIP1); the basic helix-loop-helix (bHLH) factor E47; and the Krüppel-like factor KLF8.

Meanwhile, TFs, such as the bHLH proteins (TWIST1 and TWIST2), the homeobox proteins goosecoid (GSC) and SIX1, the bHLH factor E2.2, and the forkhead-box protein FOXC2 indirectly repress E-cadherin transcription (Puisieux et al., 2014; Sato et al., 2016). The functions of TFs are regulated at the transcriptional, translational, and posttranslational levels, which are particularly controlled by TGF-β signaling (Lamouille et al., 2014), as it is known that although TGF-β acts a tumor suppressor at early step of tumorigenesis, it stimulates EMT and malignancy of cancer cells in later stages of malignant progression (Moustakas and Heldin, 2016; Costanza et al., 2017).

Tumor cells undergoing EMT are invasive; resistant to senescence, anoikis, and chemotherapeutics; and finally display stemness characteristics (Heerboth et al., 2015). EMT-associated TFs can reduce oncosuppressive mechanisms in cells that maintain epithelial traits, thereby overcoming the mutation bottleneck toward invasiveness. It is important to note that EMT is a potent source of phenotypic, metabolic and functional tumor cell plasticity (Puisieux et al., 2014). Furthermore, it is accepted that EMT can generate tumor cells having stem cell characteristics which phenotypically correspond to cancer stem cells (CSCs).

However, increasing evidence suggests that CSCs are tumor cells in intermediate state of EMT which express reduced levels of E-cadherin and increased mesenchymal markers associated with stemness and invasiveness and finally metastasis (Prieto-García et al., 2017; Shibue and Weinberg, 2017). In addition to CSCs, circulating tumor cells (CTCs) have also been shown to exhibit properties of EMT, while EMT has been postulated to be involved in CTC formation. For instance, the phenotypic analysis of CTCs from patients with metastatic breast cancer revealed that a significant number of CTCs exhibited a partial or a full EMT phenotype (Thiery and Lim, 2013; Yu et al., 2013). In addition, it has been observed that breast CTCs occurred as single cells or multicellular clusters, possessing mesenchymal properties and EMT regulators, activated TGF-β signaling along with expression of FOXP C1 transcriptional factor at gene level (Yu et al., 2013).

Intriguingly, EMT has been mostly studied in carcinoma, but there is growing evidence suggesting that cancers of organs derived from mesoderm (e.g., hematopoietic malignancies and sarcomas) (Sánchez-Tilló et al., 2014; Chou and Yang, 2015) or ectoderm (e.g., glioblastomas and melanomas) (Iwadate, 2016) also undergo EMT program to acquire an undifferentiated/mesenchymal profile (Sayan, 2014).

Modulation of Cancer Cell EMT Program by MSCs

MSCs promote cancer cell EMT program: MSCs communicate with neighboring cells through paracrine activity that involves

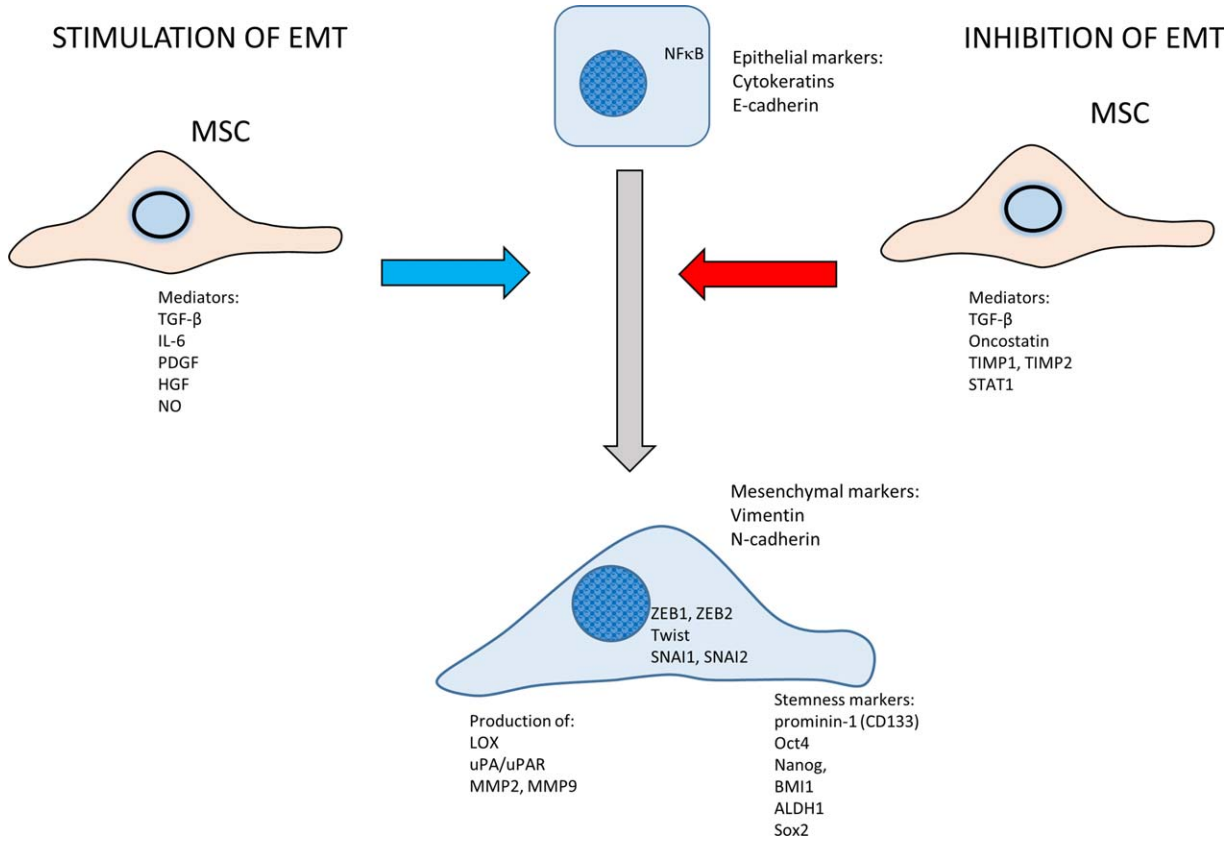

Fig. 2. Converse effects of MSCS son tumor cell EMT. TGF-β, IL-6, PDGF, HGF, NO, and miR-20 activate EMT-associated TF in tumor cells, leading to up-regulated expression of mesenchymal and stem cell markers (left, blue arrow). Inhibition of EMT-associated events by MSCs-produced factors (right, red arrow).

production of proteins/peptides; transfer of mitochondria through tunneling nanotubes and transfer of exosomes or microvesicles containing RNA and other molecules (Fig. 1). Actually, MSCs secrete various factors (cytokines, chemokines, and growth factors) and metabolites, such as prostaglandin E2, kynurenine, galectin-1, or release exosomes or microvesicles, containing proteins, mRNAs, and microRNAs altering features of tumor cells (Hass and Otte, 2012).

In addition to paracrine communication, MSCs can establish direct connection with tumor cells building gap junctions for intercellular communication, which in turns allow modification of signaling pathways (such as Notch signaling) in tumor cells (Plaks et al., 2015). Thus, aforementioned MSCs mechanisms provide to them the opportunity to influence EMT program at different cellular and molecular levels (Figs. (1 and 2)). MSCs stimulate cancer-associated EMT and induce stem-like properties, which provides cancer cells with the increased motility and invasive capabilities, together with cell survival in the circulation and in distant metastatic niches (Lazennec and Lam, 2016) (Fig. 2).

Notably, stromal-derived TGF-β is implicated in EMT of adjacent epithelial cells, while level, activation and bioavailability of TGF-β is high through the production of proteases, integrins and reactive oxygen species by the noncancerous cell compartments expression, including infiltrating immune cells and MSCs, which are dysregulated within tumor stroma. In contrast, stromal cells can be source of molecules, such are proteoglycans, fibrillins, fibulins and fibronectin, which can impair TGF-β availability and activity in cancer cells (Costanza et al., 2017).

Importantly, MSCs can be "educated" or primed in vitro by inflammatory factors to increase its capacity to induce cancer EMT. Conditioned medium of MSCs prestimulated with both of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) provokes EMT in breast cancer MCF-7 cells and pancreatic adenocarcinoma (PANC-1 and BxPC-3) cell lines. The priming of MSCs with these inflammatory factors induced elevated levels of TGF-β production by MSCs which in turn stimulated EMT in these both types of cancer cells (Trivanović et al., 2016b; Zhou et al., 2016). These studies suggest that an inflammatory tumor microenvironment produces an "activation state" of MSCs with the consequent increased expression of TGF-β that enhances cell malignancy and induces the EMT program both in vitro and in vivo.

In addition, it has been demonstrated that the elevated TGF-β expression by preconditioned MSCs with IFN-γ and TNF-α, induces both in vitro and in vivo autophagy and chemoresistance of hepatocellular carcinoma cell lines MMC-7721 and Hep-G2 (Han et al., 2014).

Moreover, it has been suggested that naïve MSCs are recruited and also "educated" or reprogrammed by gastric tumor cells. Results also point to GSC-MSCs conditioned media and hepatocyte growth factor (HGF)-mediated phosphorylation of c-MET downstream signaling which confer in vivo growth properties to GSC1 gastric cancer cells (Berger et al., 2016).

Similarly, effects of Senescence-associated secretory phenotype of MSCs have been suggested to have inducible roles in EMT of tumor cells (Laberge et al., 2012). Senescent stromal cells exposed to hypoxia, have been suggested to promote prostate cancer aggressiveness by inducing EMT. Hypoxia-induced miR-210 in young fibroblasts increases their senescence-associated features and converts them into cancer associated fibroblast-like cells, which promotes cancer cells EMT of prostate cancer cell line PC-3 in co-culture system, as demonstrated by the up-regulation of ZEB1, ZEB2, and vimentin and the down-regulation of E-cadherin EMT markers (Taddei et al., 2014).

Also, it has been observed that rat bone marrow MSCs (BM-MSCs) increased the migration and stimulated the expression of CXC chemokine receptor 4 (CXCR4) and F-actin remodeling in rat hepatoma cells, CBRH-7919 (Li et al., 2015a). In addition, cytoskeletal changes were observed in nasopharyngeal carcinoma (NPC) cells after co-cultivation with BM-MSCs. Nitric oxide (NO) produced by BM-MSCs could translocate caldesmon to podosome in Ca2+/calmodulin manner thus promoting metastatic ability of carcinoma cells through invadopodia formation, with which the NPC cells degrade the extracellular matrix (Zhang et al., 2014).

Additionally, autophagy has been shown also to be involved in regulation of cancer cell EMT. Moreover, the role of autophagy induced by various metabolic stressors (hypoxia, inflammation, starvation) in the tumor microenvironment is bidirectional. Actually, autophagy can suppress tumorigenesis before tumor development, while enhancing survival (resistance to anoikis) and metastasis of tumor cells after tumorigenesis events (Yang et al., 2015; Mowers et al., 2017; Gugnoni et al., 2016).

Intriguingly, through paracrine activity MSCs can induce EMT-associated stemness in breast tumor cells. It has been demonstrated that conditioned media from adipose tissue stem cells (ASCs) promotes the frequencies of CD44high/CD24low CSCs within 4T1 breast cancer cell population. In addition, ASCs induced expression of mesenchymal markers, fibronectin, alpha SMA and vimentin in breast cancer cells. This study revealed that platelet-derived growth factor-D (PDGF-D) produced by ASCs is involved in enhanced EMT of breast tumor cells in vivo (Devarajan et al., 2012). Also, BM-MSCs promotes de novo production of lysyl oxidase (LOX) by breast cancer cells, which is sufficient to enhance the metastasis to the lungs and bones.

Moreover, LOX is component of the CD44/Twist signaling axis. Extracellular hyaluronan induces nuclear translocation of CD44 in the breast cancer cells, triggering LOX transcription. Enzymatically active LOX stimulates Twist transcription, which mediates the MSCs-induced EMT of breast cancer cells. However, as LOX is critical for EMT but not for generation of CSCs, this study indicated distinct signaling pathways underlying the EMT and CSC generation within breast cancer cells (El Haibi et al., 2012).

In addition, it has been demonstrated that umbilical cord MSCs (UCMSCs)-derived conditioned media decreased E-cadherin expression, increased the expression of N-cadherin, and enhanced the expression of ZEB1, through activation of the ERK pathway in breast cancer cell lines MCF-7 and MDA-MB-231 (Li et al., 2015b). Furthermore, three-dimensional cultured hepatocellular carcinoma (HCC) cells were subjected to EMT by UC-MSCs co-culture. Also, HCC cells increased invasive capacities concomitant with matrix metalloproteinase (MMP)-2 expressions in a UC-MSCs-derived TGF-β fashion (Liu et al., 2016). Although TGF-β has been recognized as a master factor for the EMT induction (Xu et al., 2009), other cytokines also contribute to MSCs capacities to induce EMT in cancer cells; it has been recently described that the interaction between MSCs and gynecologic cancer cells (GCC) provokes increased levels of interleukin-6 (IL-6).

In turn, IL-6 was sufficient to induce EMT program in GCC concomitantly with elevated levels of MMP2 and MMP9, and increased cell migration and invasion comparably to TGF-β treatments (So et al., 2015). Similarly, it has been reported that BM-MSCs and cells from mesenchymal tumor, osteosarcoma, communicate by means of TGF-β and IL-6. These interactions enhance migration and stem cell-like features of HOS and MG63 osteosarcoma cell lines in vitro (Cortini et al., 2016). These results may suggest that tumor cells provoke an inflammatory response of MSCs, which in turn expressed elevated levels of IL-6 acting as a paracrine EMT factor on cancer cells.

Interestingly, HGF/c-Met signaling is recognized to be involved in regulation of breast cancer progression. Stromal cell derived HGF promotes stem cell properties of breast epithelial cells, which is associated with induction of SNAI1 and SNAI2, the repression of the luminal-regulatory genes Elf5 and Hey1, and claudin down-regulation (Di-Cico et al., 2015). Also, MSCs isolated from pancreatic tumor tissue possess characteristics of myofibroblast, which contribute to the induction of EMT of PANC-1 and MIAPaCa2 pancreatic cancer cells. MSCs-derived myofibroblasts stimulate stemness, sphere-forming capacity, in vivo tumor formation and chemoresistance of tumor cells. Furthermore, the suppression of E-cadherin expression in these pancreatic cancer cells was achieved by Notch signaling stimulated by MSCs (Kabashima-Niibe et al., 2013).

Malignant melanoma (MM) accounts for a high proportion of deaths from all skin cancers, and EMT has also been suggested to play an important role in conferring metastatic properties in MM (Li et al., 2015c). The specific role of MSCs in EMT-like process in melanoma cells has not widely investigated. Some information came from Lv et al. (2017) study, where it is shown that in B16 melanoma cells MSCs-derived conditioned medium increase invasiveness concomitantly with the induction of EMT program, which involved TGF-β-Snail axis signaling pathway. Furthermore, it has been observed that low extracellular pH (LpH) in melanoma microenvironment changes metabolic and paracrine profile of MSCs, stimulating their production of TGF-β and oxidative metabolism. LpH-treated human MSCs produce higher levels of TGF-β, which in turn mediates MSCs-derived conditioned medium to induce an EMT-like phenotype in A375M6 melanoma cells.

Moreover, the esomeprazole inhibition of LpH-induced TGF-β secretion in MSCs, a proton pump inhibitor activated by acidic medium, seems to develop a MET program as is evidenced by elevation of E-cadherin, reduction of N-cadherin and cell motility and invasiveness (Peppicelli et al., 2015). Another study also reported implication of MSCs-derived TGF-β in induction of EMT-like profile in A375, M21, M14, Hs294T, and in Mewo melanoma cells. Intriguingly, the urokinase type plasminogen activator receptor mediates the capacity of BM-MSC-medium derived TGF-β to induce EMT and increase malignancy in melanoma cells (Laurenzana et al., 2015).

As aforementioned, the exosome secretome contributes to EMT induction by MSCs. Exosomes have been described as novel mediators of cell-to-cell communication and may acts as a cargo for several biomolecules such cytokines and microRNAs, among others (Syn et al., 2016; Zhang et al., 2017). In this aspect, Shi

et al. (2016) demonstrated that BM-MSC-derived exosomes contain fibroblast growth factor 19, which mediates the induction of EMT in cancer cells. More recently, MSC-derived exosomes promotes lung cancer EMT by carrying PDGF-D, a newly identified isoform of PDGFs, concomitantly with increased both in vivo and in vitro cancer cell migration and proliferation (Huang et al., 2017). These data exemplify the role of MSC-derived exosomes as paracrine factors that increase MSCs and cancer cell interactions to the enhancement of tumor progression by means of EMT-program expression.

Emerging evidences indicate that cell–cell fusion between MSCs and tumor cells might contribute to cancer progression (Noubissi and Ogle, 2016). Xu et al. (2014) describe that cell fusion is detected both in vivo and in vitro between human BM-derived MSCs and lung cancer cells. These hybrids display the EMT features and increase cell motility and tumorigenic potential. Moreover they express stem cell markers, such as OCT4, Nanog, and Sox2. Thus, this study proposed that these hybrids represent novel nonmutational mechanism, which can contribute to altered gene expression producing high malignant cancer cell subpopulation with stem cell-like characteristic with enhanced tumorigenicity and metastatic potential. Another study using a model of cell fusion, between human UCMSCs and gastric cancer cells, demonstrated also the formed hybrids exhibit EMT process. Furthermore, fused cells display both in vivo and in vitro enhanced growth properties accompanied with increased gastric cancer cell stemness (Xue et al., 2015).

MSCs repress cancer cell EMT program: MSCs have been demonstrated to possess anti-EMT effects in development of normal tissues. For instance, prevention of EMT has been observed in model of lung injury, where it has been observed that MSCs reduced EMT program initiated by hypoxia in rat alveolar epithelial cell, anti-EMT activity of MSCs has been observed in case of renal tubular cells, while MSCs derived conditioned media attenuated albumin-induced EMT in renal epithelial cells (Uzunhan et al., 2016; Hu et al., 2015). Although there are no many evidences concerning anti-EMT effects of MSCs in cancer, there are some studies which showed such MSC activities. As endometrial mesenchymal/stromal cells regulate growth and functions of epithelial cells in endometriotic lesions, it has been suggested that stromal cells participate in pathogenesis of endometrial carcinomas. Namely, normal endometrial stromal cells were shown to inhibit the migration and invasion in endometrial adenocarcinoma cells (Ishikawa cells). This anti-EMT activity of stromal cells were followed with decreased Slug expression, increased E-cadherin expression in Ishikawa cells (Zhang et al., 2016).

Additionally, it has been shown that BM-MSCs can promote MET program in lung adenocarcinoma cells. Wang et al. (2012) demonstrated that MSC-derived Oncostatin M, which act as differentiation-promoting factor, induced MET in cancer cells mediated by STAT1 signaling pathway, paralleled to the inhibition of proliferation, cell migration, and invasion of lung adenocarcinoma cells. Furthermore, cell–cell interaction also contributes to the capacity of MSCs to reduce the EMT in head and neck squamous cell carcinoma PCI-13 cell line by inhibition of MMP14 expression and Wnt/beta-catenin signal pathway activity (Böhrnsen et al., 2015). Recently, it has been observed that BM-MSCs, although not directly associated with EMT, decreased breast cancer cell migration and invasion capacity. This study suggested that the both inhibitors of MMPs TIMP-1 and TIMP-2 mediate these MSCs effects (Clarke et al., 2015) (Fig. 2). However, this study nicely indicated that final outcome of tumor development is dependent on the balance of all anti- and pro-tumorigenic activities of MSCs.

Taken together, bidirectional interplay of MSCs and tumor cells is very complex and underlying mechanisms and the consequences of this interaction on the cancer-EMT program is not completely understood. Furthermore, it has been postulated that MSCs favor MET as reverse process of EMT in tumor cells at distant metastatic niche, thus promoting tumor cell colonization and progression that finally consolidates metastasis (del Pozo Martin et al., 2015).

Concluding Remarks and Perspectives

The notion that MSCs play important role in tumor progression, metastasis, and chemoresistance has been gaining interest in clinic settings using cell therapies. Although MSCs are well known to contribute to the healing of damaged tissues, they can be recruited to the tumor stroma and support tumor growth and progression. Several properties of MSCs are involved in the cancer cell capacity to evade immune surveillance, in promotion of angiogenesis and, what is the main purpose of this review, the induction of EMT in cancer cell. Emerging clinical and experimental data indicate that the induction of EMT by MSCs may be related to the poor prognosis and cancer recurrence, thus making MSCs as new targets for the control of tumor progression and holding promise to the develop of novel anti-tumor therapies (Ridge et al., 2017).

MSCs can use several mechanisms to promote cancer cell EMT. For instance, the inflammatory tumor niche can reprogram MSCs to secreted cytokines that directly induce EMT in cancer cells (e.g., TGF-β). Also, MSCs can augment the stromal levels of ECM degrading proteins, which contributes to cancer cell invasion, tumor microenvironment reorganization, and increases the bioavailability of growth factor inductors of EMT. It is believed that the intervention against the cancer EMT may provide opportunities to improve the efficacy of the current chemotherapies and prevent the development of resistance by cancer cells.

However, some issues should be considered before targeting MSCs in the tumor microenvironment to effectively control cancer EMT to impact tumor progression. MSCs are present in both stroma of primary tumor and secondary tumors. Thus, it will be of the great importance to modify the anti-inflammatory properties of tumor milieu toward an "inflammatory stage" that can improve immune response and affect the capacity of MSCs, in situ reprogrammed by cancer cells, which can impact the development of cancer EMT.

Moreover, interventions to inhibit either the formation or release of MSCs-derived factors or exosomes can also improve the efficacy of onco-therapies that aim to target EMT. Finally, contribution of MSCs to tumor progression is one of the many actors in cancer scenario, and it is necessary to develop combined therapies considering all cellular compartments that can contribute to the permissive TME in combination with traditional chemotherapies to prevent or control migration, proliferation and metastatic outgrowth.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this study.

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