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REVIEW

Mesenchymal stem cells in progression and treatment of cancers

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Abstract **Mesenchymal stem or stromal cells (MSCs) from bone marrow or local tissues are recruited to stroma of almost all types of cancers during initiation and/or progression of cancer. The recruited MSCs and their derivative cancer-associated fibroblasts interact with cancer cells to promote stemness, invasion and metastasis of cancer cells. Targeting these cancer-recruited MSCs and/or the interaction between MSCs and cancer cells are promising strategies to improve cancer therapy. On the other hand, the unique tumor-homing capacity of MSCs makes them a promising vehicle to deliver various anti-cancer agents. This review summarized the recent advancement of our understanding on the interaction between MSCs and cancer cells, as well as the potential of MSCs for cancer therapy.**

Keywords mesenchymal stem or stromal cells, cancer, cancer-associated fibroblasts, gene therapy, cell therapy

Introduction

The progression of tumors toward a malignant phenotype does not depend exclusively on the cell-autonomous properties of cancer cells themselves but is also deeply influenced by tumor microenvironmental elements including hypoxia, extracellular matrix (ECM) and various stromal cells (Marx, 2008). Among these stromal cells, Mesenchymal stem or stromal cells (MSCs) and the derivative Cancer-associated fibroblasts (CAFs) are rate-limiting determinants for growth and metastasis of cancers (Shimoda et al., 2010). Their roles in cancer progression include ECM remodeling, secretion of pro-tumor factors, inhibition of anti-tumor immune response, hormone production, tumor metabolism remodeling, regulation of motility and stemness, and preparation of metastatic niche (Marx, 2008).

MSCs are originally isolated from bone marrow, and later from adipose tissues and many other organs. These cells are capable of self-renewing and differentiating to bone, fat, or cartilage cells under appropriate conditions (García-Castro et al., 2010). Bone marrow MSCs serve as an essential component of niche for hematopoietic stem cell through secretion of growth factors and cytokines with trophic, immunomodulatory, anti-inflammatory, anti-apoptotic, and pro-angiogenic properties (Wu and Zhou, 2010). MSCs from bone marrow, fat and local tissues are capable of homing to stroma of various primary and metastatic cancers (Loebinger and Janes, 2010; Quante et al., 2011; Song and Li, 2011; Chaturvedi et al., 2013; Jung et al., 2013). The tumor-tropic capacity, the immuno-privileged status and the ease of harvest, culture, and transduction of MSCs made them promising vehicles for gene therapy of various invasive cancers including lung, breast, squamous-cell, colon, pancreas and cervical cancers (Loebinger et al., 2009; Grisendi et al., 2010). In addition, the combination of osteogenic potential and capability to deliver anti-cancer agents made MSCs a promising option to treat tumor-induced osteolysis (Komlev et al., 2009). However, exogenous MSCs have also shown the tendency to promote rather than inhibit cancers in many circumstances (Liu et al., 2011a; Li et al., 2012) similar to the roles of endogenous MSCs.

Homing of MSCs to tumor

MSCs are often involved in tissue remodeling after injury or chronic inflammation. Tumors resemble chronic wounds or "wounds that never heal" to form the tumor stroma (Dvorak, 1986). Inflammatory cytokines such as IL-1β (Carrero et al., 2012) or substance P (Hong et al., 2009) have been suggested

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to mediate the mobilization of MSCs after injury. For trafficking and engraftment of MSCs to the infarcted myocardium, integrins such as ITGA6 and ITGB1 and podocalyxin-like protein (PODXL) are essential (Ip et al., 2007; Lee et al., 2009b).

The dominant factors to recruit MSCs may be different for particular types of cancers. In inflammation-dependent models of gastric cancer, bone marrow MSCs are recruited to the tumor in a TGFβ- and SDF1a-dependent manner (Houghton et al., 2004; Quante et al., 2011). In primary and metastatic prostate cancer, CXCL16 is highly expressed compared with normal prostate epithelial cells, and the interaction of CXCL16 and its specific receptor CXCR6 in MSCs plays a key role in recruiting MSCs into tumors and supporting tumor growth (Jung et al., 2013). In mouse breast and ovarian cancer models, the expression of CD44 in MSCs is critical for their migration to tumors, suggesting the eseential roles of CD44 ligands such as hyaluronan (HA) and osteopontin produced by cancer cells that have been implicated as prognostic markers of cancer progression and metastases in breast, prostrate, lung, and ovarian cancers (Spaeth et al., 2013). In human breast cancer xenograft models, human breast cancer cells and MSCs expressed placental growth factor (PGF) and its cognate receptor VEGFR1, respectively, in a Hypoxia-inducible factor-dependent manner, and PGF facilitated homing of MSCs to tumors (Chaturvedi et al., 2013). In both murine and human multiple myeloma models, myeloma-produced chemokine CCL25 attracted BM-MSCs (Xu et al., 2012).

When are MSCs recruited to cancer may dependent on the inflammation and tissue damages caused by carcinogens or cancer cells. In mouse gastric cancer models caused by chronic infection with *Helicobacter* or IL-1β overexpression, bone marrow MSCs were attracted to the dysplasia lesions and contribute to the carcinogenesis (Houghton et al., 2004; Quante et al., 2011). In mouse models, established tumors release factors such as exosomes (Peinado et al., 2012) and Lysyl oxidase (Erler et al., 2009) that can act on cells in distant organs to recruit bone-marrow-derived cells (BMDCs) including MSCs, and these recruited BMDCs create an pre-metastatic niche to promote the survival and proliferation of newly arrived metastatic cells. The recuritment of MSCs into primary or metastatic cancer is illustrated in Fig. 1.

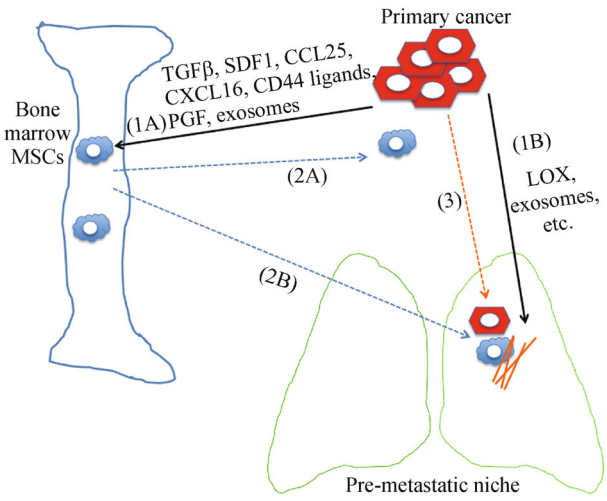

Figure 1 Recuritment of MSCs to primary or metastatic cancer. Primary cancer produces various factors to moblize MSCs in bone marrow (1A) or local tissues and to creat premetastatic niche in remote organs such as lungs (1B). Moblized MSCs migrate to primary cancer (2A) or the premetastatic niche (2B), then interact with cancer cells and promote metastasis of cancer (3).

The pro-tumor properties of MSCs

MSCs recruited to tumor stromal may promote tumor progression through multiple mechanisms. The first one is producing pro-tumor factors directly stimulating cancer cells. In 2007, Karnoub et al. demonstrated that mixing bone marrow MSCs with weakly metastatic variant of human MDA-MB-231 breast cancer cells at subcutaneous sites in a xenograft model dramatically enhanced the frequency of lung metastases, and this pro-tumor effect was attributed to the *de novo* secretion of the chemokine CCL5/RANTES from cancer-stimulated MSCs (Karnoub et al., 2007). Later, more MSC-derived pro-tumor cytokines were identified. For instances, CXCL7, CXCL10 or IL6 produced by MSCs promote metastasis and/or stemness of breast cancer (Liu et al., 2011a; Shangguan et al., 2012; Chaturvedi et al., 2013); neuregulin 1 (NRG1) secreted by BM-MSCs activates the HER2/HER3-dependent PI3K/AKT signaling cascade in colorectal cancer cells to promote their invasion and survival (De Boeck et al., 2013). A common mechanism of the direct pro-tumor effect of MSCs is promoting epithelial-mesenchymal transition (EMT) of cancer cells, which in turn promotes stemness, invasion and metastasis of cancer cells. The EMT can be induced through activation of Wnt/β-catenin signaling with MSC-derived Prostaglandin E2 (PGE2) (Li et al., 2012) or activation of CD44/Lysyl Oxidase (LOX)/TWIST signaling pathway with MSC-derived Hyaluronan acid (HA) (El-Haibi et al., 2012). Tumor necrosis factor α-induced protein 6 (TSG6), a secreted protein highly expressed by BM-MSCs (Lee et al., 2009a), enhances or induces the binding of HA to cell surface CD44 (Lesley et al., 2004), hence might also contributes to the pro-EMT effect of MSCs.

Secondly, MSCs promote angiogenesis in various organs through paracrine effects (Kinnaird et al., 2004) or endothelial differentiation (Chen et al., 2009). In a colon cancer model, MSCs stimulated by inflammatory cytokines such as IFN-γ and TNF-α in the tumor microenvironment express higher levels of vascular endothelial growth factor (VEGF) via the HIF-1α signaling pathway to enhance tumor angiogenesis,

finally leading to colon cancer growth in mice (Liu et al., 2011b). In a mouse Lewis lung carcinoma, co-injected MSCs directly supported the tumor vasculature by localizing close to vascular walls and by expressing an endothelial marker. Furthermore, coculture of MSCs with cancer cells increased secretion of multiple pro-angiogenesis factors such as leukemia inhibitory factor, macrophage colony-stimulating factor, macrophage inflammatory protein-2 and VEGF (Suzuki et al., 2011).

Thirdly, MSCs have immune inhibitory effects under various circumstances (Nasef et al., 2007). *In vitro*, MSCs protect breast cancer cells through expansion of regulatory T cells (Tregs), which is probably mediated by MSC-derived TGF-β (Patel et al., 2010). In a *Helicobacter pylori* model of gastric cancer, BM-MSCs favor the immunosuppressive T cells skewing, i.e., an increase in IL-10-secreting T cells and Tregs (Lin et al., 2013). In human pediatric malignancies, MSC-like cells isolated from tumor stroma impair NK cell cytotoxicity related with reduced expression of the activating NK cell receptors NKp44 and NKp46, and displayed a strong antiproliferative effect on peripheral blood mononuclear cells (Johann et al., 2010).

Lastly, the fusion of MSCs with cancer cells may also promote cancer progression through EMT and generation of cancer stem cells. Cocultured MSCs and breast or non-small cell lung cancer cells fused spontaneously at low frequency (1.2% –3.2%) (Rappa et al., 2012; Xu et al., 2014). The breast cancer hybrid cells acquired mesenchymal characteristics, are tumorigenic and some hybrids had an increased metastatic capacity and expression of stem cell markers. The lung cancer hybrid cells underwent EMT and acquired stem cell-like properties such as increased tumor initiating capacity. However, the evidences for the fusion of MSCs with cancer cells *in vivo* are not strong. Such fusion was obvious and frequent between human cancer cells and stromal cells of mouse or hamster ($>30\%$) (Jacobsen et al., 2006; Goldenberg et al., 2013), but the *in vivo* fusion of human cancer cells and human MSCs or stromal cells is very rare and not well characterized. The proof of fusion between cancer cells and BDMCs in human patients can only be found in cancer patients received allogeneic bone marrow transplantation. The first and only evidence was found in such a patient with metastatic melanoma, and the initiator of the metastasis was a hybrid cell acting as a stem cell or tumor-initiating cell (Lazova et al., 2013). However, whether the fusion was with MSCs or other lineage of BDMSs such as macrophages remains to be explored.

Cancer cells activate the pro-tumor effects of MSCs via multiple mechanisms. The expression of CCL5 by MSCs is probably induced by Osteopontin produced by cancer cells (Mi et al., 2011). For cancer cells expressing high level of Interleukin-1 (IL1) such as many colorectal or breast cancer cells, the pro-tumor effect of MSCs is mainly mediated by IL1 receptor (IL1R)/PGE2 pathway (Li et al., 2012). TGFβ signaling is also essential for the pro-tumor effects of BM-MSCs by induction of multiple pro-tumor factors such as SDF1 and IL6 (Quante et al., 2011; Shangguan et al., 2012).

Differentiation of MSCs to cancer associated fibroblasts

CAFs are phenotypically similar to myofibroblasts (MFs) and promote growth and metastasis of cancer cells by multiple mechanisms such as secreting pro-tumor factors (Stroncek et al., 2010) and inhibiting anti-tumor immunity (Kraman et al., 2010). CAFs are heterogeneous populations and originated from resting resident fibroblasts, epithelial and endothelial cells within the tumor, pericytes or bone marrow MSCs (Stroncek et al., 2010). A study in mouse models of pancreatic cancer and inflammation-induced gastric cancer suggested that at least 20% CAFs are originated from bone marrow MSCs (Tokar et al., 2010).

Differentiation to CAFs of human bone marrow MSCs (hBM-MSCs) can be induced by tumor-conditioned medium (TCM) (Mishra et al., 2008), indicating the essential roles of secreted factors in tumor microenvironments in CAF differentiation. Transforming growth factor β (TGF-β) is highly expressed by various carcinoma (Peter, 2009) and is required to induce CAF differentiation of mouse BM-MSCs *in vivo* (Tokar et al., 2010), and can induce expression of some CAF markers in hBM-MSCs *in vitro* (Varnat et al., 2009). Consistently, in CAFs derived from hBM-MSCs, genes in TGF-β signaling pathway are highly enriched (Mishra et al., 2008), further suggesting that TGF-β signaling might be essential for CAF differentiation of human BM-MSCs. Recently, we found that inhibiting TGF-β/Smad signaling in human BM-MSCs blocked their differentiation to CAFs in tumor microenvironments and abolished their pro-tumor effects, but did not alter their stem cell properties and tumor tropism (Shangguan et al., 2012). Particularly, the remarkable upregulation of two pro-tumor factors, CCL5 and SDF-1, from MSCs exposed to tumor microenvironments was significantly blocked by inhibiting TGF-β/Smad signaling. In mouse orthotopic breast or ovarian tumor models and a human xenograft model using SKOV-3 cells with high expression of HA synthetase 2 (HAS2), the expression of CD44 in MSCs is also critical for their differentiation to CAFs, suggesting the essential roles of CD44 ligands such as HA or osteopontin produced by cancer cells (Spaeth et al., 2013). CD44 activation by TCM stimulates Twist expression in MSCs by increased association of CD44 at the Twist1 promoter, whereas exogenously expressed Twist1 in CD44 knockdown MSCs partially restored the proangiogenic function of the MSCs, suggesting that Twist1 is essential for CD44-mediated CAF differentiation of MSCs. The interactions between cancer cells, MSCs and CAFs are illustrated in Fig. 2.

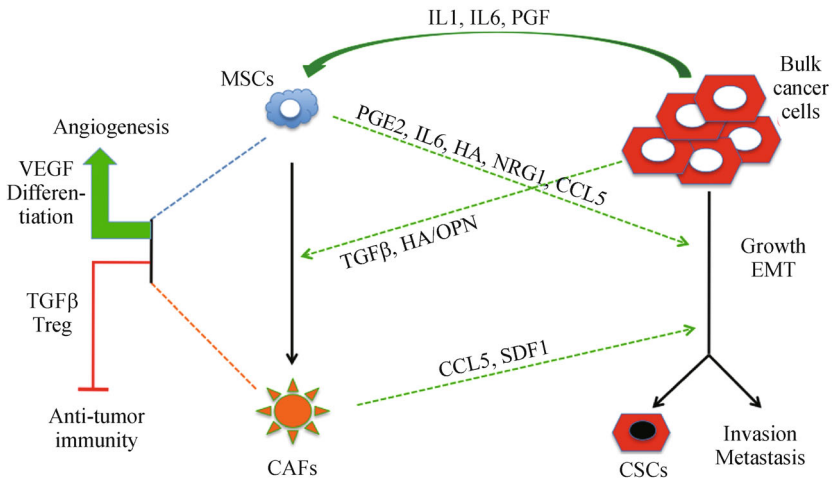

Figure 2 Interactions between cancer cells, recruited MSCs and CAFs. Cancer cells produce various factors to stimulate the production of pro-tumor factors and CAF differentiation of recurited MSCs. The pro-tumor factors produced by MSCs and CAFs promote growth and EMT of cancer cells and consequent invasion, metastasis and CSC expansion. These MSCs and CAFs also promote angiogenesis and protect cancer cells from immune destruction.

Targeting the interaction between cancer cells and MSCs for cancer treatment

Considered the essential roles of MSCs in cancer progression, targeting the factors essential for the interaction between MSCs and cancer cells is a promising strategy to improve cancer treatment and also contributes to the efficacy of many anti-cancer agents tested before. All the factors involved in homing, CAF differentiation and pro-tumor effects mentioned in Section 2 to 4 could be targeted for such purpose. For instance, Osteopontin is highly expressed by malignant cells and associated with metastasis, partially by stimulating MSCs to produce pro-metastatic cytokine CCL5. RNA aptamer blockade of osteopontin inhibits growth and metastasis of MDA-MB231 breast cancer cells (Mi et al., 2009). In surgical specimens of human colon cancer the expression of platelet-derived growth factor receptor (PDGFR) in tumor stroma is associated with vascularity and tumor stage (Kitadai et al., 2006), whereas PDGF signaling pathways are known to be crucial to migration and survival of MSCs to infarcted myocardium (Krausgrill et al., 2009). Blockade of PDGFR signaling with imatinib impairs the tumor-promoting effect of BM-MSCs in an orthotopic transplantation model of colon cancer by inhibiting the tumor homing and survival of intravenously infused MSCs (Shinagawa et al., 2013).

The intrinsic anti-tumor properties of exogenous MSCs

Human MSCs also have intrinsic anti-tumor properties under certain circumstances via various mechanisms. MSCs pretreated with TNFα inhibited the progression of lung tumors formed from MDA-MB-231 breast cancer cells and induced their apoptosis via the induction of expression of TNF-related apoptosis-inducing ligand (TRAIL) in MSCs; moreover, the TRAIL expression in MSCs was further induced by direct contact with breast cancer cells in a TLR3-dependent manner (Lee et al., 2012). The down-regulation of the Wnt signaling pathway in breast cancer cells by Dickkopf proteins (DKK1/3) derived from MSCs also contribute to the anti-tumor effort via the reduction of cancer cell proliferation (Qiao et al., 2008; Lee et al., 2012). For several lung adenocarcinoma cell lines MSCs effectively inhibited their migration, invasion, and cell-cycle progression through Oncostatin M mediated mesenchymal-epithelial transition (MET) of these cancer cells (Wang et al., 2012). For Kaposi's sarcoma, intravenously delivered MSCs were able to inhibit their growth in a mouse model via cell-cell contact-induced inhibition of Akt activity within sarcoma cells in an E-cadherin-dependent manner (Khakoo et al., 2006). In a human pancreatic carcinoma orthotopical xenograft model using PANC-1 cells, intraperitoneally injected MSCs inhibited tumor growth (Kidd et al., 2010). For mouse hepatoma, lymphoma and insulinoma, mouse BM-MSCs arrest these malignant cells at G_0/G_1 and increase their apoptosis *in vitro*, and reduced malignant ascites when hepatoma cells were co-injected intraperitoneally (Lu et al., 2008). For human glioma, human BM-MSCs suppress tumor growth through inhibition of angiogenesis likely via down-regulation of PDGF/PDGFR axis (Ho et al., 2013). In addition, microvesicles derived from human BM-MSCs inhibit *in vitro* and *in vivo* growth of HepG2 hepatoma, Kaposi's sarcoma, and Skov-3 ovarian tumor cell lines (Bruno et al., 2013), whereas those from human umbilical cord Wharton's jelly MSCs attenuate bladder tumor cell growth *in vitro* and *in vivo* (Wu et al., 2013).

Cancer therapy with engineered MSCs

The unique tumor-homing capacity and the immuno-privileged status of MSCs enable them as promising vehicles for delivering anti-cancer agents. The anti-cancer agents successfully delivered by MSCs include pro-drug enzymes, immune-stimulating cytokines, cell death inducers, oncolytic viruses, and nanoparticles. Most of these agents are introduced into MSCs by genetic engineering, whereas incorporation of drug-laden nano/microparticles on the cell surface or intracellularly has been tested recently. The approaches tested and corresponding references are summarized in Table 1. In addition to the tumor targeting, MSC-mediated delivery of many anti-cancer agents significantly improved the efficacy of these agents by protecting them from immune reaction or degradation or expressing them in the cell membrane. For instance, the effectiveness of the TRAIL recombinant protein has been limited by the short half-life of the protein and the fact that it is less potent than membrane-tethered forms of the protein, whereas MSCs expressing TRAIL effectively induce apoptosis of cancer cells in culture and in mouse models (Kolluri et al., 2013).

Generally, combination of MSC-mediated gene therapy with conventional chemo/radio-therapy such as Doxrubincine achieved better efficacy of controlling tumor (Lee et al., 2012). To eliminate the potential pro-tumor risk and other safety issues of MSC therapy, suicide genes such HSV-TK (herpes simplex thymidine kinase) or inducible caspase 9 (Di Stasi et al., 2011) should better be introduced into MSCs. Moreover, recent reports from two laboratories indicated that bone marrow MSCs expressing TRAIL together with HSV-TK killed cancer cells much more efficiently *in vitro* and *in vivo* than MSCs expressing either transgenes alone, and even achieved complete regression of metastatic cancer in lung when infused repeatedly (Kim et al., 2013; Martinez-Quintanilla et al., 2013). These data indicate that the by-stander effect of HSV-TK, i.e., generating phosphorylated metabolites of pro-drug ganciclovir that kill cells expressing the enzyme as well as adjacent cells, is ideal for improving both safety and efficacy of MSC-mediated cancer treatment.

One major issue of MSC-mediated cancer therapy is the trapping of MSCs in lung after intravenous injection (Lee et al., 2009a). Recently, a new approach circumvented this issue by reconstructing nanoghosts from MSCs. Briefly, intact MSC cell membranes are isolated (ghost cells) and homogenized into nanosized vesicles (nanoghosts). The MSC-derived nanoghosts preserve the tumor tropism of MSCs in a subcutaneous prostate cancer model, lack immunogenicity, and are cleared from blood-filtering organs due to much smaller size around 180nm (Toledano Furman et al., 2013). One dose intraperitoneal injection of TRAIL-encapsulating nanoghosts made from MSCs significantly inhibited the growth of prostate cancer for more than 70%, indicating the high efficiency of this delivery system. However, there are several limitations of this system such as the relative low encapsulation efficiency of TRAIL (30%) and huge amount of MSCs needed for cancer treatment (5×10^7 MSCs per mouse), which might be overcome by expressing membrane-bound TRAIL in MSCs and using pluripotent stem cells derived MSCs as mentioned below.

Table 1 Agents delivered by MSCs to treat cancer.

Agent	Mechanism	Cancer type	References
5-FC/ cytosine deaminase	Prodrug conversion (5-FC to 5-FU)	Subcutaneous melanoma Colon cancer Prostate cancer	Kucerova et al., 2007, 2008 Cavarretta et al., 2010
CX3CL1	Activates CTLs and NK cells	Metastatic melanoma and colon cancer	Xin et al., 2007
GCV/HSV-TK	Prodrug conversion	Subcutaneous or orthotopic glioma	Uchibori et al., 2009; Matuskova et al., 2010
IFNα	Immunostimulatory, apoptosis-inducing and anti-angiogenic	Metastatic melanoma	Ren et al., 2008a
IFNβ	Induces differentiation, S-phase accumulation and apoptosis	Orthotopic glioma; Metastatic melanoma, breast cancer, prostate cancer	Ren et al., 2008b; Seo et al., 2011a
IL12	Induces tumor-specific T cell responses, IFNγ-dependent	Melanoma and cervical cancer	Seo et al., 2011b
Oncolytic viruses	Destroy tumors by viral replication	Ovarian cancer, melanomas, acute lymphoblastic leukemia	Mader et al., 200; Bolontrade et al., 2012; Castleton et al., 2014
TRAIL	Induces apoptosis	Metastatic breast cancer; Orthotopic glioma Malignant mesothelioma	Loebinger et al., 2009; Sasportas et al., 2009; Sage et al., 2014
TRAIL + HSV-TK	Induce apoptosis, Prodrug conversion	Metastatic renal cell carcinoma, glioblastoma multiforme	Kim et al., 2013; Martinez-Quintanilla et al., 2013
Nanoparticles	Photoactivation of cell death	Osteosarcoma *in vitro*	Duchi et al., 2013

Abbreviations: 5-FC, 5-Fluorocytosine; GCV, ganciclovir, HSV-TK, herpes simplex virus thymidine kinase; IFN, interferon; IL interleukin.

Prospects

One major issue in the field of MSC research is that MSCs are being prepared with a variety of protocols in different laboratories. As a result, standardization of the cells has been extremely difficult and the data presented in different publications are difficult to compare. Hence large banks of reference cells are needed to advance the MSC research (Viswanathan et al., 2014). Moreover, MSCs from various adult tissues have a limited proliferation potential and lose some of their important biological functions as they are expanded (Larson et al., 2010). Therefore, it is difficult to prepare large banks of the cells with uniform biological activities and/or transgene expression required for experiments in large animals and for future clinical therapies. Large amounts of MSC-like cells with uniform biology properties have been derived from embryonic stem cells or iPS cells in many laboratories including mine. These pluripotent stem cells (PSC) derived MSCs express typical MSC surface markers, are capable of differentiation to osteocytes, adipocytes and chondrocytes, and have similar immunosuppressive and anti-inflammatory properties as BM-MSCs (Sánchez et al., 201; de Peppo et al., 2013). Meanwhile, these PSC-MSCs have much better expandability in vitro and regeneration capacity *in vivo*. My laboratory is testing the potential of these PSC-MSCs in cancer treatment in collaboration with Dr. Darwin Prockop's team at TAMHSC.

A particular concern of MSC-mediated cancer therapy is the pro-tumor risk of MSCs. Transducing MSCs with inducible suicide genes and inducing their suicide shortly after their homing to cancer may decrease this risk. However, MSCs significantly induced the expression of pro-EMT genes in cocultured cancer cells within 12 h (Li et al., 2012), suggesting that even the short-term effect of infused MSCs may promote metastasis and expansion of cancer stem cells. Hence, the pro-tumor potentials of MSCs should be considered cautiously for cancer therapy and approaches to reduce such risk should be explored.

Compliance with ethics guidelines

Qingguo Zhao and Fei Liu declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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