Review

Recent discoveries concerning the tumor - mesenchymal stem cell interactions

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ABSTRACT

Tumor microenvironment plays a crucial role in coordination with cancer cells in the establishment, growth and dissemination of the tumor. Among cells of the microenvironment, mesenchymal stem cells (MSCs) and their ability to evolve into cancer associated fibroblasts (CAFs) have recently generated a major interest in the field. Numerous studies have described the potential pro- or anti-tumorigenic action of MSCs. The goal of this review is to synthesize recent and emerging discoveries concerning the mechanisms by which MSCs can be attracted to tumor sites, how they can generate CAFs and by which way MSCs are able to modulate the growth, response to treatments, angiogenesis, invasion and metastasis of tumors. The understanding of the role of MSCs in tumor development has potential and clinical applications in terms of cancer management.

Contents

Abbreviations: ADSC, Adipose stromal cells; Akt, protein kinase B; BM-MSC, bone marrow mesenchymal stem cells; CAF, cancer associated fibroblast; CRC, colorectal cancer; CSC, cancer stem cell; HCC, hepatocellular carcinoma; IGF, insulin-like-growth factor; IL-1, interleukin-1; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; MMP, metalloproteinase; NK, natural killer; PCa, prostate cancer; PGE2, prostaglandin E2; TAM, tumor associated macrophage; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor.

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1. Introduction

MSCs are defined as mesenchymal stem cells or mesenchymal stromal cells, but represent commonly a large set of different types of cells. Indeed, MSCs have been isolated from different types of tissues, including in particular the bone marrow (BM-MSC), umbilical cord blood, adipose tissue (we will define them as adipose derived stromal cells), but also peripheral blood, fetal liver, lung, amniotic fluid, or placenta (for a review, [1]). All these types of MSCs retain similar characteristics with the ability to adhere strongly to plastic surfaces, are characterized by surface markers (CD14− or CD11b−, CD19− or CD79α−, CD34−, CD45−, HLA-DR−, CD73+, CD90+, CD105+) and with the potential to be differentiated into chondrocytes, osteoblasts and adipocytes under standard in vitro differentiating conditions [1]. Despite some common features with regard to the immunophenotype and differentiation potential of MSCs, these cells do vary in accordance with their direct interaction with other cells or via a paracrine fashion to the surrounding microenvironment.

The field of MSCs in tumor development has progressed tremendously since the early 2000s (for a review, [1]). In the setting of cancer therapy, the TREAT-ME1 is the first clinical trial worldwide using genetically altered MSCs for the treatment of advanced gastrointestinal tumors [2]. In this study, MSCs have been engineered to express the thymidine kinase of the herpes simplex virus (HSV-Tk) under the control of RANTES (CCL5) promoter, which is highly active in MSCs in the tumor context [3]. The RANTES/CCL5 promoter should allow tumor stroma-targeted expression of the thymidine kinase gene, which when phosphorylated by the prodrug, ganciclovir, can be incorporated into replicating DNA leading to cell death.

Although this trial has demonstrated the safety usage of modified MSCs, it is nevertheless important to execute caution since the biological properties of MSC in the tumor microenvironment have been complicated by the limited lineage-specific markers and the inter- and intra-clonal heterogeneity of MSCs. Thus, the main focus of this review is to provide an updated review of the current understanding of MSCs and its interaction with tumor cells. Apart from the unique feature of MSCs migrating toward injured and pathological lesion tissues, we will focus on the role of MSCs during the development of cancer, emphasizing on the six hallmarks of cancers, i.e. how MSCs aid in (i) enabling replicative immortality to cancer cells (ii) sustaining proliferative signal of cancer cells and cancer stem cells (iii) its action on epithelial and mesenchymal transition and metabolism of cancer cells (iv) how MSCs can evade growth suppressor (v) resist cell death and (vi) induce angiogenesis.

2. Homing of MSCs to tumor sites

Chemokines or more generally cytokines are amongst the major players responsible for MSC migration to tumors (Fig. 1), which is not surprising since chemokines are abundantly produced in tumor sites [4–6]. In addition, treatment of tumor could also promote the migration of MSCs toward tumors. Irradiation of breast tumor cells has been shown to enhance the release of TGFβ1, VEGF and platelet-derived growth factor BB (PDGF-BB) by tumor cells, which enhance the migration of MSCs towards cancer cells [7]. Furthermore, the migratory event was dependent on the upregulation of CCR2 on MSCs following exposure to irradiated cancer cells.

Using rat MSCs, Menon et al. have shown that the migration of MSCs towards cancer cells involved the up-regulation of CXCL12 in MSCs [8]. CXCL8 has been implicated for the migration of MSCs derived from human umbilical cord blood and human bone marrow [9] towards gliomas. Interestingly, even when MSCs are isolated from the same source, i.e. BM-MSCs, different cytokines have been implicated to provide the signaling cues to the migration of MSCs toward cancer cells. For example, CCL2 and CCL25 are the major chemokine responsible for stimulation human BM-MSC to migrate towards breast cancer [10] and multiple myeloma (MM) [11] respectively. Migration of human BM-MSCs towards hepatoma cells involves the release of CCL15 and CCL20 by cancer cells [12] and the chemokine macrophage inhibitory factor secreted by various cancer types can attract human BM-MSCs in a CXCR4-dependent manner [13]. Thus, the type of cytokine released that are crucial for mediating MSC migration is, in part, dependent on the tumor cell type and its niche as illustrated in Fig. 1.

Another way MSC can mediate tumor tropism is via secretion of extracellular vesicles such as the exosomes. Exosomes are small membrane vesicles secreted from cells that are important mediators of
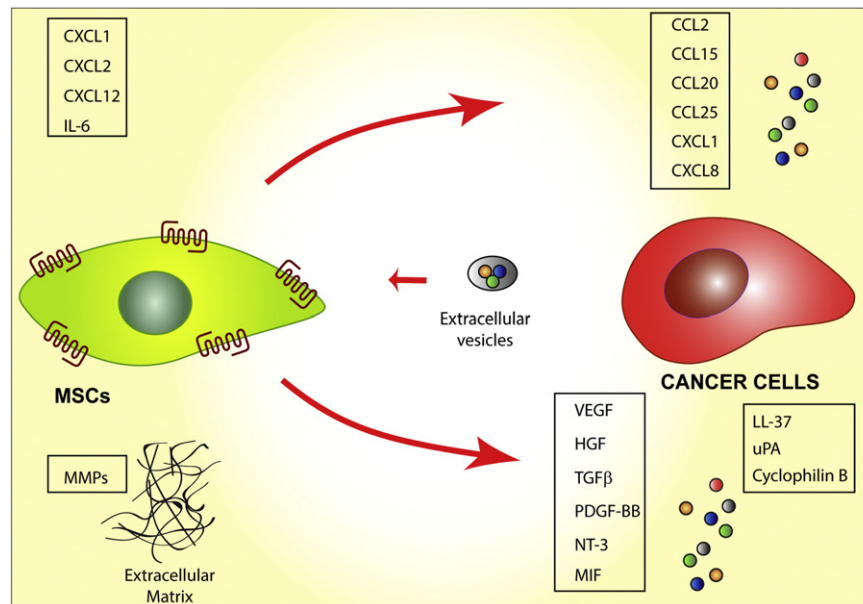
Fig. 1. Factors favoring MSc homing towards tumor cells. Cancer cells secrete a number of chemokines (CCL2, CCL15, CCL20, CCL25, CXCL1, CXCL8) which attract MSC through specific chemokine receptors at their surface. Chemokines can be directly released in the extracellular medium or incorporated into vesicles. Other cytokines including VEGF, HGF, TGFβ, PDGFF-BB, NT-3, MIF and factors such as LL-37, uPA and cyclophilin B released by tumor cells will affect the tropism of MSCs. Moreover, upon interaction with cancer cells, MSCs will secrete cytokines such as CXCL1, CXCL2, CXCL12 or IL-6 and metalloproteinases (MMPs), the latter with the ability to degrade extracellular matrix and favor migration.

intercellular communication and are implicated in the development of pathological processes. Cholangiocarcinoma cells have been shown to secrete these extracellular vesicles that promote the release of CXCL1, CCL2 and IL-6 from MSCs which aids in the migration of MSCs toward the tumor cells. In addition, conditioned media from MSCs exposed to these tumor derived extracellular vesicles could promote tumor cell proliferation through IL-6 signaling [14].

Besides cytokines, other factors are potentially involved in MSC tropism. In vivo inhibition of the leucine-leucine 37 peptides (LL-37) significantly reduce engraftment of MSCs into ovarian tumors [15]. Among other factors potentially involved in MSC chemotaxis to cancer cells, cyclophilin B and hepatocyte growth factor (HGF) have also been suggested [16]. Transforming growth factor-ss1 (TGF-ss1) and neurotrophin-3 (NT-3) contribute also to the glioma-directed tropism of human MSCs [17]. A number of human solid tumor cell lines express high levels of uPA (urokinase plasminogen activator) and soluble uPAR (urokinase plasminogen activator receptor) in tumor cell-conditioned media. uPA is one of the factors responsible for the migration of MSCs towards neuronal stem cells [18]. This paracrine signaling loop between the tumors and MSC resemble those in the injured tissues where MSCs and other inflammatory cells are recruited to the injury sites by fibrinolytic factors such as uPAR. These factors released from MSC in turn set a proteolytic environment and activate another set of proteases such as metalloproteinases (MMPs) which enable the release of cytokines and chemokines [19]. Several groups have also highlighted the crucial role MMP-1 produced by MSCs that will favor tropism through a cross talk with the CXCL12/CXCR-4 axis [12,20,21].

3. MSCs aid in replicative immortality to cancer cells

One of the hallmarks of cancer is the ability to undergo continuous proliferation. This replicative immortality is triggered by telomere dysfunction, suppression of tumor suppressors such as p53 and p16/pRb and oncogene activation. It has been demonstrated that rat MSCs undergo spontaneous transformation in vitro, possibly due to epigenetic silencing of p16 [22]. A recent study investigated the characteristics of rat MSCs before and after spontaneous transformation. In agreement

with the earlier study, p16 was markedly silenced. In addition, this research group found that transformed MSCs contain high levels of a p53 mutant that loses its ability to bind to surviving gene. As a consequence, surviving expression was markedly upregulated in these transformed MSCs which exhibited characteristics of cancer stem-like features such as loss of contact inhibition, multi-potency to mesenchymal lineages and anchorage-independent growth [23].

4. MSCs can sustain proliferative and metastatic signal of cancer cells

Multiple studies have shown pro-tumorigenic effects of MSCs which are summarized in Fig. 2. One of the first studies that reported the involvement of chemokines in the increased metastatic ability of cancer cells in the presence of MSCs was published by Weinberg's group. The authors showed that MSCs upon contact with cancer cells, MSCs released the chemokine CCL5, which was responsible for the increased metastasis of breast cancer cells [3]. The potential of CCL5 secreted by stromal on tumor invasion has also been observed with adipose-derived stromal cells [24]. Luo et al. subsequently showed that MSCs secrete CCL5 which suppresses AR signaling in prostate cancer cells (PCa) by enhancing the expression of HIF2α in PCa and promotes metastasis [25]. One explanation of the hypersecretion of CCL5 by MSCs could arise from the release by tumor cells of IGF-1 (Insulin-like-Growth Factor-1) [26] or the pro-inflammatory peptide Leucine-Leucine-37 (LL-37), which would induce not only the production of CCL5 but also of IL-6, IL-10 and VEGF which would increase angiogenesis and the growth of ovarian tumors [15]. IL-6 by itself has been shown to be produced at high levels by MSCs when they are conditioned by tumor cells and to be involved as well as VEGF secretion in the more rapidly growing of ovarian cancer cells in coculture with MSCs [27]. This role of IL-6 has also been observed in the dialog between MSCs and breast cancer cells [28].

Tumor-derived osteopontin (OPN) also induces MSC production of CCL5, which binds to integrin cell surface receptors [29]. MSCs stimulate cancer cell metastasis and upon contact with cancer cells acquire MSCs retrieved from sites of metastases exhibit a CAF phenotype with alpha-smooth muscle actin, tenascin-c, CXCL12, fibroblast-specific protein-1
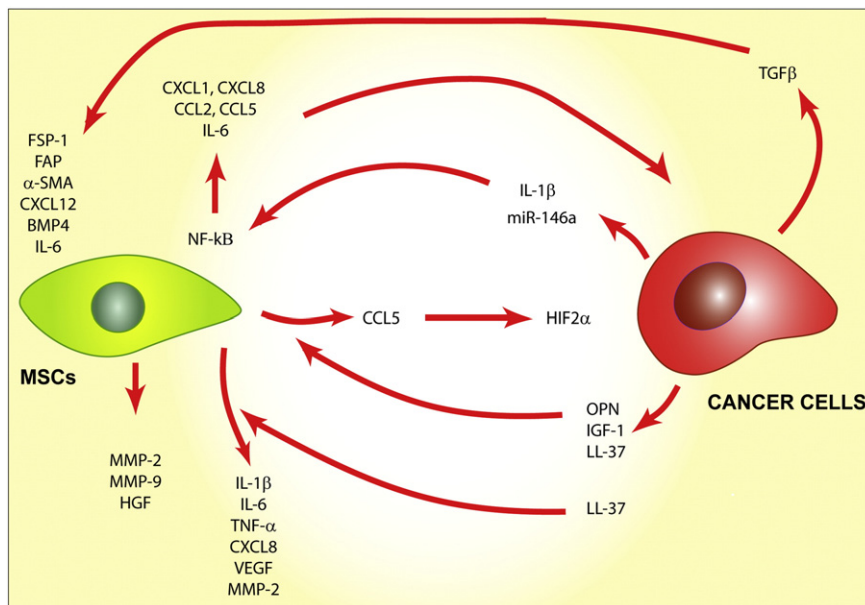

Fig. 2. A multitude of factors favoring tumor growth by MSCs. Cancer cells can release IL-1β or miR-146a (through vesicles) which can enhance NF-κB activity in MSCs and the release of multiple cytokines including in particular CXCL1 CXCL8, CCL2, CCL5 and IL-6. CCL5 is involved in an increased metastasis of cancer cells, in some cases through HIF2α-dependent mechanism. Moreover, CCL5 production by MSCs can also be induced by other factors secreted by cancer cells such as osteopontin (OPN), IGF-1 or LL-37. LL-37 has also the ability of increase the secretion of IL-1β, IL-6, TNF-α, CXCL8, VEGF or MMP-2 by MSCs. MSCs release MMP-2, MMP-9 and HGF, which will promote metastasis. Finally, upon interaction with cancer cells, MSCs will acquire a CAF phenotype favoring tumorigenesis with the production of FSP-1, FAP, α-SMA, CXCL12, BMP4 and IL-6.

and the MMP-2 and MMP-9 overexpression [29]. But the nature of cancer cells interacting with MSCs appears as a crucial point in terms of the final effect of MSCs. Indeed, we have demonstrated that the conditioned medium of metastatic breast cancer cells was able to induce the production of a number of chemokines (in particular CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, CCL2, CCL5, CCL8, CCL20) upon release of IL-1β by cancer cells and subsequent activation of NF-κB pathway in MSCs. Chemokines produced by MSCs are in turn able to increase the motility of breast cancer cells creating a vicious circle [30]. Moreover, it should be also noted that MSCs naturally produce high levels of chemokines CXCL1 and CXCL5 which increase the migration of Polyoma Virus middle T antigen (Pymt) mouse breast cancer cells [31].

Similar chemokines have been shown to be important for the promoting effects of MSCs on a number of other types of cancers. Colorectal cancer cells (CRC) induce the production of CXCL8 by MSCs, which in turn increases endothelial cell proliferation, CRC proliferation, tumor formation and angiogenesis in vivo [32]. MSCs isolated from gastric tumors (GC-MSCs) have a higher ability than BM-MSCs to stimulate the proliferation and growth of gastric cancer cells. GC-MSCs produce higher levels of pro-angiogenic factors such as VEGF, CXCL8 and CXCL2. Blocking of CXCL8 was sufficient to reduce the growth promoting effect of GC-MSCs conditioned medium [33].

Another type of action of MSCs, which sometimes also affects chemokine signaling, corresponds to the MSC-derived exosomes which can modulate tumor growth and invasion. It has been shown that exosomes derived from metastatic melanoma cells can educate bone marrow derived cells toward a pro-metastatic phenotype through mesenchymal epithelial transition (MET) and by increasing the leakiness of blood vessels [34]. Exosomes from MSCs are also able to promote both in vitro and in vivo tumor growth of nasopharyngeal carcinoma through in particular the production of FGF19 in the exosomes [35]. Exosomes produced by MSCs confer the resistance to 5-fluorouracil treated gastric cancer cells. These exosomes from MSCs enhance the calmodulin-dependent protein kinase (CaM-Ks) and RAF/MEK/ERK signaling in gastric cancer cells [36].

Growth factors are also playing a role in the control of tumor development by MSCs. TGFβ1 secretion by prostate cancer cells is able to enhance the migration of MSCs towards cancer cells in vitro [37]. TGFβ1 secretion by prostate cancer cells induces MSC transdifferentiation into CAFs. In turn, such CAFs will enhance the invasiveness of prostate cancer cells [37]. MSCs induce the migration of breast cancer cells also through the release of TGF-β and the activation of rho-associated kinase, focal adhesion kinase and matrix metalloproteinases [38]. Carnet et al. have shown that BM-MSCs enhance lung carcinoma tumor growth through trans-shedding of amphiregulin (AREG) from the tumor cell membrane by TNFα converting enzyme carried by the BM-MSC plasma membrane. The released soluble AREG activates cancer cell growth and invasion [39]. The isolation of MSCs from gastric carcinoma has shown that these educated MSCs could enhance tumor growth through the release of HGF [40]. Umbilical cord derived mesenchymal stem cells can increase tumor growth and metastasis of cholangiocarcinoma cells, through an induction of Wnt/β-catenin signaling in cancer cells [41]. BM-MSCs and acute myeloid leukemia cells interact through a mutual induction of Notch signaling in both cells which supports AML growth [42].

On the other hand MSCs could exhibit tumor suppressive effect (Fig, 3). It was shown that conditioned media derived from human fetal MSCs express high levels of the insulin growth factor binding proteins IGFBPs and can sequester free insulin-like growth factors (IGFs) to inhibit hepatocellular carcinoma cell proliferation via cell cycle arrest [43]. Dickkopf-related protein 1 (Dkk-1) secreted by the MSCs inhibits growth of breast cancer cells via depression of Wnt signaling and in particular by reducing β-catenin levels in breast cancer cells [44]. Other signaling pathways including the MAPK and Akt are also affected. Indeed, BM-MSCs can reduce the proliferation, viability and migration of NSCLC through the down-regulation of translation initiation factors (eIF4E and eIF4GI) and MAPK signaling [45]. Moreover, Khakoo et al. have shown that MSCs have anti-tumorigenic and pro-apoptotic effects on Kaposi sarcoma cells by suppressing Akt activity in cancer cells [46]. MSCs produce exosomes containing mir-16 which is able to down-regulate VEGF and VEGFR production by breast cancer cells and in turn reduce tumor growth in vivo, with a decrease of vascularization, even if it should be mentioned that most studies have shown a pro-tumorigenic effect of MSCs on breast cancer [47]. In addition, one
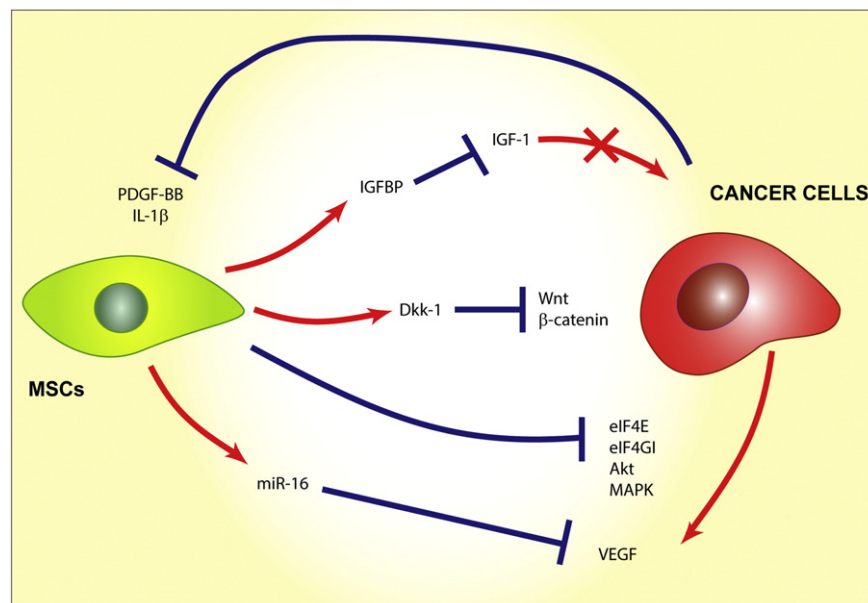

Fig. 3. Mechanisms underlying the anti-tumor effect of MSCs. MSCs release high levels of insulin growth factor proteins (IGFBP) which can sequester IGF-1 and prevent its growth stimulatory effect on cancer cells. Another way for MSCs to repress tumor growth is the secretion of Dickkopf-related protein 1 (Dkk-1) which has negative effects on Wnt and β-catenin signaling. Through the release of miR-16 in exosomes, MSCs will reduce the production of cancer cells. Moreover, even if the factors involved are not known, MSCs can have inhibitory effect on translation initiation factors such as eIF4E, eIF4GI as well as on Akt and MAPK pathways. On the other hand, in some instances, tumor cells can inhibit the production of PDGF-BB and IL-1β by MSCs, which in turn reduces angiogenesis and tumor growth.

study has shown that adipose derived stromal cells package mir-122 in exosomes which render hepatocellular carcinoma cells sensitive to chemotherapy [48]. It remained unclear why majority of the studies are in favor of positive effects, which could explain why the mechanisms of inhibition of growth or metastasis have been less investigated.

5. MSCs can sustain proliferative signal in cancer stem cells

Cancer stem cells show unique properties in terms of cancer initiation, enhanced metastasis and drug resistance. Interestingly, several studies have shown that MSCs could enhance cancer cell stemness (as illustrated in Fig. 4). This can occur through a direct action on classical genes involved in stemness. MSCs isolated from ovarian tumors increase the number of cancer stem cells (CSCs) through the bone morphogenetic protein BMP2 and BMP4 production [49]. Moreover, the same group has shown that ovarian tumor cells could secrete Hedgehog (HH), which in turn stimulate the production of BMP4 [50]. BMP4 is responsible for the enrichment of cancer stem cells and chemotherapy resistance [50]. FoxP2 seems also involved as coculture of MSCs with breast cancer cells triggers an increase of mir-199 and mir-214 expression in breast cancer cells, leading to an enhanced metastasis and cancer stem cell phenotype of breast cancer cells [51]. These 2 miRs repress Forkhead-Box P2 (FoxP2) expression and is responsible for increasing the number of cancer stem cells, favoring tumor initiation and metastasis [51]. Chemokines and some cytokines are known to play critical role in modulating cancer stem cells. Colon cancer cells produce IL-1α and IL-1β which induce the secretion of PGE2 by MSCs. PGE2 is then able to cooperate with IL-1 to increase the production of cytokines such as IL-6, CXCL1 and CXCL8 by MSCs, leading to activation of beta-catenin pathway and an increase of stem cell properties of cancer cells [52].

A number of other studies have highlighted this role of CXCR2 ligands. MSCs are able to increase the number of breast CSCs and in particular the percentage of aldehyde dehydrogenase (ALDH)-positive cells [53]. Coculture of MSCs with breast cancer cells increases the production of CXCR2 ligands (CXCL1, 5, 6, 7, 8) which are able to increase the percentage of CSCs [53]. Moreover, CXCL7 produced by MSCs can upregulate the levels of CXCR2 ligands. The same study has shown that breast cancer cells produce IL-6 with the ability to induce the expression of CXCL7 in MSCs [53]. Conditioned media from MSCs contains cytokines (IL-6, CXCL8) and induces expression of pluripotency factors (c-myc, Oct-4, Sox2) as well as the AMPK/mTOR and NF-κB pathways in colorectal cancer cell lines [54]. A similar study has shown that IL-6 produced by MSCs is responsible for the increase in the proportion of CSCs (CD133-/CD166-/EpCAM-) in the population of colorectal cancer cells, through an activation of the JAK2-STAT3 pathway in cancer cells [55]. Luo et al has shown that upregulation of CCL5 expression in BM-MSCs and PCa cells, after MSCs infiltrated into the tumor, subsequently downregulated androgen receptor (AR) signaling and increases the percentage of cancer stem cells [56]. This increase in the number of PCa stem cell then leads to the upregulation of matrix metalloproteinase 9, ZEB-1, CD133 and CXCR4 molecules, and enhanced the metastatic ability of PCa cells [56].

6. MSC's action on epithelial and mesenchymal transition and metabolism of cancer cells

Epithelial-mesenchymal transition (EMT) is a key event in tumor invasion where the epithelial cell layers lose their apico-basal polarity, undergo matrix remodeling resulting in the spread and invasiveness of cancer cells. MSCs have been reported to stimulate EMT and induce stem-like properties that allow the cancer cells to acquire enhanced motility and survival through the circulation. MSCs and cancer cells exchange multiple types of materials including exosomes, mitochondria and also cell membrane components in a bidirectional way [57]. BM-MSCs are able to transfer mitochondria to breast cancer cells, resulting in an enhanced oxidative phosphorylation, cancer cell growth and invasion [58]. Co-culture of breast cancer cells with MSCs led to an EMT-phenotype as characterized by downregulation of epithelial markers such as E-Cadherin with a corresponding upregulation of mesenchymal markers, vimentin, N-cadherin and snail [59]. Similarly, conditioned media derived from MSCs have been shown to trigger EMT in cancer cells, thereby promoting the metastatic potential of these cells [60].

A number of reports have shown that the interaction of MSCs with cancer cells leads them to acquire a cancer associated fibroblasts (CAFs) phenotype [1]. CAFs are generally characterized by a high expression of CXCL12, alpha smooth actin (α-SMA) and fibroblast surface
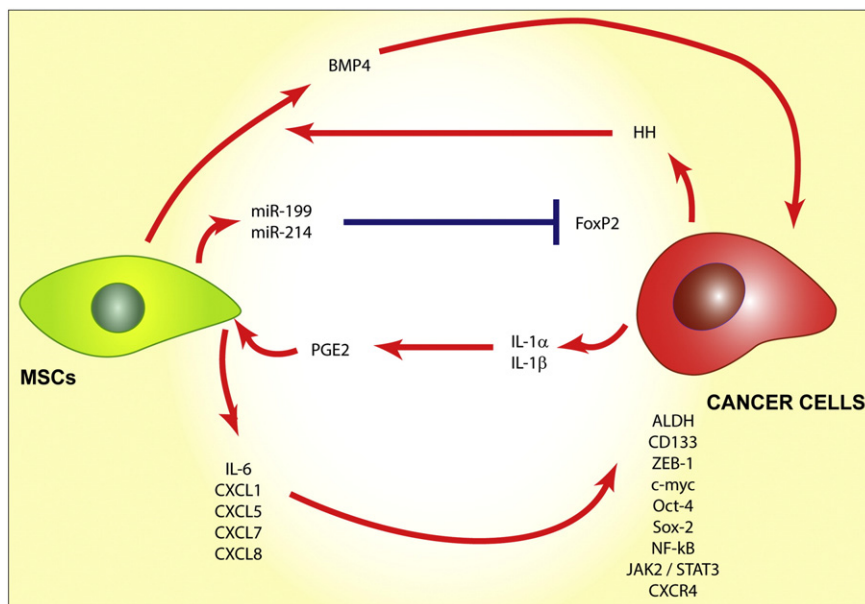
Fig. 4. MSCs promote the stemness of cancer cells. Upon release of Hedgehog (HH) by tumor cells, MSC release BMP4, which will increase the number of cancer stem cells. IL-1α and IL-1β released by cancer cells induces the production of PGE2 by MSCs, leading to the higher release of IL-6, CXCL1, CXCL5, CXCL7 and CXCL8 leading to an increase of cancer stem cell properties and the markers of stemness including Aldehyde dehydrogenase (ALDH), CD-133, ZEB-1, c-myc, Oct-4, Sox-2, NF-kB, JAK2/STAT3 and CXCR4. MSCs also release vesicles containing miR-199 and miR-214 targeting FoxP2 expression to increase stemness.

protein (FSP) [61]. CAFs have been implicated to sustain invasive tumor growth by recycling products of the anaerobic metabolism of cancer cells. MSCs could also enhance cell survival through upregulation and secretion of anti-oxidant, stanniocalcin-1 (STC1). MSC-derived STC1 decreases levels of reactive oxygen species (ROS), mitochondrial membrane potential (MMP), and increases lactate production, leading to a decreased ROS-induced apoptosis and enhanced the energy metabolism of cancer cells i.e. the Warburg Effect [62].

Further, MSCs could modulate the metabolism of cancer cells and proliferation through secretion of exosomes, the reverse is also true. In a recent study, exosomes produced from the prostate cancers could impair the adipogenic differentiation of MSCs, but favoring the differentiation of MSCs into myofibroblasts [63]. In turn, the exosome differentiated MSCs are to promote vascularization and tumor growth [63]. Coculture of MSCs with cancer cells can result in a morphological change of MSCs dependent on the expression of E-cadherin and IL-1β by cancer cells. Pharmacological inhibition of FAK, MAPKK, and actin polymerization completely abrogated MSC morphological changes [64]. Apart from cancer cells, macrophages have also been shown to interact with MSCs and increase the production by MSCs of a number of cytokines including IL-6, CCL2, 5, 7, 20 and CXCL1, 3, 6, and 8 [65]. Alternatively, MSCs have also been reported to acquire epithelial characteristics through fusion with gastrointestinal epithelial cells [66], which has been also observed between MSCs and breast cancer cells [67]. At least 20% of CAFs isolated from gastric cancer were derived from MSCs originated from the bone marrows. These CAFs, like MSCs, expressed high levels of trophic factors including IL-6, Wnt5α and BMP-4 and are recruited to tumor sites in TGF-β and CXCL12 dependent way [68].

The process of acquiring CAF phenotype or possible fusion with the surrounding epithelial cells is not well elucidated. Some reports define two classes of polarized MSCs. Toll like receptor (TLR)1–6 have been identified on primary human MSCs and have been reported that TLR stimulation enhanced the migratory function of MSCs [69]. TLR4-primed MSCs are polarized into pro-inflammatory MSC1 phenotype; whereas TLR3-primed MSCs are polarized into the classical immunosuppressive MSC2 phenotype [70]. The classification into the two phenotypes is mainly based on a distinct cytokine profile which includes an overexpression of TGF-β and its downstream effectors SMAD3 and SMAD4. MSC1 are capable of inhibiting tumor growth and metastasis, whereas MSC2 do the reverse [71].

7. How MSC can evade growth suppressor

One of the major features of MSCs is their immunosuppressive potential, which has been extensively studied and represents an attractive point for therapeutic purposes for immunological diseases [72] (Fig. 5). MSCs could regulate the proliferation, activation and effector function of T lymphocytes, antigen presenting cells and NK cells via direct cell-to-cell contact or production of soluble factors including prostaglandin E2, indoleamine 2,3-dioxygenase, tumor necrosis factor-α stimulated gene/protein 6, nitric oxide, and transforming growth factor (TGF-β)-1 [72].

MSCs are able to inhibit the proliferation of T cells, but also B cells and NK cells both in vitro and in vivo. This can favor tumor growth in allogeneic animals [73]. The pro-tumorigenic action of MSCs on tumor growth and metastasis of breast cancer cells, involves a lower cytotoxic activity of splenocytes, NK cells and CD81 T cells in vitro [74]. Moreover, tumors treated MSCs have significantly lower percentages of CD31NKp461 NKT-like, higher percentages of CD41Foxp31 T cells, increased serum levels of Th2 and decreased serum levels of Th1 cytokines, and significantly higher number of CD41 cells expressing IL-10 [74]. Immunosuppression mediated by MSC can occur via paracrine soluble factors. For example, the prostaglandin E2 (PGE2) released from MSCs can trigger the production of IL-10 by macrophages [75] and prevent the maturation of monocytes into dendritic cells [76]. Furthermore, MSCs could also push Th1 cells to secrete less IFN-γ and caused the Th2 cells to increase their secretion of the immunosuppressive IL-4 [77]. MSCs derived from cervical tumors have been shown to downregulate the surface HLA class I molecules (HLA-A*0201) [78]. As a consequence, production of IL-10 is enhanced which aid in the establishment of an immune-silenced and quiescent niche. Likewise, MSCs derived from breast cancer tumors also exhibited high levels of immunosuppressive factors including IL-10, IL-4 and TGF-β1 [79].

Indoleamine 2,3-dioxygenase (IDO) is a rate-limiting enzyme in the degradation of tryptophan (Mellor AL and Munn DH, 1999). Growth arrest in T lymphocytes was observed when the cells were exposed to tryptophan shortage provoked by IDO [80]. This resulted in the ability of the tumor cells to escape from immune surveillance. Human MSCs express IDO protein and exhibit functional IDO activity upon stimulation with IFNγ and inhibit allogeneic T-cell responses [81]. IFNγ-preconditioned MSCs not only repress T cell proliferation but could also
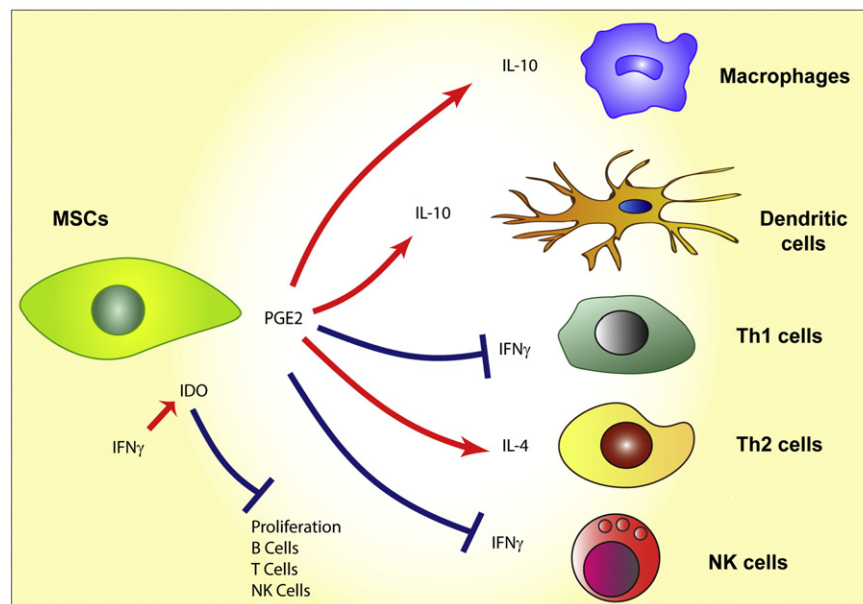
Fig. 5. A central role of PGE2 and IDO in the immunosuppressive effect of MSCs. MSCs produce Prostaglandin E2 (PGE2) which will enhance the production of IL-10 from macrophages and dendritic cells, increase the production of IL-4 by Th2 cells and reduce the release of IFNγ by Th1 cells and NK cells. Upon stimulation with IFNγ, MSCs produce also high levels of Indoleamine 2,3-dioxygenase (IDO) which is able reduce tryptophan levels and thus inhibit the growth of numerous cells including B cells, T cells and NK cells.

induce B-cell growth arrest and apoptosis in an IDO-dependent manner [82]. Inducible nitric oxide synthase (iNOS) produced by the murine MSCs also exhibit similar T cell suppression effect which led to enhance melanoma cell tumor growth [83].

Another mechanism of MSC immunosuppression is mediated through high expression of CCR2 ligands which could recruit immuno-suppressive cells such as CD11b + Ly6C + monocytes, F4/80 +, macro-phages, and CD11b + Ly6G + neutrophils to the tumor [84]. In the same line, MSCs from follicular lymphoma patients promote monocyte differentiation toward a proangiogenic and lipopolysaccharide-unresponsive phenotype close to that of (TAM) tumor-associated mac-rophages and produce higher levels of CCL2 upon coculture with malig-nant B cells [85]. Moreover, the nature of cancer cells is also important. Indeed, it was shown recently that upon interaction with breast cancer stem cells (CSCs), MSCs can promote the polarization of PBMC in T_{regs} and Th_{17}. This effect is dependent on the high interaction of CSCs with MSCs through CXCR4 and connexin 43-dependent gap junction inter-cellular communication [86].

8. Resist cell death

It is interesting to point out that MSCs are also able to confer a resis-tance to cancer drugs (Fig. 6), as well as other DNA damaging agent such as irradiation. Co-culture of MSCs and breast cancer cells confer resis-tance against trastuzumab via activation of the nonreceptor tyrosine ki-nase c-Src and downregulation of the phosphatase and tensin homolog (PTEN) [87]. MSCs have also been shown to confer cisplatin and bortezomin resistance in cancer cells by the local release of soluble fac-tors such as IL-6 and CXCL8 [88] and IL-6, IL-10, IGF-1, VEGF and Dkk-1 [11]. Some of these cytokines have been implicated in their ability to en-hance stemness of cancer cells; hence, it is not surprising that another mechanism by which MSCs confer resistance to chemotherapy is via their ability to harness properties similar to those of cancer stem cells. In a study, targeted methylation of the promoters of tumor suppressor genes in MSCs have caused the cells to transform towards tumor-initiating cells, and these cells exhibited increased resistance to cisplatin treatment [89]. MSC could also promote dormancy of breast cancer cells

via the exosome release of miR-23b which targets Myristoylated Alanine Rich Protein Kinase C Substrate (MARCKS, a promoter of cell motility and cycling, implicated in the pathogenesis of metastatic can-cers) [90]. In the same line, breast cancer cells can stimulate the produc-tion of miR-222/223 by MSCs which also induces the dormancy of cancer cells as well as the resistance to carboplatin treatments [91]. It re-mains unclear whether miR-222/223 could target cyclins. Apart from soluble cytokines, MSC could also release polyunsaturated fatty acids, in particular, polyunsaturated fatty 12-oxo-5,8,10-heptadecatrienoic acid (KHT) and hexadeca-4,7,10,13-tetraenoic acid (16:4(n-3)) [92]. Blocking the central enzymes involved in the production of these fatty acids could effectively sensitize the cancer cells against chemotherapeu-tic drugs.

MSCs have also been demonstrated to confer radioresistance. This is due to the facts that MSCs express high levels of key DNA Damage Re-sponse proteins including ATM, Chk2 and DNA Ligase IV; high levels of the anti-apoptotic proteins, Bcl-2 and Bcl-XL, and low levels of the pro-apoptotic proteins, Bim and Puma [93].

9. Modulation of angiogenesis by MSCs

One of the tumor-promoting effects of MSCs is derived from their ability to promote angiogenesis, which is one of the major hallmarks of cancer. Co-culture of MSCs with tumor cells led to elevated produc-tion of angiogenic factors such as VEGF and IL-6 [27]. VEGF secreted from MSCs has been shown to promote angiogenic sprouting in vitro while MSCs were not observed to differentiate into endothelial cells in vitro and in vivo [94]. Radiation therapy has been shown to increase the release of CXCL12, PDGF-B by tumor cells, which not only attract MSCs to the tumor site but also induces the newly recruited MSC to dif-ferentiate into pericytes, and promote vasculogenesis and tumor growth [95].

Studies have demonstrated that MSCs, as well as exosomes from MSCs, could stimulate the cancer cells to secrete VEGF which in turn promote tumor growth by activating extracellular signal-regulated ki-nase1/2 (ERK1/2) pathway [96] respectively. Likewise, IL-6 secreted by MSCs could also modulate angiogenesis and tumor cell proliferation
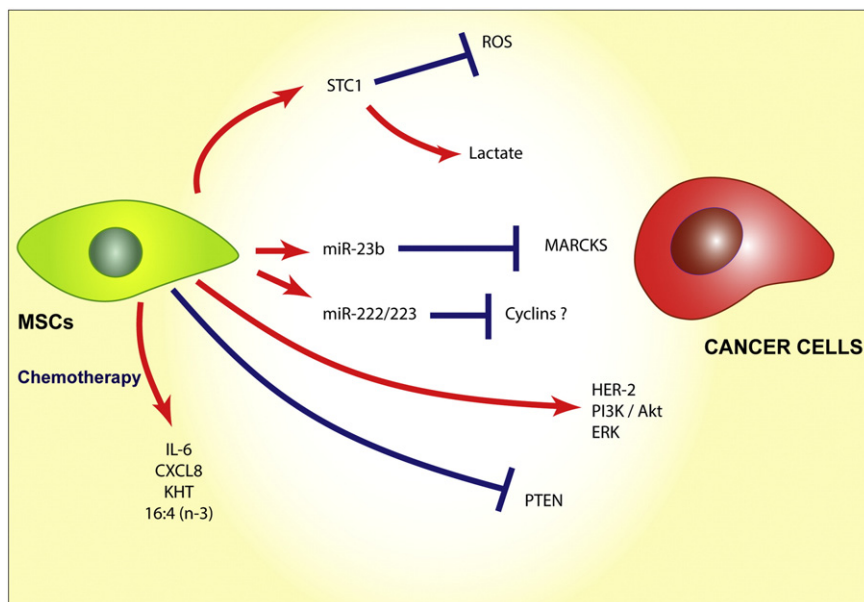

Fig. 6. MSCs favor the resistance to treatments. MSCs have multiple effects on cancer cell resistance to treatments. First, they can favor the dormancy of cancer cells through the release of miR-23b in exosomes, which will in particular target Myristoylated Alanine Rich Protein Kinase C Substrate (MARCKS) in cancer cells. Similar induction of dormancy is also promoted by miR-222/223, which could potentially target cyclins. Moreover, MSCs can activate pathways such as PI3K/Akt, ERK and the expression of HER-2 and repress PTEN signaling, which all will increase the resistance of tumor cells to treatments. Upon chemotherapy, MSCs acquire the ability to produce higher levels for IL-6, CXCL8 and polyunsaturated fatty acids such as 12-oxo-5,8,10-heptadecatrienoic acid (KHT) and hexadeca-4,7,10,13-tetraenoic acid (16:4(n-3)). Finally, MSCs increase the survival of cancer cells through the release of stanniocalcin-1 (STC1) which decreases the levels of ROS and increases lactate production, leading to an enhanced Warburg effect.

during tumor development. The IL-6 secreted from MSCs increases the secretion of endothelial cell-derived endothelin-1 (ET-1) in cancer cells [97]. ET-1 is a potent mitogen for endothelial cells, vascular smooth muscle cells and tumor cells. Interestingly, Huang and colleagues not only demonstrate that tumor growth can be efficiently inhibited by targeting the IL-6/ET-1/Akt or ERK pathway of tumor-stroma interaction [97] but that IL-6 secreted from MSC could induce non-cancer stem cells to express markers of cancer stem cells, thus increasing the ability to form tumor in vivo [55]. In breast cancer, elevated levels of IL-6 have been correlated to increased metastatic spread [98] and poor patient survival [4].

Under certain circumstances, MSCs could elicit an anti-angiogenic response via a paracrine pathway that impairs the extent of endothelial progenitor cell recruitment and capacity to form endothelial tubes [99]. Further, pro-angiogenic factors were inhibited which resulted in the abrogation of tumor growth. Interestingly, MSC exosomes-derived from bone marrow of mice harboring multiple myeloma had higher levels of IL-6 and these MSCs were shown to promote tumor growth. In contrast, MSC exosomes-derived from normal bone marrow inhibited the growth of the tumor cells [100].

10. Remarks and perspectives

There is no doubt that MSC can have profound effects the outcome of tumor development. The reason why this action is positive or negative remains to establish some studies, including ours, begin to give some tracks including the origin of MSCs or the nature of tumor cells used in the experimental settings. Understanding how MSCs function is essential to control or target MSCs in therapeutic strategies. It is striking to observe that MSCs have the ability to act on all steps of carcinogenesis, including cancer stem cell arising, tumor growth, EMT, cancer metastasis, angiogenesis as well as the resistance to different types of disease treatments. Moreover, MSCs have a tropism for tumor sites and are therefore particularly attractive to be considered as drug carriers. However, it is at present unclear if one should consider using naïve MSC cells or MSC modified with appropriate therapeutic genes. If so, the recommended dosage/site of isolation, donor variability, possible transformations of MSCs due to long term in vitro culture passages and choice of viral vector used to introduce the therapeutic genes into MSC should be carefully considered. Alternatively, one could consider exploiting the therapeutic factors secreted from MSCs that had prior exposure to drugs. However, the mechanisms involved are complicated by the nature of material exchanges between MSCs and cancer cells, like membrane fusion or mitochondria exchange and a variety of growth factors, metabolites or fatty acids. These are often hard to qualify and/ quantify, making the relationship of MSCs and tumor cells more mysterious and clinical applications for possible cancer treatment more difficult. The future challenges of the field will certainly be the understanding of the key features of cells surrounding MSCs, which will dictate the pro- or anti-cancer properties of MSCs. Moreover, to achieve a better treatment of patients, future clinical approaches will need to use strategies to inhibit the dialog between MSCs and cancer cells in particular.

Conflicts of interest

The authors declare that they have no conflict of interest to disclose.

Acknowledgements

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