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Bone marrow-derived mesenchymal stem cells and the tumor microenvironment

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Abstract Over the last decade, there has been a growing interest in the role of mesenchymal stem cells (MSC) in cancer progression. These cells have the potential to give rise to a variety of mesenchymal cells like osteoblasts, chondrocytes, adipocytes, fibroblasts, and muscle cells. In contrast to their hematopoetic counterparts, MSC are not as clearly defined, which makes the interpretation of their role in cancer progression more complex. However, the nature of the relationship between MSC and tumor cells appears dual. Primary and metastatic tumors attract MSC in their microenvironment where they become tumor-associated fibroblasts, affect tumor cell survival and angiogenesis, and have an immunomodulatory function, and vice versa in the bone marrow MSC attract tumor cells and contribute to a microenvironment that promotes osteolysis, tumor growth, survival, and drug resistance. Whether MSC are pro- or anti-tumorigenic is a subject of controversial reports that is in part explained by the complexity of their interaction with tumor cells and the large range of cytokines and growth factors they produce. The study of these interactions is a fertile ground of investigation that—as already demonstrated in the case of myeloma—should lead to novel therapeutic approaches in cancer. In this article, the biology and role of MSC in cancer is reviewed with a primary focus on bone marrow-derived MSC.

Keywords Tumor microenvironment · Mesenchymal stem cells · Bone marrow · Metastasis

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1 Introduction

Mesenchymal stem cells (MSC) have been the subject of an increased interest. Because of their ability to give rise to bone, cartilage, fat, and muscle, their role in regenerative medicine has been extensively studied and the fact that they can be recruited at sites of inflammation and tissue repair has prompted their potential use as tissue regenerative cells and tools for gene delivery [1]. A major source of these cells is the bone marrow where they represent, with hematopoietic stem cells (HSC), the two stem cell populations housed in this organ. The recent suggestion that MSC can be recruited by tumors has triggered a series of studies aimed at examining their potential role in cancer progression. The relationship between MSC and tumor cells is in fact dual. Primary and metastatic tumors actively attract MSC from the bone marrow and other sites where they become tumor-associated fibroblasts (TAF) and contribute to the tumor microenvironment; vice versa, MSC

attract tumor cells in the bone marrow and when in contact with tumor cells produce a variety of cytokines that affect tumor cell growth and survival. Although we recognize that MSC other than those from the bone marrow can play a role in cancer progression, in this review article we have focused on the relationship between bone marrow-derived MSC (BMDMSC) and tumor cells.

2 What are mesenchymal stem cells?

MSC are typically characterized by their ability to differentiate into a variety of mesenchymal cells, including osteoblasts, chondrocytes, adipocytes, muscle cells, pericytes, reticular fibroblasts, and even neural cells. In the bone marrow, they provide the microenvironmental regulation that controls HSC quiescence and proliferation [2-4]. MSC represent an extremely rare cell type within the bone marrow, comprising 0.01% to 0.001% of all mononuclear cells, compared to 1% for the HSC population [5, 6]. This rarity has made the identification of the MSC niche within the bone marrow difficult, although surface marker expression analysis suggests a perivascular location [7]. Whereas the stem cell for hematopoietic lineage is well characterized, the phenotype of true stem cells responsible for the multipotent stromal lineage remains ill defined. The term "MSC" itself is a nebulous one, denoting not only the pluripotent mesenchymal stem cell defined by Caplan [2] but also stromal stem cells, multipotent stromal cells, mesenchymal stromal cells, and multipotent adult progenitor cells (MAPC) [8]. The discovery of the presence of MSC in tissues other than the bone marrow, such as the dental pulp and adipose tissues, further impedes a clear phenotypic definition [9]. MSC likely represent a heterogeneous cell population of multipotent and committed progenitor cells.

Murine multipotent bone marrow MSC were originally identified by Friedenstein on the basis of their adherence to tissue culture plastic *in vitro*, their ability to form colony-forming unit-fibroblasts (CFU-F) *in vivo*, and their potential for differentiation into adipocytic, osteocytic, chondrocytic, and muscular lineages [10]. They were also shown to be able to differentiate following implantation *in vivo* [11]. However, the relationship between these cells and Caplan's MSC, which represent the progenitor of all connective lineages in bone marrow and elsewhere, is still undetermined. As such, these cells are more appropriately designated "mesenchymal stromal cells" [12]. Since Friedenstein's original findings, numerous other laboratories have developed methods for the isolation of multipotent mesenchymal cells from bone marrow utilizing different culture conditions, such as the addition of various hormonal supplements, the use of higher (> 10%) concentrations of horse and bovine serum, and of extracellular matrix (ECM) proteins such as collagen and fibronectin. Depletion of hematopoietic cell contaminants by elimination of non-adherent cells or by surface marker-based negative selection is also routinely used to separate MSC from HSC [8, 13]. All these methods have allowed the reproducible expansion of a heterogeneous mixture of spindle cells, star-shaped cells, and large flattened cells that express cell surface markers indicative of self-renewal and multipotency [14-16]. The identification of subpopulations of MSC with varying degrees of commitment to one or more stromal cell types by specific antibodies is common during culture expansion *in vitro* [17].

There is not a single cell surface marker that uniquely characterizes MSC. Human and murine MSC are typically negative for the hematopoietic markers CD34 and CD45, although freshly isolated MSC often contain subpopulations of cells that express a low level of these markers [18, 19]. These CD34 and CD45 positive cell populations tend to disappear after a few passages [20], suggesting that they represent a contaminating population of hematopoietic cells rather than a true *in vivo* MSC subtype. Human MSC typically are positive for the surface markers CD44 (H cell adhesion molecule [HCAM]), CD73 (5'-nucleotidase), CD90 (Thy-1 surface antigen), CD105 (endoglin), CD106 (vascular cell adhesion molecule-1 [VCAM-1]), and STRO-1[21]. Murine MSC share this expression pattern, with the exception of STRO-1, but express the stem cell antigen-1 (Sca-1) [4]. Selection of "pure" MSC is usually based on a combination of these markers, as their expression overlaps with other cell types found in the bone marrow [22]. However, not all marrow stromal cells capable of multipotency will necessarily express all these markers *in vivo*. Consequently, relatively pure MSC populations obtained by panel sorting do not necessarily represent the total of all multipotent stromal subtypes.

The identification of MSC *in vivo* is thus rendered complicated by the lack of a specific surface marker or gene expression profile that is exclusive to these cells [22]. The trypsin-resistant antigen STRO-1 remains the best marker despite its shared expression on endothelial progenitor cells, as it has been found to enrich the CFU-F population from bone marrow isolates by 100-fold [23]. Unfortunately, the absence of STRO-1 expression in mice, combined with its undetermined structural and functional characteristics, limits the use of this marker in pre-clinical studies [24]. New surface markers with high differential expression on MSC compared to other bone marrow cells have been recently proposed, including low-affinity nerve growth factor receptor (LNGFR/CD271) and integrin alpha-1 (CD49a), both of which have been used to purify a relativity homogeneous population of multipotent cells from bone marrow [17, 24-26].

MSC and their subtypes have shown remarkable plasticity *in vitro*, demonstrating their ability to generate both mesenchymal and non-mesenchymal lineages of bone marrow and peripheral tissues [27]. MSC share the expression of a number of key genes with embryonic stem cells (ESC), namely, the transcription factors *OCT-4* and *SOX-2*, which are involved in the maintenance of pluripotency [28]. At higher passages, the loss of *OCT-4* and *SOX-2* expression in MSC correlates with a reduction in self-renewal and multipotent function, confirming the importance of these early genes in the regulation of MSC phenotype [20]. Additionally, MSC are positive for the ESC surface marker SSEA-4 [29]. Taken together, these findings indicate that MSC or a subpopulation of these cells can be maintained in a highly primitive state of differentiation in culture.

The differentiation of MSC into lineage specific cells is controlled by external factors in the environment, including cell–cell and cell–ECM adhesion and cytokine, chemokine, and growth factor availability [8, 30]. For example, the chondrogenic potential of MSC is tightly regulated by cell surface interactions [31], based on the high production of cartilage proteoglycans seen in pellet-cultured MSC compared to monolayer culture. Maturing chondrocytes have different ECM binding requirements than MSC, as they downregulate integrin $\alpha_5\beta_1$ (fibronectin receptor) during differentiation [32]. A number of genes expressed upon differentiation of MSC into mature cells of mesenchymal bone marrow lineages (adipocyte, osteocyte, and chondrocyte) have been well characterized and provide insight into the cellular and molecular processes governing MSC phenotypic and functional differentiation. The transcription factors RUNX-2 and OSTERIX control the differentiation of osteoblasts and the formation of bone [9, 33]. These genes, although expressed at basal levels in undifferentiated MSC in culture, are also upregulated during *in vitro* chondrogenesis of adipose-derived stromal cells [34]. The differentiation of MSC into adipocytes is highly dependent on the peroxisome proliferator-activated receptor gamma (PPARγ) proteins, as well as the C/CAAT enhancer binding proteins [35]. The selection of the osteoblastic or adipogenic differentiation pathway in cultured MSC is also influenced by physical constraints. Densely packed cultures favor differentiation into adipocytes, while lower cell densities allow space for the larger osteoblastic cells [36]. Surprisingly, this plasticity of lineage is maintained in mature osteoblasts, as they have been found to transdifferentiate into adipocytes *in vitro*. The age-related accumulation of bone marrow adipocytes accompanied by a loss of osteoblasts provides evidence for bone marrow stromal transdifferentiation *in vivo* as well [37]. Cardiac myogenesis of MSC is associated with increased expression of transcription factors GATA-4 and Nkx2.5, while skeletal myogenesis is induced by the factors MyoD and myogenin [38]. Smooth muscle differentiation can be induced via mechanical strain, again highlighting the importance of cell surface effects in regulating MSC phenotype [39]. Differentiation into pericytes requires α-smooth muscle actin (SMA) polymerization which is controlled by Rho-associated kinase (ROCK) and the myosin light chain that become expressed in MSC as they differentiate into this cell type. As expected, polymerization of α-SMA is also important in smooth muscle differentiation of MSC [40].

A number of soluble mediators display powerful effects on MSC proliferation and differentiation. Bone morphogenic proteins (BMP), which are members of the TGF-β family, stimulate the differentiation of MSC into osteocytes, chondrocytes, and adipocytes [41]. Selection of a particular lineage is dependent on the receptor engaged, with BMP receptor-IA and -IB inducing adipocyte or osteoblast differentiation, respectively [42]. Additionally, BMP when coupled with Wnt inhibit the proliferation of undifferentiated MSC [43]. In contrast, transforming growth factor (TGF)-β1 stimulates the proliferation of MSC while suppressing differentiation [44-46]. This inhibitory effect on MSC differentiation seems restricted to later stages of differentiation, as TGF-β1 contributes to early chondrogenesis as well as the expansion of immature osteoprogenitors [47, 48], although the opposite effects on these osteogenic cells have been reported [49]. TGF-β activates inhibitory Smads which suppress BMP signaling, providing a molecular basis for the antagonistic effects of different TGF-β family members [46]. The Wnt family of proteins influence MSC phenotype through both canonical and non-canonical signaling pathways, but their effect seems concentration dependent [50]. Canonical Wnt3a increases proliferation of MSC [51], while non-canonical Wnt5a suppresses proliferation [52], although high levels of canonical Wnt may also have an inhibitory effect [53]. Similarly, canonical Wnt3a inhibits late-stage osteogenesis but shows a stimulatory effect at high doses [51, 53]. Although canonical Wnt1 and Wnt3a suppress terminal osteoblast differentiation, canonical Wnt does stimulate the differentiation of preosteoblasts [54] and promotes the effects of BMP-2 on alkaline phosphatase expression and osteoblast mineralization [55]. Canonical Wnt4 signaling enhances terminal chondrocyte differentiation, while non-canonical Wnt5a suppresses this effect [56]. Canonical Wnt4 also inhibits early chondrocyte differentiation but may act in concert with TGF-β to induce chondrogenesis [57, 58]. Canonical Wnt are also important inducers of myogenesis in MSC [59]. The cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)-α provide another example of antagonistic control over MSC phenotype, as these molecules suppress adipogenesis and enhance osteogenesis through PPARγ inhibition [60]. Platelet-derived growth

factor (PDGF) mediates the differentiation of MSC into pericytes by activating through the receptors PDGFR-α, ROCK, and the polymerization of α-SMA. In contrast, PDGFR-β signaling inhibits ROCK and promotes α-SMA depolymerization [40].

Several laboratories have demonstrated that MSC can give rise to non-stromal cells *in vitro*, although the ability of these cells to functionally integrate *in vivo* is questionable [61]. Verfaillie et al. described the isolation of a subpopulation of bone marrow progenitors with greater proliferative and multipotent capability than MSC, producing stromal lineages as well as endothelial cells (EC), myocytes, and neuroectodermal cells *in vitro* [62]. These cells were designated MAPC, and were later shown to generate ectodermal, mesodermal, and endodermal lineages *in vivo* [63]. It is possible that MAPC are in fact progenitors for MSC, but full characterization of this subpopulation has been hindered by difficulties in repeating the original isolation and expansion [8]. Another laboratory has generated functional neurons and skeletal muscle *in vivo* by engraftment of MSC cultured as 3D spheroids [64]. As these MSC spheres no longer express the pluripotency markers OCT-4 and SOX-2, they likely represent a more differentiated subtype of stromal progenitor.

3 Tumors recruit MSC to their microenvironment

MSC display homing and engraftment at injury sites in a number of pathological conditions such as inflammation, tissue repair and also neoplasia [65]. The innate tropism of MSC for tumors has been confirmed by both *in vitro* and *in vivo* migration assays. *Ex vivo*-expanded MSC are easily tracked following intravenous (i.v.) injection in mice, utilizing fluorescence, bioluminescence, positron emission, and magnetic resonance-based reporter labeling [66-68]. Although the migration of endogenous BMDMSC to tumors has not been firmly established, labeled MSC engrafted in bone marrow of sublethally irradiated mice have been shown to populate the stroma of distally implanted tumors, where they become TAF and tumor-associated myofibroblasts [69, 70].

The mechanisms involved in the recruitment of MSC into tumors exhibit significant overlap with the migration and activation of inflammatory cells in tissue repair processes. The angiogenic molecule vascular endothelial cell growth factor (VEGF), which acts to recruit EC, can induce the homing of MSC to tumor sites in murine glioma models [71]. There is also a robust, dose dependent migration response of MSC to tumor-produced TGF-ss1, IL-8, and neurotropin (NT)-3, all of which also function as chemoattractants for leukocytes and EC [72]. Other growth factors with strong immunogenic properties can also recruit MSC into primary tumors, including epidermal growth factor (EGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), and PDGF [73, 74]. Additionally, a number of chemokines and their receptors have been implicated in MSC homing, although their contribution is not always clear. CCL 2 (MCP-1) has been shown to recruit MSC [75], while CXCL12 stromal-derived factor-1 (SDF-1) and its receptor CXCR4, which is expressed by a small proportion of MSC, also play a role, although conflicting results have been reported [74, 76-78].

Along with soluble growth factors and chemokines, ECM proteases that are activated at injury sites contribute to attracting MSC. Urokinase plasminogen activator (uPA) and urokinase plasminogen activator receptor (uPAR), which together activate plasminogen into plasmin and are abundantly expressed by many solid tumors, elicit a significant MSC migration compared to tumors with low capability to activate plasminogen. The exact mechanism is however unknown but may involve higher levels of IL-6, IL-8, and MCP-1 expression in association with higher levels of uPA and soluble uPAR [79]. Another protease, matrix metalloproteinase (MMP)-1, seems to play a role in MSC homing. MMP-1 mediates the cleavage of the G-protein protease-activated receptor (PAR)-1 present on MSC. Activation of PAR-1 stimulates MSC migration, and blocking PAR-1 cleavage blocks their migration toward human glioma cells [80]. It should be noted that there are many other molecules at the surface of tumor cells that could contribute to the ability of tumors to recruit MSC as shown by the strong migration response of MSC to membrane fractions of tumor extracts [74].

4 MSC and tumors: friends or foes?

Once they are incorporated into a tumor, MSC contribute with other cells like myofibroblasts, endothelial cells, pericytes, and inflammatory cells to create a microenvironment that evokes the environment of a chronic wound [81] (Fig. 1). *In vivo* tracking of labeled MSC indicate that they can differentiate into fibroblasts, pericytes, and myofibroblasts within the tumor mass [82] and can become TAF or carcinoma-associated fibroblasts [83, 84]. These cells display characteristics of myofibroblasts expressing α-SMA and fibroblast activation markers like fibroblast activating protein (FAP). They also express ECM proteins associated with aggressiveness like tenascin-c and thrombospondin-1 (TSP-1), ECM remodeling enzymes like stromelysin-1, and growth factors like HGF, EGF, and IL-6. BMDMSC exposed to tumor-conditioned media display TAF markers, as do MSC co-injected subcutaneously with tumor cells in mice. MSC are an important source of inflammatory cytokines that affect tumor cells and immune

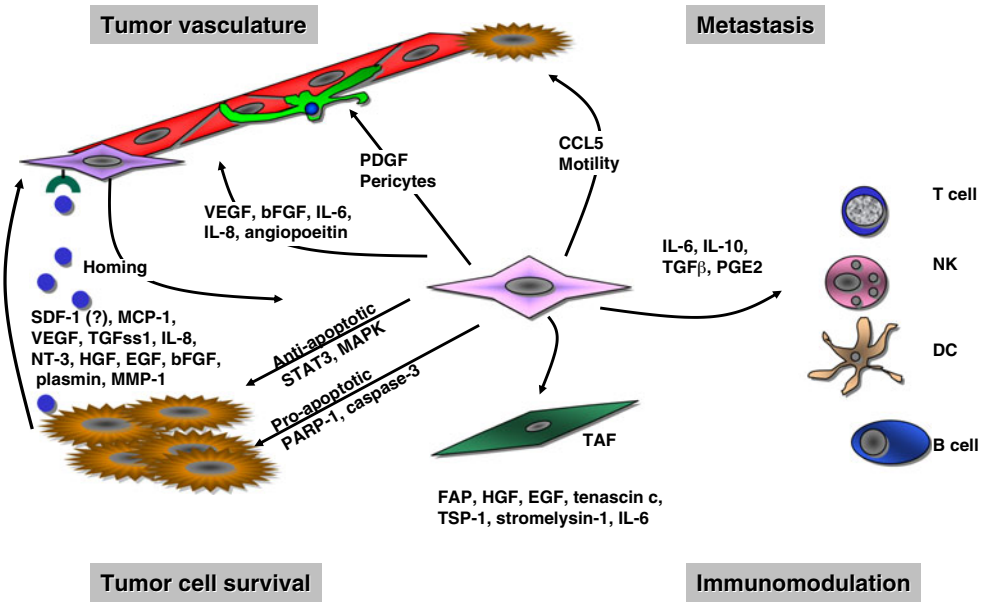

Fig. 1 Interactions between MSC and tumor cells in primary tumors. Tumor cells secrete growth factors and cytokines that promote the homing of MSC in primary tumors. MSC have four main effects on tumor cells: (1) They affect cell survival having a pro- or an anti-apoptotic effect on tumor cells. (2) They contribute to the tumor vasculature by producing angiogenic factors and by contributing to the perivasculature as they differentiate into pericytes. (3) Through the production of CCL5, MSC promote tumor cell motility and metastasis to distant organs. (4) They have an immunomodulatory role inhibiting Th1 lymphocytes, dendritic cells, B cells, and NK cells

cells. Upon exposure to a pro-inflammatory peptide made of 37 leucine residues (LL-37), MSC secrete several cytokines like IL-6, IL-10, CCL5 (RANTES), VEGF which promote angiogenesis and growth of ovarian cancer cells [85].

The reported net effects of MSC and their derivatives on the progression of primary tumors can be pro- as well as anti-tumorigenic and vary widely as a function of the source of MSC and the tumor model used. MSC injected i.v. in Kaposi sarcoma (KS)-bearing nude mice inhibit the growth of KS cells and co-culture of MSC with KS cells reduces the proliferation of KS cells *in vitro*. This effect is mediated by a contact-dependent inhibition of Akt-signaling [86]. In contrast, MSC injected i.v. in human osteosarcoma tumor-bearing nude mice stimulate tumor growth and osteosarcoma cell proliferation is increased *in vitro* in the presence of MSC-conditioned media, suggesting a contact-independent mechanism [76]. CCL5 appears to play a role as tumor cell proliferation is stimulated by CCL5 treatment and inhibited in the presence of an anti-CCL5 antibody [87]. BMDMSC also stimulate the growth of human colon carcinoma *in vivo* [88], as well as the formation of larger tumor foci in human ovarian carcinoma-bearing nude mice [83]. In a 3D assay, MSC increases the proliferation of ovarian carcinoma cells through the production of IL-6, and conditioned media from ovarian carcinoma cells increase the production of VEGF, TGF-β, and IL-6 by MSC, pointing to a paracrine signaling loop between MSC and tumor cells driving growth and cytokine production [83]. Opposite proliferative effects in MSC–tumor interactions have also been reported in syngeneic tumor models. In the 4 T1 mouse mammary tumor model, tumor growth was not greater in mice that received i.v. injections of MSC than in those that did not [89]. However, in A17 mesenchymal tumor cells derived from spontaneous HER-2/neu transgenic tumors, a faster onset of subcutaneous tumor development was reported when tumor cells were co-injected with MSC [90].

The paradoxical effect of MSC in tumor growth is currently poorly understood, as only a limited number of studies have examined the mechanisms underlying the interactions between MSC and tumor cells. These studies however have pointed to a very diversified role of MSC that includes a regulatory function on apoptosis and angiogenesis and an immunomodulatory role.

Tumor-engrafted MSC and their derivatives influence the apoptotic machinery of transformed cells, leading to both cell death and survival responses depending on the tumor model and in particular the source and differentiated state of MSC. For example, MSC that have undergone adipocytic differentiation protect acute promyelocytic leukemia cells from all-trans retinoic acid-induced apoptosis *in vitro* [91]. Leptin produced by these differentiated MSC was found to promote survival through activation of the signal transduction activator of transcription (STAT)3 and mitogen-activating protein kinase pathways in tumor cells. Similarly, MSC protects neuroblastoma cells from H_2O_2-induced oxidative stress by their capacity to produce and activate antioxidant enzymes and to downregulate superoxide dismutase [92]. In contrast, MSC isolated from umbilical cord blood or adipose tissue and injected i.v. in human mammary carcinoma tumor-bearing mice stimulate rather than inhibit apoptosis in tumor cells as demonstrated by an increased cleavage of PARP-1 and caspase-3 [93]. Other studies examining the effect of MSC on tumor cell apoptosis have pointed to their ability to upregulate p21 and caspase-3 in murine hepatoma and lymphoma cells and rat insulinoma cells [94].

The effect of MSC on the tumor vasculature is complex. MSC can exert a paracrine activity on EC via secreted

growth factors and cytokines and can directly contribute to the formation of blood vessels. MSC secrete many proangiogenic factors, including VEGF, angiopoietin, IL-6, IL-8, TGF-β, PDGF, bFGF, and FGF-7 [73]. The production of these factors by MSC is enhanced by tumor cell-conditioned media as it promotes MSC differentiation into TAF [83]. TGF-α, which is upregulated during tissue repair and plays a key role in epithelial malignant transformation, increases VEGF production in MSC by activation of map kinase kinase (MEK) and phospho-inositol-3 kinase (PI3-K) [95, 96]. VEGF produced by MSC induces the sprouting of human umbilical vein EC *in vitro* and increases tumor vessel density in a human pancreatic carcinoma xenograft model. This effect is blocked by downregulating VEGF in MSC by siRNA prior to their i.v. injection in tumor-bearing mice [97].

MSC also physically contribute to vasculogenesis. As previously discussed, MSC can differentiate into pericytes and mural cells around tumor blood vessels and thus contribute to the formation of a mature vasculature in tumors [98]. Whether MSC could also contribute to the formation of the endothelium is however less clear. There is some experimental evidence suggesting that MSC may differentiate into EC as they form tubes in implanted matrigel plugs *in vivo* and express EC markers in the presence of angiogenic factors [99]. However, recent studies of MSC exposed to VEGF indicate that only a very few cells (0.01%) acquire endothelial markers *in vitro* and none *in vivo* [97]. The effect of MSC on angiogenesis is also not always stimulatory. Recent work indicates that, while MSC will intercalate with endothelial cells *in vitro*, forming stable gap–junctional complexes via connexin 43, high levels of endothelium-engrafted MSC will lead to breakdown of the capillary network [100]. Reactive oxygen species produced by MSC also induce apoptosis in EC following co-implantation in matrigel, and this effect can be blocked by treatment with antioxidants. Similarly, direct intratumoral injection of MSC in B16 melanoma tumors has been shown to reduce vessel density and to increase caspase-3 dependent apoptosis [100].

The immunomodulatory function of MSC is a third element that influences tumor development [101]. In general, the effect of MSC on the immune system is aimed at promoting immunotolerance and tumor progression. MSC display suppressive effects on both innate and humoral immunity by inhibiting T cell proliferation [102, 103], dendritic cell maturation [104], and natural killer (NK)- and B-cell activation [105], while simultaneously increasing the production of regulatory T-cells (Treg) [9, 106]. In pre-clinical studies, co-injection of MSC allowed B16 melanoma cells to grow in an allogeneic background, avoiding a vigorous immune-rejection response [107]. *In vitro* assays confirmed this effect to be mediated by a reduction in CD8+ T cell proliferation, combined with increased generation of CD8+ Treg. Conversely, clinical studies of cancer patients undergoing hematopoeitic stem cell transplantation revealed that co-implantation of MSC, intended to reduce graft-versus-host disease (GVHD), had no effect on disease progression in either breast or hematologic malignancies [108-110]. However, a more recent study of post-chemotherapeutic co-transplantation of HSC and MSC in patients with hematologic malignancies showed a greater rate of relapse in patients who received both MSC and HSC, compared to those who received only HSC [111].

5 MSC contribute to the establishment of distant metastasis

Two potential roles for MSC in metastasis have been recognized, their ability to colonize metastatic tumors and their ability to promote the metastatic behavior of malignant cells in the primary tumor. The migration of MSC toward established lung metastatic lesions in murine models *in vivo* has been documented by a number of modalities, such as magnetic resonance imaging in mammary tumor-bearing mice injected i.v. with iron-labeled MSC [112]. Interestingly, MSC exhibit differences in phenotypic potential based on their localization to primary or secondary tumors as, for example, in syngeneic subcutaneous and metastatic mammary carcinomas, firefly luciferase-labeled MSC exhibited osteoblastic differentiation after homing to lung nodules but became adipocytic upon migration to subcutaneous tumor sites [89]. Whether MSC that home and infiltrate metastatic lesions promote or inhibit tumor cell growth has been the subject of conflicting reports in primary tumors. For example, i.v. injection of MSC had no effect on lung weight of mice bearing syngeneic mammary carcinoma metastasis [89], and i.v. injection of MSC derived from umbilical cord blood or adipose tissue reduced the formation of metastatic lung modules in mammary carcinoma-bearing mice [93].

Similarly, different effects of MSC in primary tumors on their metastatic potential have been reported. Adipose and cord blood-derived MSC reduce metastatic spread when co-injected with tumor cells subcutaneously. In contrast, subcutaneously implanted human mammary carcinomas co-injected with MSC acquire an increased metastatic potential when compared to tumor cells alone [113]. The pro-metastatic effect of MSC was found to be mediated by the ability of MSC to secrete the promotility chemokine CCL5 (RANTES) as the increase in metastasis observed with co-injection of MSC was abolished when tumor-bearing mice were treated with an anti-CCL5 antibody or when CCL5 expression in MSC was suppressed by siRNA.

Similar studies by other investigators demonstrated an increase in the number of metastatic lesions in nude mice bearing orthotopic osteosarcomas following i.v. injection of MSC that was also CCL5 dependent [76].

6 MSC contribute to a pro-tumorigenic environment in the bone marrow

Because the bone marrow is a major source of MSC, much attention has been paid to their potential role in promoting bone marrow and bone metastasis. These studies indicate that, in the bone marrow, MSC play an important pro-tumorigenic role by contributing to the formation of a microenvironment that promotes osteolytic bone metastasis and tumor cell proliferation and that provides tumor cells with a sanctuary against cytotoxic drugs (Fig. 2). As they differentiate into osteoblasts and form the osteoblastic niche, BMDMSC produce chemoattractant proteins like SDF-1 and MCP-1 that not only attract and retain HSC but also are potent chemoattractants for circulating tumor cells like B leukemia cells, breast cancer cells, or myeloma cells [114-116].

When homed in the bone marrow, tumor cells interact with MSC and their progeny through adhesion-dependent and adhesion-independent mechanisms. Much of the contributory role of MSC to progression in the bone marrow has been initially learned from studies in multiple myeloma [117]. In the case of this malignancy, the adherent contact between myeloma cells and BMDMSC and their progeny appears to be the dominant mechanism of interaction. Human myeloma cell lines express a variety of CAM like HCAM (CD44), VLA-4 (CD49/CD29), ICAM-1(CD54), NCAM (CD56), VCAM-1 (a ligand for $\alpha_4\beta_1$ integrin), and LFA-3 (CD58) that promote their adhesion to ECM proteins like fibronectin [118] and to stromal cells [117, 119, 120]. Upon contact with myeloma cells, MSC express growth factors and cytokines, like IL-6 which is a potent osteoclast-activating factor that contributes to osteolysis in myeloma [121]. Adhesion of myeloma cells to fibronectin via VLA-4 or to stromal cells also promotes the survival of tumor cells and their resistance to cytotoxic drugs [122], a process that involves IL-6-mediated STAT3 signaling [123] and is enhanced by cyclo-oxygenase-2 (Cox-2)-mediated production of PGE2 [124]. Cell–cell contact between MSC and myeloma cells

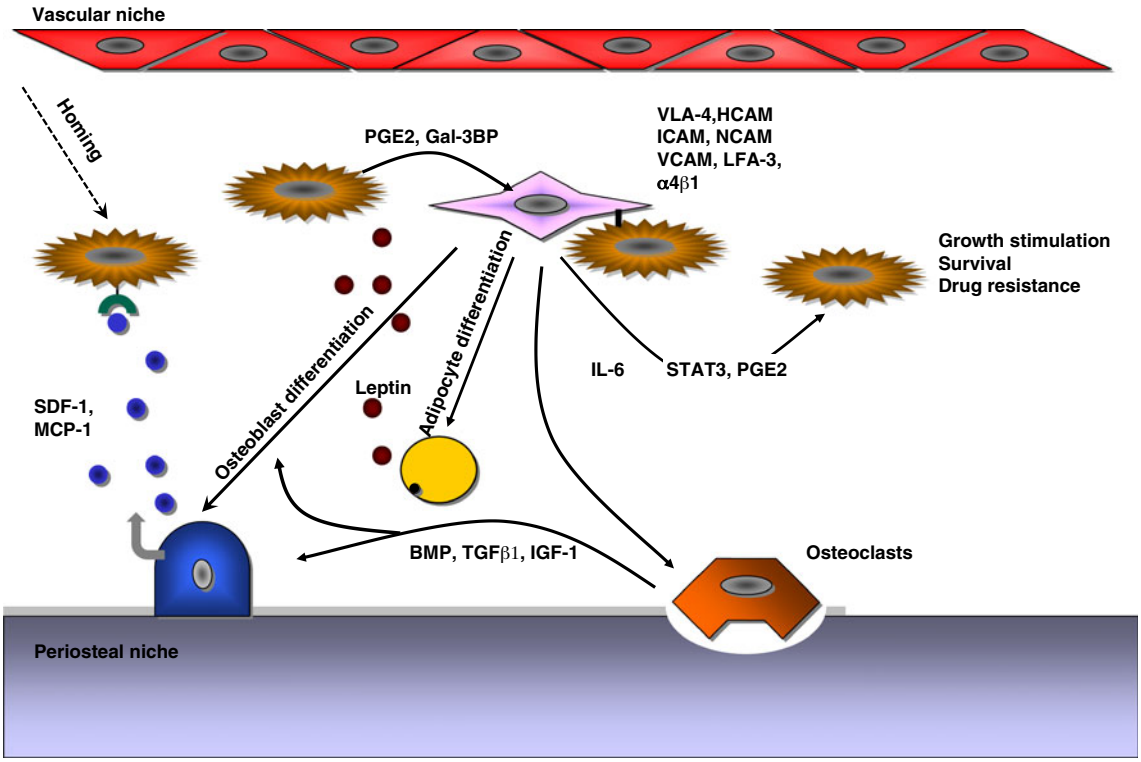

Fig. 2 Interactions between MSC and tumor cells in the bone marrow. As they differentiate into osteoblasts, MSC contribute to the periosteal niche and secrete chemokines that promote the homing of tumor cells in the bone marrow. Tumor cells (e.g., neuroblastoma) secrete soluble factors like PGE2 and Gal-3BP that stimulate the production of cytokines by MSC, including IL-6. Similarly, contact between tumor cells (e.g., myeloma) and MSC via CAM stimulates cytokine expression by MSC. IL-6 is a potent stimulator of osteoclasts but also promotes tumor cell growth, survival, and resistance to chemotherapeutic agents. The degradation on the bone matrix by osteoclasts releases in the bone marrow microenvironment soluble growth factors like BMP, TGFβ-1, and IGF-I that affect the differentiation of MSC and their expression of cytokines and growth factors

via VCAM-1 and $\alpha_4\beta_1$ integrin also enhances the osteoclastic gene activity of myeloma cells [121].

Adhesion-independent mechanisms of interaction between tumor cells and BMDMSC also play an important role in bone and bone marrow metastasis. This is exemplified by studies published in our laboratory on human neuroblastoma, the second most common solid tumor in children [125]. This cancer that originates from cells derived of the neural crest frequently metastasizes to the bone marrow (70.5%) and the bone (55.7%) [126]. As in myeloma, the interaction between neuroblastoma cells and MSC in the bone marrow microenvironment has a pro-tumorigenic effect that is in part mediated by the production of IL-6 by MSC [127]. However, in contrast to myeloma, the stimulation of IL-6 expression in MSC does not require cell–cell or cell–ECM adhesion but is mediated by soluble factors produced by neuroblastoma cells. Among those are PGE2 [128] and galectin-3 binding protein/Mac2, a 90-kDa glycoprotein produced by neuroblastoma cells that interacts with its binding partner, galectin-3, present in MSC [129].

Thus, in both myeloma and neuroblastoma, IL-6 appears at the center of the interaction between tumor cells and MSC in the bone marrow microenvironment acting as a potent pro-tumorigenic factor. IL-6 has several pro-tumorigenic activities in the bone marrow. It acts as a potent activator of osteoclasts and thus stimulates osteolysis. As a consequence, growth factors bound to the bone matrix like TGF-β, BMP, and IGF-1 are released and affect tumor growth and MSC differentiation [130, 131]. IL-6 also directly affects tumor cells. Many tumor cells do not produce IL-6 but express the heterodimeric IL-6 receptor (gp80 and gp130). Exposure of these tumor cells to IL-6 in the bone marrow microenvironment activates ERK ½ and STAT3 which stimulate cell proliferation and survival [132, 133]. IL-6 also promotes tumor cell survival by upregulating the expression of survival proteins like Bcl2, Bcl_{XL}, survivin, and x-linked inhibitor of apoptosis [132, 134] and multidrug resistance-associated proteins including MDR and MRP [135, 136] that confer to tumor cells resistance to cytotoxic agents [137, 138]. Central to this effect of IL-6 is STAT3, one of the major signaling pathways downstream of the IL-6 receptor [132, 133, 138]. Thus, IL-6 produced by MSC contributes to the formation of a microenvironment in the bone marrow that not only promotes tumor growth but also provides tumor cells a sanctuary against the cytotoxic effects of chemotherapeutics agents [122, 123].

Considering that MSC represent a very small percentage of cells in the bone marrow, it is unclear whether they are in sufficient number to have an impact on tumor cells *in vivo*. A central question therefore is whether they maintain their pro-tumorigenic function as they differentiate into osteoblasts, chondrocytes, adipocytes, or muscle cells. Although this question has not been fully examined, some data suggest that it is the case. For example, adipocytes have a pro-tumorigenic activity and contribute to drug resistance [139]. Osteoblasts promote the engraftment of leukemic cells in the bone marrow and protect them from chemotherapy-induced apoptosis [139], as they produce the soluble Wnt antagonist sFRP-1 that confers resistance to daunomycin [140]. The effect of chondrocytes and myoblasts in cancer progression in the bone marrow has not been explored so far.

7 MSC in cancer therapy

Over the last decade, MSC derived from bone marrow or other tissues like dental pulp have been considered for their potential as a source of new tissue because of their ability to generate cartilage, bone, muscle, and myocardium and for their capacity to home to injured organs as well as to serve as gene delivery tools. However, despite intensive research by a large number of laboratories over the last several years, their true potential in tissue repair remains unclear [1]. Although animal data and some human data support a beneficial effect in diseases like arthritis [141] or myocardial infarct [142], the mechanisms of their action in tissue regeneration remains poorly understood.

Because MSC will also home to tumors and metastatic sites, they have been considered as novel cell-based delivery agents in cancer [143, 144]. The efficacy of engineered MSC to systematically deliver pro-drug activating enzymes or cytokines with anti-cancer activity to the site of primary tumors and at metastatic sites has been recently tested in preclinical models. For example, the systemic administration of MSC engineered to express recombinant TRAIL in brain glioma-bearing mice has an anti-tumor effect [145] and coinjection of human prostate cancer cells with adipose tissue-derived MSC engineered to express the suicide gene cytosine deaminase induces a complete tumor regression upon treatment of mice with the pro-drug 5 fluoro-cytosine [146]. Treatment of mice implanted intracranially with U87 human glioma cells with human BMDMSC engineered to produce interferon beta inhibits tumor growth and increases survival [147]. To translate these observations into human clinical trials will however require convincing evidence that MSC effectively colonize primary tumors and/or metastatic lesions in cancer patients through non-invasive imaging techniques and that their administration is safe. As we have previously discussed, MSC are the source of many chemokines and cytokines that can be anti- or pro-tumorigenic for tumor cells and contribute to a state of immunotolerance. In view of the potential pro-tumorigenic function of MSC in cancer progression and a lack of clear understanding of the underlying mechanisms, it remains prudent to hold clinical

trials with these cells in cancer patients until their role is better understood. The recent report that co-transplantation of MSC with HSC in patients with hematological malignancies prevented GVHD but was associated with a higher relapse rate supports the use of extreme caution before large-scale clinical trials are performed [111]. In contrast, clinical trials using agents targeting cytokines produced by MSC in the tumor microenvironment or interfering with the interaction between tumor cells and MSC should be a fertile ground of investigation. Clinical trials in myeloma targeting IL-6 for example have been initiated [148, 149].

8 Conclusions

It is clear that MSC and their progeny are not innocent bystanders in the tumor microenvironment. They are actively recruited by tumor cells and vice versa, they contribute to attracting tumor cells to the bone marrow. In tumors, they act as regulators of apoptosis, angiogenesis, and immune tolerance, and when in contact with tumor cells they enhance proliferation, survival, and drug resistance. Like tumor-associated macrophages, MSC can be friend or foe of cancer cells, depending on their origin, their degree of differentiation, and the type of tumor cells they interact with. Our understanding of the mechanisms that control the interaction between MSC and tumor cells is still at an early stage although some pathways, like the IL-6/STAT3 pathway, have been shown to play a central role. To better understand these mechanisms and in particular to examine how they are affected as MSC differentiate into their progeny is a critical area of future investigation that is needed to better define their role in cancer progression and their potential as therapeutic agents or targets.

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References

1. Prockop, D. J. (2009). Repair of tissues by adult stem/progenitor cells (MSCs): controversies, myths, and changing paradigms. *Molecular Therapy, 17*, 939–946.
2. Caplan, A. I. (1994). The mesengenic process. *Clinics in Plastic Surgery, 21*, 429–435.
3. Valtieri, M., & Sorrentino, A. (2008). The mesenchymal stromal cell contribution to homeostasis. *Journal of Cellular Physiology, 217*, 296–300.
4. Dennis, J. E., & Charbord, P. (2002). Origin and differentiation of human and murine stroma. *Stem Cells, 20*, 205–214.
5. Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science, 284*, 143–147.
6. Civin, C. I., Trischmann, T., Kadan, N. S., Davis, J., Noga, S., Cohen, K., et al. (1996). Highly purified CD34-positive cells reconstitute hematopoiesis. *Journal of Clinical Oncology, 14*, 2224–2233.
7. Shi, S., & Gronthos, S. (2003). Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. *Journal of Bone and Mineral Research, 18*, 696–704.
8. Wagner, W., & Ho, A. D. (2007). Mesenchymal stem cell preparations—comparing apples and oranges. *Stem Cell Reviews and Reports, 3*, 239–248.
9. Vaananen, H. K. (2005). Mesenchymal stem cells. *Annals of Medicine, 37*, 469–479.
10. Friedenstein, A. J., Piatetzky-Shapiro, I. I., & Petrakova, K. V. (1966). Osteogenesis in transplants of bone marrow cells. *Journal of Embryology and Experimental Morphology, 16*, 381–390.
11. Friedenstein, A. J., Chailakhyan, R. K., Latsinik, N. V., Panasyuk, A. F., & Keiliss-Borok, I. V. (1974). Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning *in vitro* and retransplantation *in vivo*. *Transplantation, 17*, 331–340.
12. Horwitz, E. M., Le Blanc, K., Dominici, M., Mueller, I., Slaper-Cortenbach, I., Marini, F. C., et al. (2005). Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy, 7*, 393–395.
13. Wagner, W., Feldmann, R. E., Jr., Seckinger, A., Maurer, M. H., Wein, F., Blake, J., et al. (2006). The heterogeneity of human mesenchymal stem cell preparations—evidence from simultaneous analysis of proteomes and transcriptomes. *Experimental Hematology, 34*, 536–548.
14. Lodie, T. A., Blickarz, C. E., Devarakonda, T. J., He, C., Dash, A. B., Clarke, J., et al. (2002). Systematic analysis of reportedly distinct populations of multipotent bone marrow-derived stem cells reveals a lack of distinction. *Tissue Engineering, 8*, 739–751.
15. Tropel, P., Noel, D., Platet, N., Legrand, P., Benabid, A. L., & Berger, F. (2004). Isolation and characterisation of mesenchymal stem cells from adult mouse bone marrow. *Experimental Cell Research, 295*, 395–406.
16. Colter, D. C., Sekiya, I., & Prockop, D. J. (2001). Identification of a subpopulation of rapidly self-renewing and multipotential adult stem cells in colonies of human marrow stromal cells. *Proceedings of the National Academy of Sciences of the United States of America, 98*, 7841–7845.
17. Battula, V. L., Treml, S., Bareiss, P. M., Gieseke, F., Roelofs, H., de Zwart, P., et al. (2009). Isolation of functionally distinct mesenchymal stem cell subsets using antibodies against CD56, CD271, and mesenchymal stem cell antigen-1. *Haematologica, 94*, 173–184.
18. Kaiser, S., Hackanson, B., Follo, M., Mehlhorn, A., Geiger, K., Ihorst, G., et al. (2007). BM cells giving rise to MSC in culture have a heterogeneous CD34 and CD45 phenotype. *Cytotherapy, 9*, 439–450.
19. Copland, I., Sharma, K., Lejeune, L., Eliopoulos, N., Stewart, D., Liu, P., et al. (2008). CD34 expression on murine marrow-derived mesenchymal stromal cells: impact on neovascularization. *Experimental Hematology, 36*, 93–103.
20. Conget, P. A., & Minguell, J. J. (1999). Phenotypical and functional properties of human bone marrow mesenchymal progenitor cells. *Journal of Cellular Physiology, 181*, 67–73.
21. Roche, S., Delorme, B., Oostendorp, R. A., Barbet, R., Caton, D., Noel, D., et al. (2009). Comparative proteomic analysis of human mesenchymal and embryonic stem cells: towards the

definition of a mesenchymal stem cell proteomic signature. *Proteomics, 9*, 223–232.
22. Kemp, K. C., Hows, J., & Donaldson, C. (2005). Bone marrow-derived mesenchymal stem cells. *Leukaemia & Lymphoma, 46*, 1531–1544.
23. Simmons, P. J., & Torok-Storb, B. (1991). Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. *Blood, 78*, 55–62.
24. Jones, E., & McGonagle, D. (2008). Human bone marrow mesenchymal stem cells *in vivo*. *Rheumatology (Oxford), 47*, 126–131.
25. Rider, D. A., Nalathamby, T., Nurcombe, V., & Cool, S. M. (2007). Selection using the alpha-1 integrin (CD49a) enhances the multipotentiality of the mesenchymal stem cell population from heterogeneous bone marrow stromal cells. *Journal of Molecular Histology, 38*, 449–458.
26. Stewart, K., Monk, P., Walsh, S., Jefferiss, C. M., Letchford, J., & Beresford, J. N. (2003). STRO-1, HOP-26 (CD63), CD49a and SB-10 (CD166) as markers of primitive human marrow stromal cells and their more differentiated progeny: a comparative investigation *in vitro*. *Cell and Tissue Research, 313*, 281–290.
27. Prockop, D. J. (1997). Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science, 276*, 71–74.
28. Izadpanah, R., Trygg, C., Patel, B., Kriedt, C., Dufour, J., Gimble, J. M., et al. (2006). Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. *Journal of Cellular Biochemistry, 99*, 1285–1297.
29. Gang, E. J., Bosnakovski, D., Figueiredo, C. A., Visser, J. W., & Perlingeiro, R. C. (2007). SSEA-4 identifies mesenchymal stem cells from bone marrow. *Blood, 109*, 1743–1751.
30. Mackay, A. M., Beck, S. C., Murphy, J. M., Barry, F. P., Chichester, C. O., & Pittenger, M. F. (1998). Chondrogenic differentiation of cultured human mesenchymal stem cells from marrow. *Tissue Engineering, 4*, 415–428.
31. Denker, A. E., Haas, A. R., Nicoll, S. B., & Tuan, R. S. (1999). Chondrogenic differentiation of murine C3H10T1/2 multipotential mesenchymal cells: I. Stimulation by bone morphogenetic protein-2 in high-density micromass cultures. *Differentiation, 64*, 67–76.
32. Goessler, U. R., Bieback, K., Bugert, P., Heller, T., Sadick, H., Hormann, K., et al. (2006). *In vitro* analysis of integrin expression during chondrogenic differentiation of mesenchymal stem cells and chondrocytes upon dedifferentiation in cell culture. *International Journal of Molecular Medicine, 17*, 301–307.
33. Menicanin, D., Bartold, P. M., Zannettino, A. C., & Gronthos, S. (2009). Genomic profiling of mesenchymal stem cells. *Stem Cell Reviews and Reports, 5*, 36–50.
34. Rich, J. T., Rosova, I., Nolta, J. A., Myckatyn, T. M., Sandell, L. J., & McAlinden, A. (2008). Upregulation of Runx2 and Osterix during *in vitro* chondrogenesis of human adipose-derived stromal cells. *Biochemical and Biophysical Research Communications, 372*, 230–235.
35. Sekiya, I., Larson, B. L., Vuoristo, J. T., Cui, J. G., & Prockop, D. J. (2004). Adipogenic differentiation of human adult stem cells from bone marrow stroma (MSCs). *Journal of Bone and Mineral Research, 19*, 256–264.
36. McBeath, R., Pirone, D. M., Nelson, C. M., Bhadriraju, K., & Chen, C. S. (2004). Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment. *Developmental Cell, 6*, 483–495.
37. Schilling, T., Noth, U., Klein-Hitpass, L., Jakob, F., & Schutze, N. (2007). Plasticity in adipogenesis and osteogenesis of human mesenchymal stem cells. *Molecular and Cellular Endocrinology, 271*, 1–17.
38. Akavia, U. D., Veinblat, O., & Benayahu, D. (2008). Comparing the transcriptional profile of mesenchymal cells to cardiac and skeletal muscle cells. *Journal of Cellular Physiology, 216*, 663–672.
39. Park, J. S., Chu, J. S., Cheng, C., Chen, F., Chen, D., & Li, S. (2004). Differential effects of equiaxial and uniaxial strain on mesenchymal stem cells. *Biotechnology and Bioengineering, 88*, 359–368.
40. Ball, S. G., Shuttleworth, C. A., & Kielty, C. M. (2007). Platelet-derived growth factor receptor-alpha is a key determinant of smooth muscle alpha-actin filaments in bone marrow-derived mesenchymal stem cells. *International Journal of Biochemistry and Cell Biology, 39*, 379–391.
41. Wang, E. A., Israel, D. I., Kelly, S., & Luxenberg, D. P. (1993). Bone morphogenetic protein-2 causes commitment and differentiation in C3H10T1/2 and 3 T3 cells. *Growth Factors, 9*, 57–71.
42. Chen, D., Ji, X., Harris, M. A., Feng, J. Q., Karsenty, G., Celeste, A. J., et al. (1998). Differential roles for bone morphogenetic protein (BMP) receptor type IB and IA in differentiation and specification of mesenchymal precursor cells to osteoblast and adipocyte lineages. *Developments in Cell Biology, 142*, 295–305.
43. Liu, Z., Tang, Y., Qiu, T., Cao, X., & Clemens, T. L. (2006). A dishevelled-1/Smad1 interaction couples WNT and bone morphogenetic protein signaling pathways in uncommitted bone marrow stromal cells. *Journal of Biological Chemistry, 281*, 17156–17163.
44. Locklin, R. M., Oreffo, R. O., & Triffitt, J. T. (1999). Effects of TGFbeta and bFGF on the differentiation of human bone marrow stromal fibroblasts. *Cell Biology International, 23*, 185–194.
45. Jian, H., Shen, X., Liu, I., Semenov, M., He, X., & Wang, X. F. (2006). Smad3-dependent nuclear translocation of beta-catenin is required for TGF-beta1-induced proliferation of bone marrow-derived adult human mesenchymal stem cells. *Genes and Development, 20*, 666–674.
46. Maeda, S., Hayashi, M., Komiya, S., Imamura, T., & Miyazono, K. (2004). Endogenous TGF-beta signaling suppresses maturation of osteoblastic mesenchymal cells. *EMBO Journal, 23*, 552–563.
47. Roelen, B. A., & Dijke, P. (2003). Controlling mesenchymal stem cell differentiation by TGFBeta family members. *Journal of Orthopaedic Science, 8*, 740–748.
48. Gazit, D., Zilberman, Y., Turgeman, G., Zhou, S., & Kahn, A. (1999). Recombinant TGF-beta1 stimulates bone marrow osteoprogenitor cell activity and bone matrix synthesis in osteopenic, old male mice. *Journal of Cellular Biochemistry, 73*, 379–389.
49. Walsh, S., Jefferiss, C., Stewart, K., & Beresford, J. N. (2003). TGFbeta1 limits the expansion of the osteoprogenitor fraction in cultures of human bone marrow stromal cells. *Cell and Tissue Research, 311*, 187–198.
50. Ling, L., Nurcombe, V., & Cool, S. M. (2009). Wnt signaling controls the fate of mesenchymal stem cells. *Gene, 433*, 1–7.
51. Boland, G. M., Perkins, G., Hall, D. J., & Tuan, R. S. (2004). Wnt 3a promotes proliferation and suppresses osteogenic differentiation of adult human mesenchymal stem cells. *Journal of Cellular Biochemistry, 93*, 1210–1230.
52. Baksh, D., Boland, G. M., & Tuan, R. S. (2007). Cross-talk between Wnt signaling pathways in human mesenchymal stem cells leads to functional antagonism during osteogenic differentiation. *Journal of Cellular Biochemistry, 101*, 1109–1124.
53. De Boer, J., Wang, H. J., & Van Blitterswijk, C. (2004). Effects of Wnt signaling on proliferation and differentiation of human mesenchymal stem cells. *Tissue Engineering, 10*, 393–401.
54. Eijken, M., Meijer, I. M., Westbroek, I., Koedam, M., Chiba, H., Uitterlinden, A. G., et al. (2008). Wnt signaling acts and is regulated in a human osteoblast differentiation dependent manner. *Journal of Cellular Biochemistry, 104*, 568–579.

55. Lee, H., Herrmann, A., Deng, J. H., Kujawski, M., Niu, G., Li, Z., et al. (2009). Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors. *Cancer Cell, 15*, 283–293.
56. Hartmann, C., & Tabin, C. J. (2000). Dual roles of Wnt signaling during chondrogenesis in the chicken limb. *Development, 127*, 3141–3159.
57. Bergwitz, C., Wendlandt, T., Kispert, A., & Brabant, G. (2001). Wnts differentially regulate colony growth and differentiation of chondrogenic rat calvaria cells. *Biochimica et Biophysica Acta, 1538*, 129–140.
58. Tuli, R., Tuli, S., Nandi, S., Huang, X., Manner, P. A., Hozack, W. J., et al. (2003). Transforming growth factor-beta-mediated chondrogenesis of human mesenchymal progenitor cells involves N-cadherin and mitogen-activated protein kinase and Wnt signaling cross-talk. *Journal of Biological Chemistry, 278*, 41227–41236.
59. Ridgeway, A. G., Petropoulos, H., Wilton, S., & Skerjanc, I. S. (2000). Wnt signaling regulates the function of MyoD and myogenin. *Journal of Biological Chemistry, 275*, 32398–32405.
60. Suzawa, M., Takada, I., Yanagisawa, J., Ohtake, F., Ogawa, S., Yamauchi, T., et al. (2003). Cytokines suppress adipogenesis and PPAR-gamma function through the TAK1/TAB1/NIK cascade. *Nature Cell Biology, 5*, 224–230.
61. Phinney, D. G., & Prockop, D. J. (2007). Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair–current views. *Stem Cells, 25*, 2896–2902.
62. Reyes, M., Lund, T., Lenvik, T., Aguiar, D., Koodie, L., & Verfaillie, C. M. (2001). Purification and ex vivo expansion of postnatal human marrow mesodermal progenitor cells. *Blood, 98*, 2615–2625.
63. Jiang, Y., Jahagirdar, B. N., Reinhardt, R. L., Schwartz, R. E., Keene, C. D., Ortiz-Gonzalez, X. R., et al. (2002). Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature, 418*, 41–49.
64. Shiota, M., Heike, T., Haruyama, M., Baba, S., Tsuchiya, A., Fujino, H., et al. (2007). Isolation and characterization of bone marrow-derived mesenchymal progenitor cells with myogenic and neuronal properties. *Experimental Cell Research, 313*, 1008–1023.
65. Hall, B., Andreeff, M., & Marini, F. (2007). The participation of mesenchymal stem cells in tumor stroma formation and their application as targeted-gene delivery vehicles. *Handbook of Experimental Pharmacology,* 263-283.
66. Wu, X., Hu, J., Zhou, L., Mao, Y., Yang, B., Gao, L., et al. (2008). *In vivo* tracking of superparamagnetic iron oxide nanoparticle-labeled mesenchymal stem cell tropism to malignant gliomas using magnetic resonance imaging. Laboratory investigation. *Journal of Neurosurgery, 108*, 320–329.
67. Hung, S. C., Deng, W. P., Yang, W. K., Liu, R. S., Lee, C. C., Su, T. C., et al. (2005). Mesenchymal stem cell targeting of microscopic tumors and tumor stroma development monitored by noninvasive *in vivo* positron emission tomography imaging. *Clinical Cancer Research, 11*, 7749–7756.
68. Kidd, S., Spaeth, E., Dembinski, J. L., Dietrich, M., Watson, K., Klopp, A., et al. (2009). Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using *in vivo* bioluminescent imaging. *Stem Cells, 27*, 2614–2623.
69. Ishii, G., Sangai, T., Oda, T., Aoyagi, Y., Hasebe, T., Kanomata, N., et al. (2003). Bone-marrow-derived myofibroblasts contribute to the cancer-induced stromal reaction. *Biochemical and Biophysical Research Communications, 309*, 232–240.
70. Direkze, N. C., Hodivala-Dilke, K., Jeffery, R., Hunt, T., Poulsom, R., Oukrif, D., et al. (2004). Bone marrow contribution to tumor-associated myofibroblasts and fibroblasts. *Cancer Research, 64*, 8492–8495.
71. Schichor, C., Birnbaum, T., Etminan, N., Schnell, O., Grau, S., Miebach, S., et al. (2006). Vascular endothelial growth factor a contributes to glioma-induced migration of human marrow stromal cells (hMSC). *Experimental Neurology, 199*, 301–310.
72. Birnbaum, T., Roider, J., Schankin, C. J., Padovan, C. S., Schichor, C., Goldbrunner, R., et al. (2007). Malignant gliomas actively recruit bone marrow stromal cells by secreting angiogenic cytokines. *Journal of Neuro-Oncology, 83*, 241–247.
73. Feng, B., & Chen, L. (2009). Review of mesenchymal stem cells and tumors: executioner or coconspirator? *Cancer Biotherapy & Radiopharmaceuticals, 24*, 717–721.
74. Spaeth, E., Klopp, A., Dembinski, J., Andreeff, M., & Marini, F. (2008). Inflammation and tumor microenvironments: defining the migratory itinerary of mesenchymal stem cells. *Gene Therapy, 15*, 730–738.
75. Dwyer, R. M., Potter-Beirne, S. M., Harrington, K. A., Lowery, A. J., Hennessy, E., Murphy, J. M., et al. (2007). Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. *Clinical Cancer Research, 13*, 5020–5027.
76. Xu, W. T., Bian, Z. Y., Fan, Q. M., Li, G., & Tang, T. T. (2009). Human mesenchymal stem cells (hMSCs) target osteosarcoma and promote its growth and pulmonary metastasis. *Cancer Letters, 281*, 32–41.
77. Hara, M., Murakami, T., & Kobayashi, E. (2008). *In vivo* bioimaging using photogenic rats: fate of injected bone marrow-derived mesenchymal stromal cells. *Journal of Autoimmunity, 30*, 163–171.
78. Wynn, R. F., Hart, C. A., Corradi-Perini, C., O'Neill, L., Evans, C. A., Wraith, J. E., et al. (2004). A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. *Blood, 104*, 2643–2645.
79. Gutova, M., Najbauer, J., Frank, R. T., Kendall, S. E., Gevorgyan, A., Metz, M. Z., et al. (2008). Urokinase plasminogen activator and urokinase plasminogen activator receptor mediate human stem cell tropism to malignant solid tumors. *Stem Cells, 26*, 1406–1413.
80. Ho, I. A., Chan, K. Y., Ng, W. H., Guo, C. M., Hui, K. M., Cheang, P., et al. (2009). Matrix metalloproteinase 1 is necessary for the migration of human bone marrow-derived mesenchymal stem cells toward human glioma. *Stem Cells, 27*, 1366–1375.
81. Dvorak, H. F. (1986). Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *New England Journal of Medicine, 315*, 1650–1659.
82. Kidd, S., Spaeth, E., Klopp, A., Andreeff, M., Hall, B., & Marini, F. C. (2008). The (in) auspicious role of mesenchymal stromal cells in cancer: be it friend or foe. *Cytotherapy, 10*, 657–667.
83. Spaeth, E. L., Dembinski, J. L., Sasser, A. K., Watson, K., Klopp, A., Hall, B., et al. (2009). Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. *PLoS ONE, 4*, e4992.
84. Mishra, P. J., Mishra, P. J., Humeniuk, R., Medina, D. J., Alexe, G., Mesirov, J. P., et al. (2008). Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. *Cancer Research, 68*, 4331–4339.
85. Coffelt, S. B., Marini, F. C., Watson, K., Zwezdaryk, K. J., Dembinski, J. L., LaMarca, H. L., et al. (2009). The pro-inflammatory peptide LL-37 promotes ovarian tumor progression through recruitment of multipotent mesenchymal stromal cells. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 3806–3811.
86. Khakoo, A. Y., Pati, S., Anderson, S. A., Reid, W., Elshal, M. F., Rovira, I. I., et al. (2006). Human mesenchymal stem cells exert

potent antitumorigenic effects in a model of Kaposi's sarcoma. *Journal of Experimental Medicine, 203*, 1235–1247.
87. Soria, G., & Ben Baruch, A. (2008). The inflammatory chemokines CCL2 and CCL5 in breast cancer. *Cancer Letters, 267*, 271–285.
88. Zhu, W., Xu, W., Jiang, R., Qian, H., Chen, M., Hu, J., et al. (2006). Mesenchymal stem cells derived from bone marrow favor tumor cell growth *in vivo*. *Experimental and Molecular Pathology, 80*, 267–274.
89. Wang, H., Cao, F., De, A., Cao, Y., Contag, C., Gambhir, S. S., et al. (2009). Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging. *Stem Cells, 27*, 1548–1558.
90. Galie, M., Konstantinidou, G., Peroni, D., Scambi, I., Marchini, C., Lisi, V., et al. (2008). Mesenchymal stem cells share molecular signature with mesenchymal tumor cells and favor early tumor growth in syngeneic mice. *Oncogene, 27*, 2542–2551.
91. Tabe, Y., Konopleva, M., Munsell, M. F., Marini, F. C., Zompetta, C., McQueen, T., et al. (2004). PML-RARalpha is associated with leptin-receptor induction: the role of mesenchymal stem cell-derived adipocytes in APL cell survival. *Blood, 103*, 1815–1822.
92. Lanza, C., Morando, S., Voci, A., Canesi, L., Principato, M. C., Serpero, L. D., et al. (2009). Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect *in vivo*. *Journal of Neurochemistry, 110*, 1674–1684.
93. Sun, B., Roh, K. H., Park, J. R., Lee, S. R., Park, S. B., Jung, J. W., et al. (2009). Therapeutic potential of mesenchymal stromal cells in a mouse breast cancer metastasis model. *Cytotherapy, 11* (289–98), 1.
94. Lu, Y. R., Yuan, Y., Wang, X. J., Wei, L. L., Chen, Y. N., Cong, C., et al. (2008). The growth inhibitory effect of mesenchymal stem cells on tumor cells *in vitro* and *in vivo*. *Cancer Biology & Therapy, 7*, 245–251.
95. Wang, Y., Crisostomo, P. R., Wang, M., Markel, T. A., Novotny, N. M., & Meldrum, D. R. (2008). TGF-alpha increases human mesenchymal stem cell-secreted VEGF by MEK- and PI3-K- but not JNK- or ERK-dependent mechanisms. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 295*, R1115–R1123.
96. Lee, D. C., Fenton, S. E., Berkowitz, E. A., & Hissong, M. A. (1995). Transforming growth factor alpha: expression, regulation, and biological activities. *Pharmacological Reviews, 47*, 51–85.
97. Beckermann, B. M., Kallifatidis, G., Groth, A., Frommhold, D., Apel, A., Mattern, J., et al. (2008). VEGF expression by mesenchymal stem cells contributes to angiogenesis in pancreatic carcinoma. *British Journal of Cancer, 99*, 622–631.
98. Rajantie, I., Ilmonen, M., Alminaite, A., Ozerdem, U., Alitalo, K., & Salven, P. (2004). Adult bone marrow-derived cells recruited during angiogenesis comprise precursors for periendothelial vascular mural cells. *Blood, 104*, 2084–2086.
99. Al Khaldi, A., Eliopoulos, N., Martineau, D., Lejeune, L., Lachapelle, K., & Galipeau, J. (2003). Postnatal bone marrow stromal cells elicit a potent VEGF-dependent neoangiogenic response *in vivo*. *Gene Therapy, 10*, 621–629.
100. Otsu, K., Das, S., Houser, S. D., Quadri, S. K., Bhattacharya, S., & Bhattacharya, J. (2009). Concentration-dependent inhibition of angiogenesis by mesenchymal stem cells. *Blood, 113*, 4197–4205.
101. Sotiropoulou, P. A., & Papamichail, M. (2007). Immune properties of mesenchymal stem cells. *Methods in Molecular Biology, 407*, 225–243.
102. Di Nicola, M., Carlo-Stella, C., Magni, M., Milanesi, M., Longoni, P. D., Matteucci, P., et al. (2002). Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood, 99*, 3838–3843.
103. Plumas, J., Chaperot, L., Richard, M. J., Molens, J. P., Bensa, J. C., & Favrot, M. C. (2005). Mesenchymal stem cells induce apoptosis of activated T cells. *Leukemia, 19*, 1597–1604.
104. Rutella, S., Danese, S., & Leone, G. (2006). Tolerogenic dendritic cells: cytokine modulation comes of age. *Blood, 108*, 1435–1440.
105. Corcione, A., Benvenuto, F., Ferretti, E., Giunti, D., Cappiello, V., Cazzanti, F., et al. (2006). Human mesenchymal stem cells modulate B-cell functions. *Blood, 107*, 367–372.
106. Prevosto, C., Zancolli, M., Canevali, P., Zocchi, M. R., & Poggi, A. (2007). Generation of CD4+ or CD8+ regulatory T cells upon mesenchymal stem cell–lymphocyte interaction. *Haematologica, 92*, 881–888.
107. Djouad, F., Plence, P., Bony, C., Tropel, P., Apparailly, F., Sany, J., et al. (2003). Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. *Blood, 102*, 3837–3844.
108. Nauta, A. J., & Fibbe, W. E. (2007). Immunomodulatory properties of mesenchymal stromal cells. *Blood, 110*, 3499–3506.
109. Koc, O. N., Gerson, S. L., Cooper, B. W., Dyhouse, S. M., Haynesworth, S. E., Caplan, A. I., et al. (2000). Rapid hematopoietic recovery after coinfusion of autologous-blood stem cells and culture-expanded marrow mesenchymal stem cells in advanced breast cancer patients receiving high-dose chemotherapy. *Journal of Clinical Oncology, 18*, 307–316.
110. Lazarus, H. M., Koc, O. N., Devine, S. M., Curtin, P., Maziarz, R. T., Holland, H. K., et al. (2005). Cotransplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. *Biology of Blood and Marrow Transplantation, 11*, 389–398.
111. Ning, H., Yang, F., Jiang, M., Hu, L., Feng, K., Zhang, J., et al. (2008). The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. *Leukemia, 22*, 593–599.
112. Loebinger, M. R., Kyrtatos, P. G., Turmaine, M., Price, A. N., Pankhurst, Q., Lythgoe, M. F., et al. (2009). Magnetic resonance imaging of mesenchymal stem cells homing to pulmonary metastases using biocompatible magnetic nanoparticles. *Cancer Research, 69*, 8862–8867.
113. Karnoub, A. E., Dash, A. B., Vo, A. P., Sullivan, A., Brooks, M. W., Bell, G. W., et al. (2007). Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature, 449*, 557–563.
114. Burger, J. A., & Kipps, T. J. (2002). Chemokine receptors and stromal cells in the homing and homeostasis of chronic lymphocytic leukemia B cells. *Leukaemia & Lymphoma, 43*, 461–466.
115. Molloy, A. P., Martin, F. T., Dwyer, R. M., Griffin, T. P., Murphy, M., Barry, F. P., et al. (2009). Mesenchymal stem cell secretion of chemokines during differentiation into osteoblasts, and their potential role in mediating interactions with breast cancer cells. *International Journal of Cancer, 124*, 326–332.
116. Urashima, M., Chen, B. P., Chen, S., Pinkus, G. S., Bronson, R. T., Dedera, D. A., et al. (1997). The development of a model for the homing of multiple myeloma cells to human bone marrow. *Blood, 90*, 754–765.
117. Cook, G., Dumbar, M., & Franklin, I. M. (1997). The role of adhesion molecules in multiple myeloma. *Acta Haematologica, 97*, 81–89.
118. Uchiyama, H., Barut, B. A., Chauhan, D., Cannistra, S. A., & Anderson, K. C. (1992). Characterization of adhesion molecules on human myeloma cell lines. *Blood, 80*, 2306–2314.

119. Faid, L., Van, R. I., De Waele, M., Facon, T., Schots, R., Lacor, P., et al. (1996). Adhesive interactions between tumour cells and bone marrow stromal elements in human multiple myeloma. *European Journal of Haematology, 57*, 349–358.
120. Thomas, X., Anglaret, B., Magaud, J. P., Epstein, J., & Archimbaud, E. (1998). Interdependence between cytokines and cell adhesion molecules to induce interleukin-6 production by stromal cells in myeloma. *Leukaemia & Lymphoma, 32*, 107–119.
121. Michigami, T., Shimizu, N., Williams, P. J., Niewolna, M., Dallas, S. L., Mundy, G. R., et al. (2000). Cell–cell contact between marrow stromal cells and myeloma cells via VCAM-1 and alpha(4)beta(1)-integrin enhances production of osteoclast-stimulating activity. *Blood, 96*, 1953–1960.
122. Damiano, J. S., Cress, A. E., Hazlehurst, L. A., Shtil, A. A., & Dalton, W. S. (1999). Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. *Blood, 93*, 1658–1667.
123. Shain, K. H., Yarde, D. N., Meads, M. B., Huang, M., Jove, R., Hazlehurst, L. A., et al. (2009). Beta1 integrin adhesion enhances IL-6-mediated STAT3 signaling in myeloma cells: implications for microenvironment influence on tumor survival and proliferation. *Cancer Research, 69*, 1009–1015.
124. Hoang, B., Zhu, L., Shi, Y., Frost, P., Yan, H., Sharma, S., et al. (2006). Oncogenic RAS mutations in myeloma cells selectively induce cox-2 expression, which participates in enhanced adhesion to fibronectin and chemoresistance. *Blood, 107*, 4484–4490.
125. Maris, J. M., Hogarty, M. D., Bagatell, R., & Cohn, S. L. (2007). Neuroblastoma. *Lancet, 369*, 2106–2120.
126. Dubois, S. G., Kalika, Y., Lukens, J. N., Brodeur, G. M., Seeger, R. C., Atkinson, J. B., et al. (1999). Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. *Journal of Pediatric Hematology/Oncology, 21*, 181–189.
127. Sohara, Y., Shimada, H., Minkin, C., Erdreich-Epstein, A., Nolta, J. A., & DeClerck, Y. A. (2005). Bone marrow mesenchymal stem cells provide an alternate pathway of osteoclast activation and bone destruction by cancer cells. *Cancer Research, 65*, 1129–1135.
128. Ara, T., Song, L., Shimada, H., Keshelava, N., Russell, H. V., Metelitsa, L. S., et al. (2009). Interleukin-6 in the bone marrow microenvironment promotes the growth and survival of neuroblastoma cells. *Cancer Research, 69*, 329–337.
129. Fukaya, Y., Shimada, H., Wang, L. C., Zandi, E., & DeClerck, Y. A. (2008). Identification of Gal-3 binding protein as a factor secreted by tumor cells that stimulates interleukin-6 expression in the bone marrow stroma. *Journal of Biological Chemistry, 283*, 18573–18581.
130. Kakonen, S. M., Selander, K. S., Chirgwin, J. M., Yin, J. J., Burns, S., Rankin, W. A., et al. (2002). Transforming growth factor-beta stimulates parathyroid hormone-related protein and osteolytic metastases via Smad and mitogen-activated protein kinase signaling pathways. *Journal of Biological Chemistry, 277*, 24571–24578.
131. Guise, T. A. (2000). Molecular mechanisms of osteolytic bone metastases. *Cancer, 88*, 2892–2898.
132. Brocke-Heidrich, K., Kretzschmar, A. K., Pfeifer, G., Henze, C., Loffler, D., Koczan, D., et al. (2004). Interleukin-6-dependent gene expression profiles in multiple myeloma INA-6 cells reveal a Bcl-2 family-independent survival pathway closely associated with Stat3 activation. *Blood, 103*, 242–251.
133. Aggarwal, B. B., Sethi, G., Ahn, K. S., Sandur, S. K., Pandey, M. K., Kunnumakkara, A. B., et al. (2006). Targeting signal-transducer-and-activator-of-transcription-3 for prevention and therapy of cancer: modern target but ancient solution. *Annals of the New York Academy of Sciences, 1091*, 151–169.
134. Yamagiwa, Y., Marienfeld, C., Meng, F., Holcik, M., & Patel, T. (2004). Translational regulation of x-linked inhibitor of apoptosis protein by interleukin-6: a novel mechanism of tumor cell survival. *Cancer Research, 64*, 1293–1298.
135. Lee, G., & Piquette-Miller, M. (2001). Influence of IL-6 on MDR and MRP-mediated multidrug resistance in human hepatoma cells. *Canadian Journal of Physiology and Pharmacology, 79*, 876–884.
136. Dreuw, A., Hermanns, H. M., Heise, R., Joussen, S., Rodriguez, F., Marquardt, Y., et al. (2005). Interleukin-6-type cytokines upregulate expression of multidrug resistance-associated proteins in NHEK and dermal fibroblasts. *Journal of Investigative Dermatology, 124*, 28–37.
137. Efferth, T., Fabry, U., & Osieka, R. (2002). Interleukin-6 affects melphalan-induced DNA damage and repair in human multiple myeloma cells. *Anticancer Research, 22*, 231–234.
138. Pu, Y. S., Hour, T. C., Chuang, S. E., Cheng, A. L., Lai, M. K., & Kuo, M. L. (2004). Interleukin-6 is responsible for drug resistance and anti-apoptotic effects in prostatic cancer cells. *Prostate, 60*, 120–129.
139. Ishikawa, F., Yoshida, S., Saito, Y., Hijikata, A., Kitamura, H., Tanaka, S., et al. (2007). Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region. *Nature Biotechnology, 25*, 1315–1321.
140. De Toni, F., Racaud-Sultan, C., Chicanne, G., Mas, V. M., Cariven, C., Mesange, F., et al. (2006). A crosstalk between the Wnt and the adhesion-dependent signaling pathways governs the chemosensitivity of acute myeloid leukemia. *Oncogene, 25*, 3113–3122.
141. Arthur, A., Zannettino, A., & Gronthos, S. (2009). The therapeutic applications of multipotential mesenchymal/stromal stem cells in skeletal tissue repair. *Journal of Cellular Physiology, 218*, 237–245.
142. Hare, J. M., & Chaparro, S. V. (2008). Cardiac regeneration and stem cell therapy. *Current Opinion in Organ Transplantion, 13*, 536–542.
143. Fritz, V., & Jorgensen, C. (2008). Mesenchymal stem cells: an emerging tool for cancer targeting and therapy. *Current Stem Cell Research & Therapy, 3*, 32–42.
144. Hall, B., Dembinski, J., Sasser, A. K., Studeny, M., Andreeff, M., & Marini, F. (2007). Mesenchymal stem cells in cancer: tumor-associated fibroblasts and cell-based delivery vehicles. *International Journal of Hematology, 86*, 8–16.
145. Sasportas, L. S., Kasmieh, R., Wakimoto, H., Hingtgen, S., van de Water, J. A., Mohapatra, G., et al. (2009). Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 4822–4827.
146. Cavarretta, I. T., Altanerova, V., Matuskova, M., Kucerova, L., Culig, Z., & Altaner, C. (2010). Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth. *Molecular Therapy, 18*, 223–231.
147. Nakamizo, A., Marini, F., Amano, T., Khan, A., Studeny, M., Gumin, J., et al. (2005). Human bone marrow-derived mesenchymal stem cells in the treatment of gliomas. *Cancer Research, 65*, 3307–3318.
148. Nishimoto, N., & Kishimoto, T. (2006). Interleukin 6: from bench to bedside. *Nature Clinical Practice Rheumatology, 2*, 619–626.
149. Fulciniti, M., Hideshima, T., Vermot-Desroches, C., Pozzi, S., Nanjappa, P., Shen, Z., et al. (2009). A high-affinity fully human anti-IL-6 mAb, 1339, for the treatment of multiple myeloma. *Clinical Cancer Research, 15*, 7144–7152.