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Involvement of Mesenchymal Stem Cells in Breast Cancer Progression

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1. Introduction

For many reasons, mesenchymal stem cells (MSCs) have lately received much attention. Their plasticity, their tropism for wounds and cancer, their ability to assist in tissue regeneration, their immunomodulary activities, their effects on cancer development and finally their usefulness as drug-delivery vectors made MSCs a prime target for many researchers worldwide. Many aspects of MSC functions have been covered by recent reviews (Beyer Nardi & da Silva Meirelles, 2006; Kidd et al., 2008; Klopp et al., 2011; Krabbe et al., 2005; Patel et al., 2008; Uccelli et al., 2008; Wislet-Gendebien et al., 2005; Yen & Yen, 2008). In this review, we are summarizing the current knowledge on the communication of MSCs with breast cancer cells and its consequences for breast cancer progression.

2. General aspects of MSC biology

2.1 What are mesenchymal stem cells?

Mesenchymal stem cells, also called multipotent mesenchymal stromal cells, were first described as stromal cells residing in the bone marrow (Friedenstein et al., 1966). They have stem cell-like characteristics (Caplan, 1991; Friedenstein & Kuralesova, 1971), a fibroblast-like appearance and features different from cells of the haematopoietic lineages. Those features include the ability to differentiate to osteoblasts, chondrocytes and adipocytes (Friedenstein et al., 1974; Noth et al., 2002; Pittenger et al., 1999). MSCs may also play a role in haematopoiesis, as MSCs have been shown to be involved in forming niches for the haematopoietic stem cells and to regulate the activities of these cells (Ehninger & Trumpp, 2011; Mendez-Ferrer et al., 2010; Omatsu et al., 2010; Sacchetti et al., 2007). MSCs are rare in the bone marrow. Only 1 of 34,000 nucleated cells in this tissue were determined to be MSCs (Wexler et al., 2003). Though much is known about MSCs today, there are still no specific markers available that clearly define a cell as an MSC. In 2006, the International Society for Cellular Therapy published a list of minimal criteria instead (Dominici et al., 2006) that are now commonly used to identify MSCs. Among these criteria are two functional features, the potential to differentiate to osteoblasts, chondrocytes and adipocytes as mentioned above and the ability to adhere to plastic. The latter feature allows the separation of MSCs from the other bone marrow cell populations, as cells of the haematopoietic lineages are non-adherent cells (Beyer Nardi & da Silva Meirelles, 2006). Other critieria used to characterize
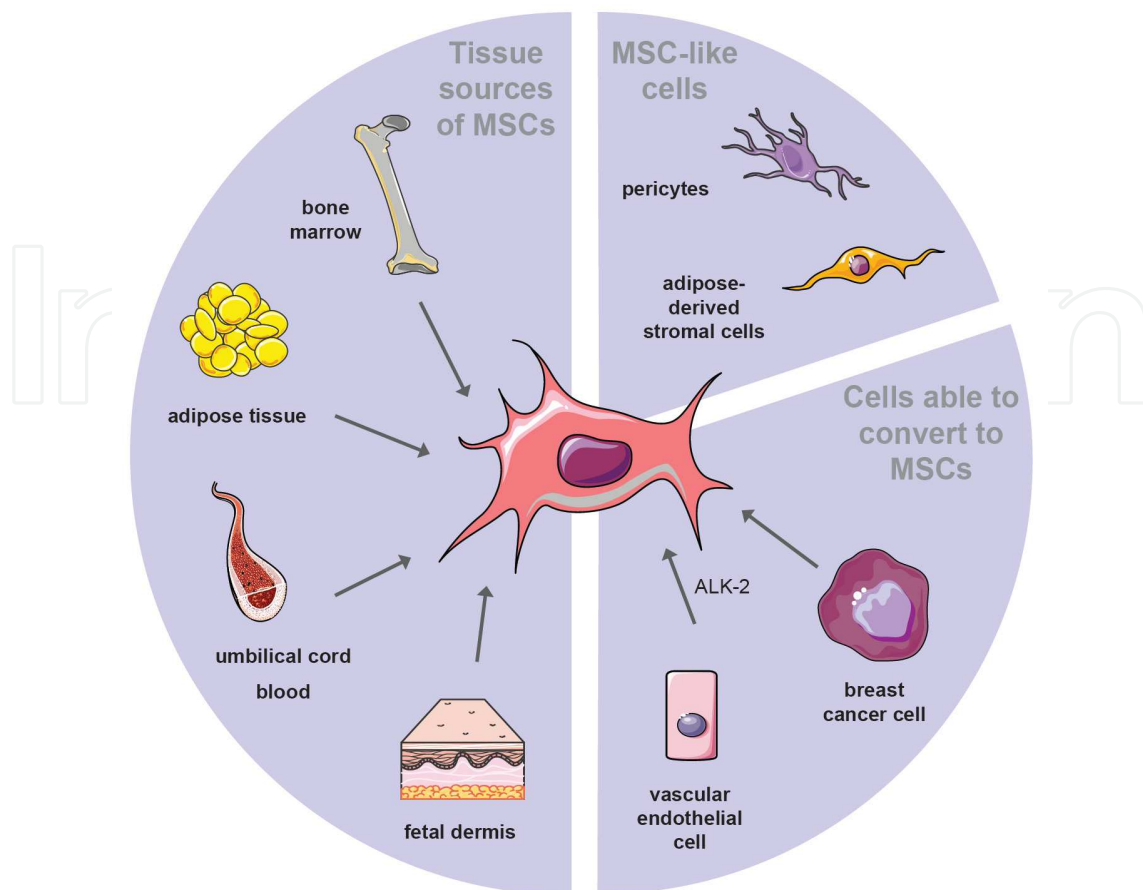
Fig. 1. Sources of MSCs. The cartoon depicts the different sources from which MSCs can be isolated (left), the cells that can convert to MSCs (right, bottom) and cells that display MSC-like features (right, top). Details are described in the text. ALK-2 = activin-like kinase-2.

MSCs are the expression profiles of certain proteins. MSCs express CD105 (endoglin), CD73 (ecto 5'-nucleotidase) and CD90 (Thy-1) and are deficient of CD45 (pan-leukocyte marker), CD34 (marker for primitive haematopoietic progenitors and endothelial cells), CD14 and CD11 (marker for monocytes and macrophages), CD79α and CD19 (marker for B-cells) and HLA-DR (MSCs not stimulated by IFN-γ). Bone marrow is not the only source of MSCs, other tissues are suitable to isolate MSCs as well (Fig. 1). Among these tissues are human adipose tissue (Zuk et al., 2002), umbilical cord blood (Sun et al., 2010), fetal dermis tissue (Qiao et al., 2008a), pancreatic tissue (Seeberger et al., 2006) and breast milk (Patki et al., 2010). More MSC sources are expected (Ding et al., 2011). Recently, menstrual blood and endometrium have been shown to contain MSCs. It is likely that most MSCs found in other tissues originated from the bone marrow. However, there is also evidence that some tissues, such as the adipose tissue, may produce their own MSCs (Bianco, 2011; Zhao et al., 2010). The MSC pool of a tissue may be expanded by dedifferentiation of differentiated cells (Fig. 1). This has been demonstrated for vascular endothelial cells that, under certain conditions, can undergo endothelial-to-mesenchymal transition to convert to MSCs (Medici et al., 2010). Some tissue-specific MSCs may be known for many years by other names (Fig. 1). Adipose-derived stromal cells or preadipocytes are likely to be MSCs residing in adipose tissue (Locke et al., 2011; Manabe et al., 2003; Zuk et al., 2002). Pericytes isolated from skeletal muscles or non-muscle tissues have recently be found to show the typical characteristics of

MSCs (Crisan et al., 2008). It is possible that MSCs from different sources may not be identical and may behave differently (Zhao et al., 2010). In fact, environmental conditions, such as the supply with growth factors or oxygen, have been shown to change the behavior of MSCs (Krinner et al., 2010; Sanchez et al., 2011). Even a population of MSCs derived from a single source may not be homogenous and may have different developmental potentials (Phinney, 2002). This hypothesis was confirmed by Wicha and his co-workers who demonstrated that MSCs from bone marrow contain at least two subpopulations, one that expresses and one that lacks the stem cell marker ALDH-1 (aldehyde dehydrogenase-1) (Liu et al., 2011). These two subpopulations behaved also functionally different (see 4.3).

2.2 Plasticity of MSCs

In addition to the ability to mature to osteoblasts, chondrocytes and adipocytes, MSCs are also capable of differentiating to fibroblasts (Mishra & Banerjee, 2011). This conversion may be of particular importance in cancer, where MSCs that colonize a cancerous lesion switch to a particular type of fibroblast-like cells, the carcinoma-associated fibroblast (CAF) (Mishra et al., 2008; Spaeth et al., 2009). This may have consequences for tumor progression (see 4.4). The differentiation potential of MSCs goes far beyond the ability to differentiate towards the mesodermal lineage (Uccelli et al., 2008). Differentiation of MSCs to cells of ectodermal and endodermal lineages have been demonstrated as well. E.g., MSCs derived from adipose tissue were shown to be able to differentiate to endothelial cells (Zuk et al., 2002), while pancreatic MSCs could become hepatocytes (Seeberger et al., 2006). In addition, MSCs from umbilical cord blood were shown to have the potential to switch to cells displaying features of neural cells (Li et al., 2005; Park et al., 2007; Tondreau et al., 2004), though, in some cases, the neural phenotype may have caused by fusions of MSCs with neurons (Krabbe et al., 2005; Wislet-Gendebien et al., 2005). Under certain conditions, MSCs can also become epithelial cells, such as lung or renal epithelium-like cells (Kale et al., 2003; Lin et al., 2003; Ortiz et al., 2003; Rojas et al., 2005).

3. Attracted to wounds and cancer

3.1 Tropism towards injured tissue: MSCs as "repair" cells

MSCs are believed to play an important role in wound healing. Chemokines and cytokines as secreted by inflammatory cells seem to chemoattract MSCs to injured tissues (Brooke et al., 2007). E.g., Kidd and his co-workers reported that, when inoculated into wounded mice, labeled MSCs were preferentially detected in wounds, whereas, in non-injured mice, MSCs settled in lung, liver and spleen (Kidd et al., 2009). MSCs are attracted to many types of organs after injury, such as heart after myocardial infarction (Barbash et al., 2003), kidney after glomeruli damage (Ito et al., 2001), injured muscles (Natsu et al., 2004), bleomycin-damaged lung (Ortiz et al., 2003) and brain after stroke (Chen et al., 2001; Mahmood et al., 2003). Interestingly, homing to the injured brain could be specifically blocked by an antibody directed to the chemokine MCP-1 (monocyte chemotactic protein-1)/CCL2 (Wang et al., 2002) suggesting that MCP-1/CCL2 is an important chemoattractant for MSCs. In the injured tissue, MSCs were found to help to regenerate this tissue. MSCs accomplish this goal partly by directly converting to those cells specifically needed to restore the function of the tissue. It is therefore tempting to consider the MSC as a general repair cell (Dittmer, 2010). Numerous reports support this hypothesis. E.g., bone marrow-derived MSCs were demonstrated to facilitate healing of injured muscles by differentiating to muscle progenitor

cells (Natsu et al., 2004). In bleomycin-injured lung, MSCs switched to a phenotype typical for lung epithelial cells (Ortiz et al., 2003; Rojas et al., 2005). In the damaged myocardium, bone marrow-derived MSCs converted to cardiomyocytes (Toma et al., 2002; Wang et al., 2001). In ischemically injured renal tubules, MSCs are able to become tubular epithelial cells (Kale et al., 2003; Lin et al., 2003). In kidneys after anti-Thy1 antibody-induced glomerulonephritis, MSCs have been shown to mature to mesangial cells (Ito et al., 2001). And in diabetic mice, MSCs induced the number of pancreatic islets to increase and enhanced insulin production (Hess et al., 2003; Lee et al., 2006). The affinity of MSCs to injured tissue can be utilized for therapy (Brooke et al., 2007; Tocci & Forte, 2003). MSCs can be used as vectors to deliver drugs to injured tissues. Examples are BDNF (brain-derived neurotrophic factor)- or insulin-secreting MSCs to improve recovery from stroke (Kurozumi et al., 2004) or to treat diabetes (Xu et al., 2007), respectively. MSCs have also been used in clinical trials (Herberts et al., 2011). Most of the clinical trials with MSCs were carried out to treat patients with heart disease (Prockop & Olson, 2007). In many cases, patients' conditions improved suggesting that MSCs have positive effects on tissue repair also in humans.

3.2 Tropism towards cancer: MSCs are attracted to breast cancer lesions

Given the fact that MSCs are entering wounds to facilitate tissue repair, MSCs are of great value to maintain body functions. However, the affinity of MSCs to wounds may be of disadvantage to people who are suffering from cancer. In support of the view that a tumor is a wound that never heals (Dvorak, 1986), MSCs were also found to be attracted to cancerous lesions (Kidd et al., 2009) where they may promote tumor progression. Importantly, wounds and cancers secrete a similar cocktail of inflammatory cytokines and chemokines (Kidd et al., 2008). Among them are MSC-attracting factors, such as the growth factors PDGF (platelet-derived growth factor) and IGF-1 (insulin-like growth factor-1), the cytokines IL-6 (interleukin-6) and IL-8 as well as the chemokines MCP-1/CCL2, RANTES/CCL5, MDC (macrophage-derived chemokine)/CCL22 and SDF-1 (stromal-derived factor-1)/CXCL12 (Dwyer et al., 2007,Ponte, 2007 #228; Kim et al., 2011; Liu et al., 2011). It was confirmed that MSCs express the corresponding receptors for these ligands, i.e. PDGFR (PDGF receptor), IGFR (insulin growth factor receptor), IL-6R, gp130, CXCR1, CCR2, CCR3, CCR4 and CXCR4 (Dwyer et al., 2007,Ponte, 2007 #228; Kim et al., 2011; Liu et al., 2011). The susceptibility of MSCs to chemoattractants can be enhanced by certain factors. E.g., TNFα (tumor necrosis factor α) was shown to increase the response of MSCs to certain chemokines by upregulating the expression of the receptors CCR2, CCR3 and CCR4 (Ponte et al., 2007). Many studies demonstrated that MSCs are attracted by tumors. In one study, the bone marrow of a mouse was replaced by the bone marrow from a transgenic mouse that expressed beta-galactosidase and MSC migration monitored from the bone marrow towards a prostate tumor xenograft (Ishii et al., 2003). It was found that X-gal positive MSCs colonized the tumor and differentiated to fibroblasts and endothelial cells. In a similar experimental setting, Direkze and co-workers could show that MSCs enter pancreatic insulinoma and convert to myofibroblasts (Direkze et al., 2004). Also breast cancer cells have been shown to chemoattract MSCs *in vitro* as well as *in vivo* (Dittmer et al., 2009; Dwyer et al., 2007; Goldstein et al., 2010; Klopp et al., 2007; Lin et al., 2008; Ling et al., 2010; Liu et al., 2011; Mishra et al., 2008; Pulukuri et al., 2010; Rattigan et al., 2010; Ritter et al., 2008; Zielske et al., 2009). Most breast cancer studies with MSCs were performed with luminal A-type

MCF-7 cells and mesenchymal (basal-B)-type MDA-MB-231 cells. In some investigations, also luminal A-type T47D, basal A-type MDA-MB-468, murine 4T1 breast cancer cells and primary human breast cancer were used. In all cases, breast cancer cells stimulated MSC migration. However, the chemoattractive potency differed among the different breast cancer cell subtypes. E.g., the highly invasive MDA-MB-231 cells were more potent than the weakly invasive MCF-7 cells in stimulating migration of MSCs *in vitro* and *in vivo* (Dittmer et al., 2009; Goldstein et al., 2010; Ritter et al., 2008). Hence, it seems that MSCs have a higher affinity to more aggressive tumors. It is well established that factors secreted by breast cancer cells are responsible for MSC attraction (Fig. 2). IL-6 is one factor that is secreted by breast cancer cells and acts as a chemoattractant for MSCs (Liu et al., 2011; Rattigan et al., 2010). In response to IL-6, MSCs not only enhance their migratory activity, but also secrete chemokines, such as CXCL7 (see 4.3) (Liu et al., 2011). Interestingly, hypoxic conditions as often found in tumors trigger breast cancer cells to produce more IL-6 which further enhances migration of MSCs (Rattigan et al., 2010). Hypoxia also affects MSCs directly in
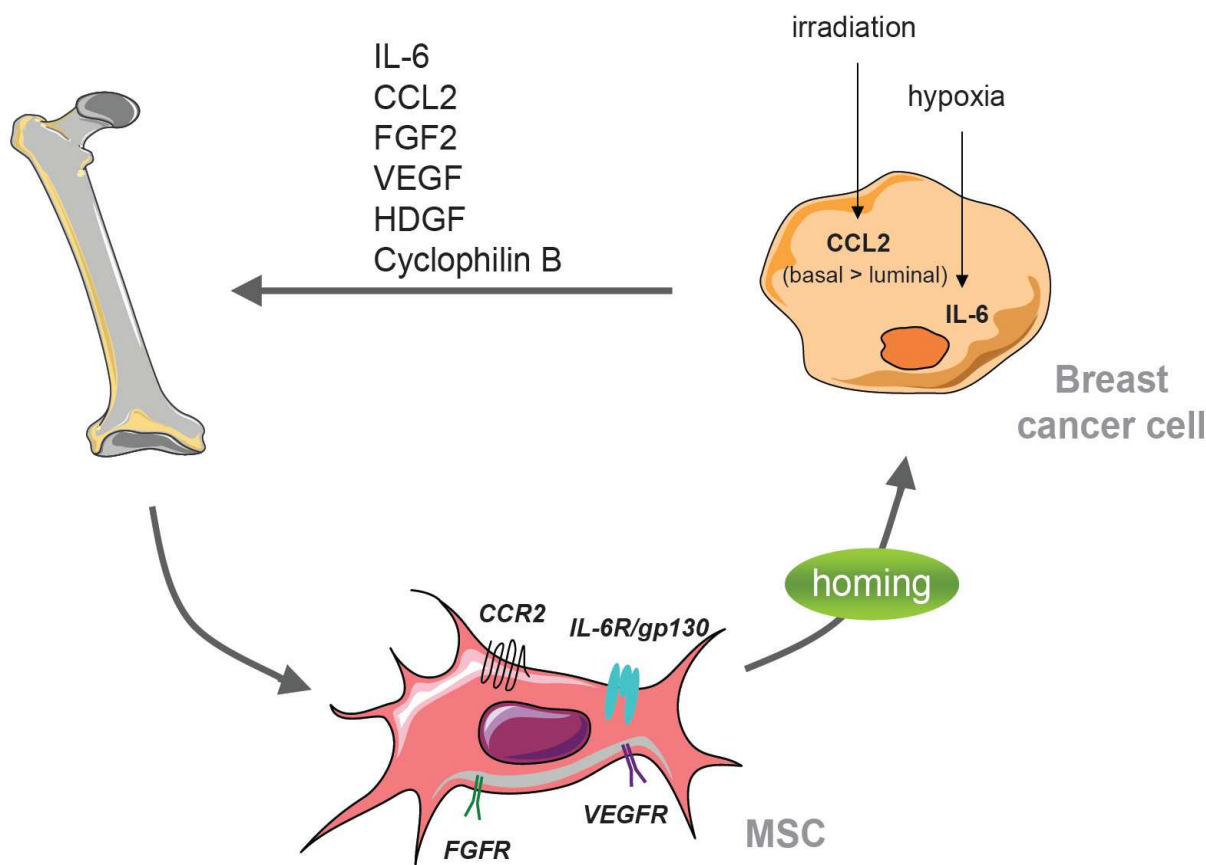

Fig. 2. Chemoattraction of MSCs to breast cancer cells. Breast cancer-derived cytokines and growth factors stimulate MSCs to migrate towards the tumor. Irradiation or hypoxia increase the CCL2 or IL-6 secretion, respectively, by breast cancer cells. Basal-type breast cancer cells seem to produce more CCL-2 than luminal A-type breast cancer cells. IL-6(R) = interleukin-6 (receptor), FGF(R) = fibroblast growth factor (receptor), VEGF(R) = vascular endothelial growth factor (receptor), HDGF = hepatoma-derived growth factor.

that it increases their proliferative activity and their expression of stem cell and differentiation markers (Grayson et al., 2006). Besides IL-6, breast cancer cell-derived FGF-2, VEGF (vascular endothelial growth factor), cyclophilin B and HDGF (hepatoma-derived growth factor) were demonstrated to induce migration of MSCs (Lin et al., 2003; Ritter et al., 2008). Another important tumor-derived chemoattractant was shown to be the chemokine MCP-1/CCL2 (Dwyer et al., 2007) which is recognized by MSCs via the receptor CCR2 (Lu et al., 2006; Wang et al., 2002). Interestingly, mesenchymal (basal B-type) MDA-MB-231 cells produce more MCP-1/CCL2 than luminal A-type T47D cells, which may explain why more aggressive breast cancer cells have a higher potential to stimulate MSC migration. In primary breast cancer, which contains both an epithelial and a stromal compartment, the stromal compartment seems to be the major source of MCP-1/CCL2 (Dwyer et al., 2007). Irradiation of tumors was found to increase the expression of MCP-1/CCL2 and, along with it, the potential to recruit MSCs to tumors (Zielske et al., 2009). This further supports the notion that MCP-1/CCL2 plays an important role in attracting MSCs to tumors. The efficiency of recruitment of MSCs to tumors may also depend on inherent features of MSCs. MSCs overexpressing uPA (urokinase plasminogen activator) have a higher ability to migrate towards breast and prostate cancer cells than their vector-treated counterparts (Pulukuri et al., 2010). Given their similar tropism to injuries and cancer (Kidd et al., 2009), MSCs are a promising tool for therapeutic intervention of cancer (Motaln et al., 2010) as much as they are for treating injuries. MSCs engineered to express anti-cancer drugs can be used as vectors to deliver toxic loads to tumor cells. In many studies with engineered MSCs, MSCs were forced to express TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), a membrane protein that induces apoptosis of tumor cells, but not of normal cells (Walczak et al., 1999). Using mouse xenografts, it could be shown that TRAIL-expressing MSCs are able to eradicate many kinds of tumor cells, including glioma, cervival, pancreatic, colon and breast cancer cells (Grisendi et al., 2010; Loebinger et al., 2009; Menon et al., 2009; Sonabend et al., 2008; Yang et al., 2009). MSC-delivered TRAIL can induce apoptosis by upregulating caspase 8 (Grisendi et al., 2010). TRAIL-expressing MSCs were also able to attack metastatic breast cancer cells and to significantly reduce pulmonary metastatic load in mice (Loebinger et al., 2009). In contrast to recombinant TRAIL, which has a short half life in plasma, TRAIL-expressing MSCs allow prolonged TRAIL exposure (Grisendi et al., 2010). Other approaches use MSCs that were engineered to express IFN-β (interferon-β) or transduced with CRAds (conditionally replicating adenoviruses) (Dembinski et al., 2009; Ling et al., 2010; Stoff-Khalili et al., 2007). In another setting, MSCs were transfected with enzymes to locally convert a relatively non-toxic substance into a toxin. Examples are MSCs expressing HSV-TK (herpes simplex virus-thymidine kinase) which catalyses the conversion of the prodrug ganciclovir to a toxic compound (Conrad et al., 2011) and MSCs loaded with cytosine deaminase which induces the deamination of 5-fluorocytosine to the chemotherapeutic drug 5-fluorouracil (Kucerova et al., 2008; You et al., 2009). In both cases, the non-toxic prodrug was systemically administered to tumor-bearing mice. MSCs can also be engineered such that they boost immune responses to cancer cells. MSCs engineered to express Her2 (human epidermal receptor2), a receptor tyrosine kinase often overexpressed in breast cancer (Theillet, 2010), can act as antigen-presenting cells to induce an immune reaction against Her2-exposing breast cancer cells (Romieu-Mourez et al., 2010). However, it should be noted that caution should be exercised when using MSCs as therapeutic tools as

MSCs may be able to transform to sarcoma cells (Burns et al., 2008; Gjerstorff et al., 2009; Li et al., 2009; Mohseny & Hogendoorn, 2011; Riggi et al., 2008; Rosland et al., 2009). Currently, there is a debate about whether the MSC and not a primitive neuroectodermal cell is the cell of origin of Ewing's sarcoma (Lin et al., 2011).

3.3 Immunosuppression by MSCs: Consequences for wound healing and cancer progression

It is well established that MSCs act anti-inflammatory by modulating the activities of cells of the innate and the adaptive immune system (Rasmusson, 2006; Uccelli et al., 2008; Yagi et al., 2010). Among the affected cells are antigen-presenting dendritic cells, tumor cell-targeting natural killer cells, neutrophils and B- as well as T-lymphocytes. MSCs block antigen presentations by dendritic cells (Jiang et al., 2005; Ramasamy et al., 2007), inhibit the proliferation of activated T-lymphocytes (Bartholomew et al., 2002; Di Nicola et al., 2002; Krampera et al., 2003; Rasmusson et al., 2005), activate regulatory T cells (T$_{regs}$) that suppress T-effector cells (Aggarwal & Pittenger, 2005; Patel et al., 2010; Selmani et al., 2008), inhibit the activity of cytotoxic T-lymphocytes (Rasmusson et al., 2003) and block the proliferation of natural killer cells (Aggarwal & Pittenger, 2005; Sotiropoulou et al., 2006; Spaggiari et al., 2008). Direct and indirect interactions of MSCs with immune cells are made responsible for the anti-inflammatory activity of the MSCs (Uccelli et al., 2008). The indirect effects are mediated by a number of cyto- and chemokines as secreted by MSCs. Among them are TGFβ1 (transforming growth factor β1) which stimulates the proliferation of inhibitory T$_{regs}$ (Patel et al., 2010), IL-6 shown to inhibit neutrophil proliferation (Raffaghello et al., 2008) and prostaglandin E2 that inhibits antigen presentation by dendritic cells as well as proliferation of T-effector cells (Aggarwal & Pittenger, 2005; Bartholomew et al., 2002; Di Nicola et al., 2002; Glennie et al., 2005; Jiang et al., 2005; Krampera et al., 2003; Ramasamy et al., 2007; Rasmusson et al., 2005; Selmani et al., 2008). In the mouse model, the anti-inflammatory effects of MSCs were also linked to increased phagocytosis and enhanced elimination of bacteria (Mei et al., 2010). However, due to differences in the anti-sepsis defense in mice and men, it is unclear whether these data allow the prediction of an MSC-induced anti-sepsis effect also in humans (Monneret, 2009). It is likely that, by down-modulating the immune response, MSCs prevent excessive inflammation in injuries. This is thought to be the second way by which MSCs facilitate regeneration of the injured tissue. While for that reason the anti-inflammatory effect of MSCs may be beneficial for a patient with an injury, it may be however detrimental to a cancer patient. By inducing local immunosuppression cancer-residing MSCs may help cancer cells to escape immune surveillance.

4. Communication between MSCs and breast cancer cells

4.1 The cytokine cocktail secreted by MSCs

MSCs secrete a plethora of cytokines and chemokines. In addition to the immuno-regulatory proteins, such as TGFβ1, IL-6 and prostaglandin E2, MSCs produce many other interleukins, including IL-7, IL-8 and IL-9, CC-type chemokines (CCL1, 2, 5, 8, 11, 15, 16, 20, 22, 26, and 27), CXC-type chemokines (CXCL1, 5, 6, 10, 11, 12, 13, and 16) and other factors, such as TIMP (tissue inhibitor of metalloproteases) -1 and -2, TNFα and β, PDGF A and B, G-CSF (granulocyte colony-stimulating factor), HGF (hepatocyte growth factor), VEGF and angiopoietin (Parekkadan et al., 2007). The syntheses of these factors can be further stimulated. E.g., IL-6 induces the expression of CXCL7, which further enhances the

expression levels of IL-6, IL-8, CXCL5 and CXCL6 (Liu et al., 2011). TGFα (transforming growth factor α) was found to stimulate MSCs to secrete more IL-6, IL-8, angiopoietin-2, G-CSF, HGF, VEGF and PDGF-BB (De Luca et al., 2010). TNFα forced MSCs to increase their expression of CXCL9, CXCL10 and CXCL11 (Shin et al., 2010). Exposure of MSCs to conditioned medium from tumor cells also stimulate expression of chemokines, such as CXCL2 and CXCL12 (Menon et al., 2007). Direct interactions of cancer cells with MSCs may as well contribute to the rise of chemokine secretion by MSCs. Direct contacts of MSCs with MDA-MB-231 breast cancer cells were found to strongly upregulate the production of RANTES/CCL5 (Karnoub et al., 2007).

4.2 Modulatory effects of MSCs on breast cancer cell function

MCF-7 cells are ERα-positive luminal A-type breast cancer cells that show many features of normal breast epithelial cells, including the formation of E-cadherin-based cell-cell interactions and the ability to generate multicellular 3D-aggregates that can mature to lumen-containing spheroids (dit Faute et al., 2002; do Amaral et al., 2010). Decreased expression or complete loss of E-cadherin has been linked to epithelial-mesenchymal transition (EMT) and increased cellular migration of breast epithelial cells as well as to metastasis (Cano et al., 2000; Chua et al., 2007; Mani et al., 2008; Onder et al., 2008). We and others have shown that MSCs negatively interfere with the E-cadherin status of MCF-7 cells either by downregulation of the full length protein (Fierro et al., 2004; Hombauer & Minguell, 2000; Klopp et al., 2010) or by increasing E-cadherin shedding as triggered by the transmembrane protease ADAM10 (a disintegrin and metalloprotease 10) (Dittmer et al., 2009). It is noteworthy that as few as one MSC per 500 MCF-7 cells was sufficient to induce E-cadherin shedding. E-cadherin shedding leads to extracellular E-cadherin fragments that may block E-cadherin-based cell-cell contacts by competing with membrane-bound E-cadherin proteins (Ryniers et al., 2002). Hence, both downregulation of E-cadherin expression and increased E-cadherin shedding may decrease the strength of E-cadherin-based cell-cell interactions. With intercellular adhesions weakened cellular migration may increase. In fact, MSCs have been shown to significantly enhance the migratory activity of MCF-7 cells (Dittmer et al., 2009; Rhodes et al., 2010). Also along with the destabilization of cell-cell contacts, disruption of the architecture of MCF-7 spheroids was observed. It is interesting that, despite these changes in the E-cadherin status, MSCs did not induce EMT of MCF-7 cells, as indicated by the failure of MSCs to stimulate the expression of mesenchymal markers, such as vimentin or snail (Dittmer et al., 2009; Klopp et al., 2010). However, in the luminal A-type T47D breast cancer cell line, MSCs not only downregulated E-cadherin levels, but also increased expression of vimentin, snail, twist and N-cadherin (Martin et al., 2010) suggesting that, under certain conditions, MSCs can induce EMT of breast cancer cells. MSCs were also shown to increase the proliferation of MCF-7 cells in a dose-dependent manner (Fierro et al., 2004; Klopp et al., 2010; Rhodes et al., 2010; Sasser et al., 2007a). These effects may be mediated by IL-6, VEGF and/or SDF-1/CXCL12 as secreted by MSCs (Fig. 3) (Fierro et al., 2004; Sasser et al., 2007b). MSCs or similarly IL-6 induced the phosphorylation of STAT3 (signal transducer and activator of transcription 3) on tyrosine-705 in MCF-7 cells (Sasser et al., 2007b). Incubation of MSCs with TGFα, a ligand of the EGFR (epidermal growth factor receptor), further stimulated the secretion of IL-6 and other factors (De Luca et al., 2010). This suggests that TGFα-primed MSCs would even be more effective in promoting proliferation of MCF-7 cells. MSCs also enhanced the tumorigenic activity of
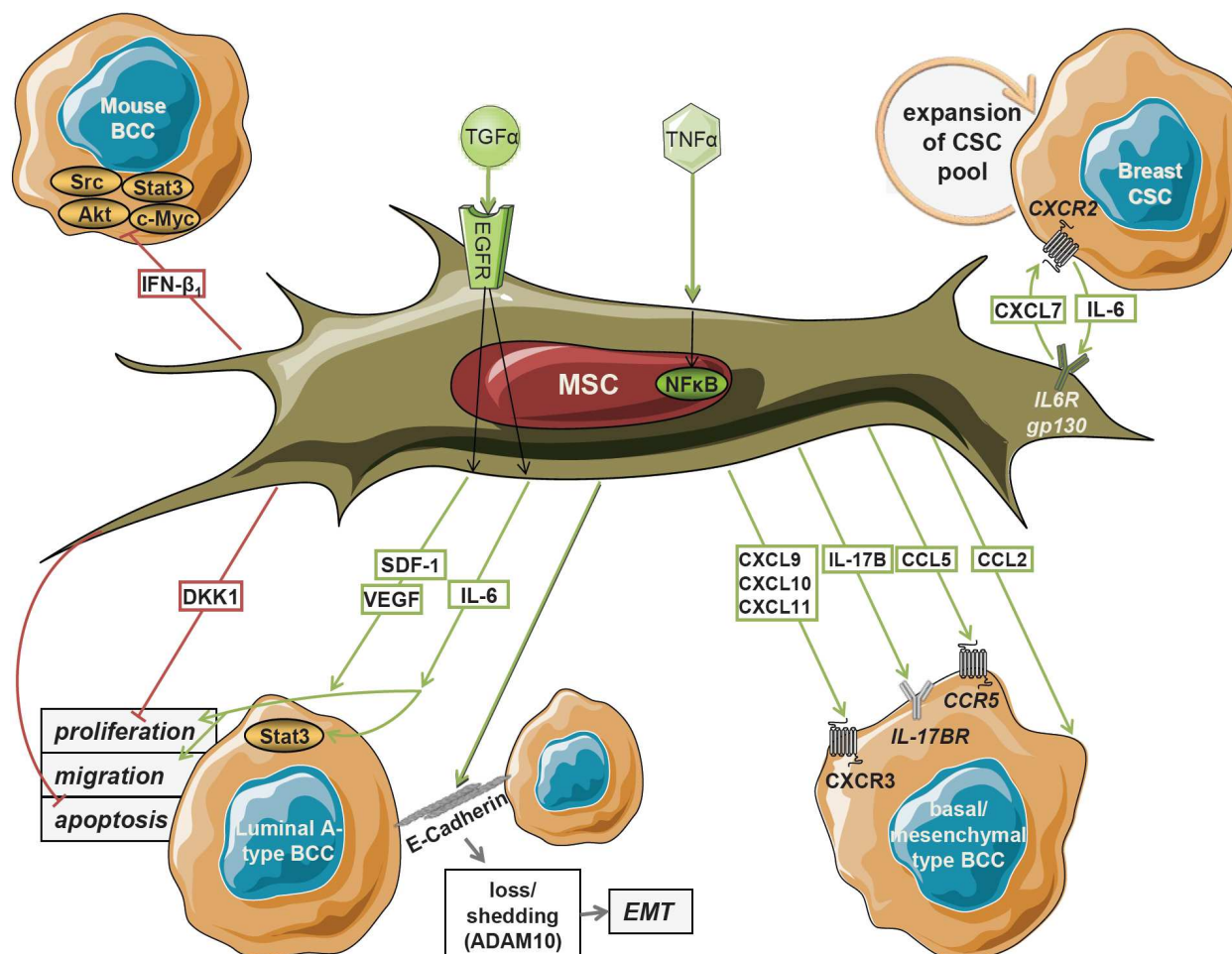
Fig. 3. Paracrine actions of MSCs on breast cancer cells (BCCs). The effects of MSCs on luminal A and basal/mesenchymal subtype BCCs, on murine BCCs and on cancer stem cells (CSCs) are separately displayed. IL-6/-17B(R) = interleukin-6/-17B (receptor), VEGF = vascular endothelial growth factor, SDF-1 = stromal-derived factor-1, DKK = dickkopf, INF-β_1 = interferon β_1, TGFα = transforming growth factor α, TNFα = tumor necrosis factor α, EGFR = epidermal growth factor receptor, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B-cells, Stat3 = signal transducer and activator of transcription 3, ADAM10 = a disintegrin and metalloprotease 10, EMT = epithelial-to-mesenchymal transition.

MCF-7 cells. In mouse xenografts, MCF-7 tumor formation and growth were fostered by MSCs (Klopp et al., 2010). Though ERα-positive MCF-7 cells are dependent on estrogen for growth, MSCs may even trigger estrogen-independent proliferation of MCF-7 cells (Rhodes et al., 2009). The estrogen-independent growth may nevertheless be dependent on ER, as the proliferation-promoting effect of MSCs on MCF-7 cells was found to be blocked by ER-specific inhibitor ICI 182780 (Rhodes et al., 2010). It is thought that, by a yet unknown mechanism, MSCs activate ER which, in turn, stimulates the expression of SDF-1/CXCL12, a chemokine shown to trigger the proliferation of MCF-7 cells. Growth-stimulating effects of MSCs were also found on other ERα-positive breast cancer cell lines, including T47D, BT474 and ZR-75-1 (Sasser et al., 2007a) and may be dependent on similar mechanisms as those on MCF-7 cells. There are also two reports that show that MSCs are able to inhibit the proliferation of MCF-7 cells (Goldstein et al., 2010; Qiao et al., 2008a). Dickkopf-1 (DKK-1) secreted by MSCs and known to block differentiation and to promote proliferation of MSCs

by an autocrine mechanism (Pinzone et al., 2009) may be responsible for this effect (Qiao et al., 2008a). As an inhibitor of the Wnt/β-catenin pathway, DKK-1 was shown to downregulate β-catenin activity and, concomitantly, to reduce the expression of proliferation-promoting proteins c-Myc and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) in MCF-7 cells (Qiao et al., 2008a; Qiao et al., 2008b). Why some studies showed stimulatory while others demonstrated inhibitory effects of MSCs on MCF-7 cell proliferation is not clear yet. Qiao et al. used human fetal dermal tissue as a source to isolate MSCs for their study (Qiao et al., 2008a). In this case, the different MSC sources may have accounted for the contradictory results. Since MSCs are a heterogeneous population (Uccelli et al., 2008), a different environment may drive the selection of a certain subtype of MSCs with features distinct to the bone-marrow MSC population. In particular, types and amounts of chemokines/cytokines these MSC populations secrete might be different. The importance of environmental conditions for the ability of MSCs to interfere with breast cancer functions is nicely demonstrated in a study that compared serum-exposed MSCs with serum-deprived MSCs (Sanchez et al., 2011). Serum-deprived MSCs were found to be more effective than serum-exposed MSCs in protecting MCF-7 cells from apoptotic death by secreting pro-survival factors. MSCs also modulate the functions of highly aggressive ERα-negative MDA-MB-231 cells (Fig. 3). Two studies demonstrated that MSCs increase the invasive and metastatic behavior of these breast cancer cells (Goldstein et al., 2010; Karnoub et al., 2007). In one study, this effect was found to be mediated by IL-17B (Goldstein et al., 2010). In the other study, the chemokine RANTES/CCL5 was shown to be responsible (Karnoub et al., 2007). Paracrine feedback loops between breast cancer cells and MSCs seem to be important for these effects. It could be shown that MDA-MB-231 cells stimulate the expression of RANTES/CCL5 in MSCs by secreting osteopontin which binds to MSC surface integrins which then leads to the activation of AP-1, a transcription factor able to induce the transcription of the RANTES/CCL5 gene (Mi et al., 2011). MCP-1/CCL2 is another chemokine whose secretion can be stimulated when MSCs are co-cultured with MDA-MB-231 cells (Molloy et al., 2009). MCP-1/CCL2 belongs to those chemokines that enhance the motility of MDA-MB-231 cells. Other migration-promoting chemokines are CXCR3 ligands CXCL9, CXCL10 and CXCL11 (Shin et al., 2010). These CXCL chemokines also increase the activity of Rho GTPases and the expression of MMP-9 (matrix metalloprotease-9). These chemokines may be of particular importance when MSCs are exposed to TNFα which was found to induce CXCL gene transcription through a mechanism involving NF-κB (Fig. 3). One group also demonstrated inhibitory effects of MSCs on MDA-MB-231 cells (Sun et al., 2009; Sun et al., 2010). According to their data, MSCs suppress the proliferative, migratory, tumor-initiating and metastatic activities of MDA-MB-231 cells and induce apoptosis of these cells by interfering with the AKT/mTOR (mammalian target of rapamycin) pathway. Different to the other investigations, these studies were performed with MSCs isolated from human umbilical cord blood or adipose tissue. Hence, as discussed above, source-dependent features of MSC isolates may be responsible for these contradictory results. Also murine metastatic 4T1 breast cancer cells were shown to be affected by MSCs (Ling et al., 2010). Using a syngeneic, immunocompetent murine model, Ling and colleagues demonstrated that murine MSCs enter 4T1 tumors to deliver IFN-β to the tumor. This factor then inhibited cancer growth by inducing the inactivation of STAT3, Src and AKT and by triggering the downregulation of c-Myc and MMP-2 (matrix metalloprotease-2). Interestingly, human MSCs engineered to

secrete IFN-β have also a suppressing effect on growth of MDA-MB-231 cells in mouse xenografts (Studeny et al., 2004). It may well be that the ratio of tumor-suppressing vs. tumor-promoting factors as secreted by MSCs determine whether MSCs promote or inhibit tumor growth. This ratio could be different among different MSC isolates.

4.3 MSCs, EMT and breast cancer stem cells

There is growing evidence that, in accordance with the hierarchical model of cancer development (Visvader & Lindeman, 2008), breast cancer is driven by cancer stem cells (CSCs) (Liu & Wicha, 2010). Breast CSCs are characterized by high expression of surface marker CD44 and low expression of CD24 (Fillmore & Kuperwasser, 2007). Another useful breast CSC marker is ALDH-1 (Ginestier et al., 2007). A recent study showed that MSCs increase the pool of CSCs in breast cancer lines, including MCF-7, SUM149 and SUM159 cells (Liu et al., 2011). Interestingly, bone marrow-derived MSCs themselves show also a hierarchical organization with only a minority of cells expressing the stem cell marker ALDH-1. And only those ALDH-1 positive MSCs were able to interfere with the CSC pool. Wicha and his co-workers showed that the MSC/breast cancer interaction generated a cytokine network which is initiated by IL-6 as secreted by breast cancer cells (Liu et al., 2011). IL-6 induces the production of CXCL7 in MSCs which, in turn, triggers the expression of a number of other cytokines and chemokines, namely IL-6, IL-8, CXCL6 and CXCL5, in both MSCs and breast cancer cells. This mixture of secreted factors then stimulates the expansion of the CSC pool. In line with the observation that MSCs induce the CSC pool to expand is the finding that MSCs stimulated mammosphere formation of normal mammary epithelial cells (Klopp et al., 2010). Evidence has been accumulated suggesting that the generation of mammospheres depends on the presence of mammary stem cells (Dontu et al., 2003). Hence, the number of mammospheres formed is supposed to be a measure of the number of mammary stem cells present (Charafe-Jauffret et al., 2008). A recent study on breast cancer patients support the notion of a link between MSCs and breast cancer stem cells (De Giorgi et al., 2011). It showed that the relative number of disseminated CD44$^+$/CD24$^{low/-}$/ALDH-1$^+$ breast cancer stem cells correlated with the relative number of MSCs in the bone marrow. Recently, it has been found that epithelial cells after having undergone full EMT display stem cell-like characteristics, including expression of CD44 and ALDH-1 (Mani et al., 2008; May et al., 2011). EMT is linked to E-cadherin loss and the expression of mesenchymal markers. As mentioned above, MSCs have been shown to reduce E-cadherin expression or to induce E-cadherin shedding in luminal A-type, epitheloid breast cancer cells, such as MCF-7 and T47D. In T47D, this downregulation of E-cadherin was accompanied with increased expression of mesenchymal markers suggesting that MSCs may induce at least partial EMT of breast cancer cells. Hence, MSCs may not only be able to trigger the CSC pool to expand, but also to force new CSCs to be generated from the pool of non-CSC breast cancer cells by EMT. These MSC-induced new CSCs may have other features than the CSCs of the existing pool and may further contribute to tumor heterogeneity and progression (Visvader & Lindeman, 2008). Another interesting observation is that the gene expression profile of mesenchymal (basal-type) breast cancer cells show similarities to the expression profile of MSCs (Marchini et al., 2010) suggesting that this type of breast cancer cell and MSCs have also common functions. In support of this notion, a recent study showed that mesenchymal breast cancer cells generated by

transformation of human mammary epithelial cells by SV40 T-antigen and forced expression of EMT-inducing proteins had the potential to undergo adipogenic and chondrogenic differentiation. Also, these mesenchymal breast cancer cells were attracted to wounds and tumors, a feature typical for MSCs. The latter observation may shed a new light on a phenomenon called tumor-self seeding (Leung & Brugge, 2009). Tumor-self seeding describes the ability of metastasized cells to circulate back to the primary tumor. Chemoattraction to the primary tumor was shown to be driven by IL-6 and IL-8. As mentioned above, IL-6 is highly active on MSCs and triggers the production of a number of chemokines (Leung & Brugge, 2009). Based on these data, it is tempting to assume that MSCs are also generated from breast cancer cells (Fig. 1) and that these MSCs containing the mutations (and epigenetic changes) of the breast cancer cells they derived from play a role in breast cancer metastasis and tumor-self seeding. Nestin[+] - MSCs have been reported to share with haematopoietic stem cells the same niche in the bone marrow (Mendez-Ferrer et al., 2010). This niche might also be available for breast cancer-derived MSCs and allow these cells to survive in this tissue. An exciting hypothesis would be to assume that, at least in some cases of breast cancer, dormancy (Pantel et al., 2009; Willis et al., 2010) is caused by breast cancer-derived MSCs that are caught in these niches. The niches could fulfill two functions in order to maintain dormancy, preventing the cells from proliferating while, at the same time, protecting them from death-inducing signals. The bone marrow seems to be an attractive tissue for circulating tumor cells to home and form micrometastasis which is an early event in breast cancer development (Pantel et al., 2009). The number of such disseminated breast cancer cells in bone has been linked to prognosis of breast cancer patients. MSCs may also play a role in this early entry of breast cancer cells into bone marrow (Corcoran et al., 2008). MSCs were shown to facilitate the migration of MCF-7 and T47D breast cancer cells across bone marrow endothelial cells *in vitro* and to be in close contact with bone-metastasized breast cancer cells *in vivo*. Evidence was presented that these MSC/breast cancer cell interactions may require the chemokine receptor CXCR4 as well as its ligand SDF-1/CXCL12. Hence, it might be possible that breast cancer-derived MSCs not only would be able to home to the bone marrow and induce tumor dormancy, but also to help other breast cancer cells to enter this tissue and form micrometastasis. The breast cancer cell may not be the only non-stem cell which may be able to convert to an MSC. Vascular endothelial cells have been shown to become MSC-like cells as well as displaying typical MSC features, such as the ability to differentiate to osteoblasts, chondrocytes and adipocytes, upon treatment with ALK2 (activin-like kinase-2), TGFβ2 or BMP4 (bone morphognetic protein-4) (Medici et al., 2010). This suggests that certain non-stem cells under certain conditions can be an additonal source for generating MSCs. These cells may have different features compared to those MSCs that derived from the bone marrow.

4.4 MSCs and carcinoma-associated fibroblasts

Besides differentiating to osteoblast, chondrocytes and adipocytes, MSCs are able to convert to neural cells or to undergo transdifferentiation to different kinds of epithelial cells (Uccelli et al., 2008; Wislet-Gendebien et al., 2005). In tumors, MSCs can also differentiate to the carcinoma-associated fibroblasts (CAFs) (Mishra et al., 2008; Spaeth et al., 2009). These cells are different to normal fibroblasts/myofibroblasts in that they are able to stimulate tumor progression (Olumi et al., 1999) and show higher proliferative and migratory activity (Schor

et al., 1988). Defined as myofibroblasts, CAFs share features with both smooth muscle cells and fibroblasts (Mueller & Fusenig, 2004). CAFs are found in many cancers, including breast cancer (Chauhan et al., 2003), and are linked to tumor invasion and proliferation (De Wever & Mareel, 2003; Tlsty & Coussens, 2006). They are responsible for a phenomenon called desmoplasia and promote angiogenesis and inflammation (Orimo et al., 2005; Tlsty & Coussens, 2006). Interestingly, CAFs secrete factors that are also produced by MSCs. In particular, CAFs and MSCs both secrete IL-6 and SDF-1/CXCL12, cytokines able to induce the proliferation of luminal A-type MCF-7 breast cancer cells (Bhowmick et al., 2004; Fierro et al., 2004; Mishra et al., 2008; Orimo et al., 2005; Sasser et al., 2007b). In addition, both cell types were found to interfere similarly with the response of MCF-7 and MDA-MB-231 breast cancer cells to inhibitors of mTOR and B-RAF (Dittmer et al., 2011). Differentiation of MSCs to CAFs requires the exposure of MSCs to conditioned medium from tumor cells over several weeks (Mishra et al., 2008; Spaeth et al., 2009). Conditioned medium from MDA-MB-231 breast cancer cells and from Skov-3 ovarian cancer cells were similar effective in inducing a MSC/CAF conversion which was accompanied by increased expression of CAF markers, such as tenascin-C, α-smooth muscle actin and IL-6. What are the consequences of this finding? As soon as MSCs enter a tumor, they will be bombarded with a cocktail of cytokines as produced by the tumor cells and may receive additional signals by direct cell-cell contacts. This may then force MSCs to lose their stemness and to undergo differentiation towards CAFs. By converting to CAFs, MSCs may not further be able to act also suppressive on tumor cells and may only keep their potency to promote tumor progression. Hence, the differentiation of MSCs to CAFs may be as much of a benefit for a progressing tumor as is the differentiation of MSCs to particular cells for an injured tissue to be repaired (Dittmer, 2010).

5. Conclusions

MSCs display an astounding plasticity and have shown to differentiate to cells as different as neurons and epithelial cells. The main function of MSCs is likely to promote tissue regeneration after injuries and, since tumors are probably wounds that never heal, also to support repair of tumoral lesions. However, tumors may misguide MSCs and "misuse" them for their "own benefit". Primary tumors may particularly profit from MSCs when they differentiate to tumor-promoting CAFs. MSCs may further facilitate breast cancer to metastasize by helping breast cancer cells to enter the bone marrow as well as by increasing the pool of metastasizing breast cancer stem cells. Most of the interactions between MSCs and tumor cells are mediated by cytokines as secreted by both cell types. Paracrine feedback mechanisms may further increase cytokine concentrations at places where these cells communicate with each other and may attract other cell types, such as macrophages, that are known to support tumor progression. To interfere with the interaction between MSCs and breast cancer cells treatments may be considered involving the inhibition of the activities of key cytokines, such as IL-6 (Liu & Wicha, 2010), which are important for both attraction of MSCs to breast cancer and expansion of the breast cancer stem cell pool by MSCs. On the other hand, there is also evidence that MSCs may have suppressive effects on breast cancer. Different sources from which MSCs were isolated may partially account for these contradictory results. Further studies are necessary to clarify this controversy, before conclusions can be drawn in terms of treatment of breast cancer patients. Certainly, when

engineered to produce anti-tumor factors, MSCs possess anti-tumoral effects and may be used as trojan horses that enter and eradicate tumor cells. Drug-carrying MSCs may have a great advantage over "naked" drugs since they may deliver drugs more selectively and more efficiently at places where they are meant to act.

6. Acknowledgment

7. References

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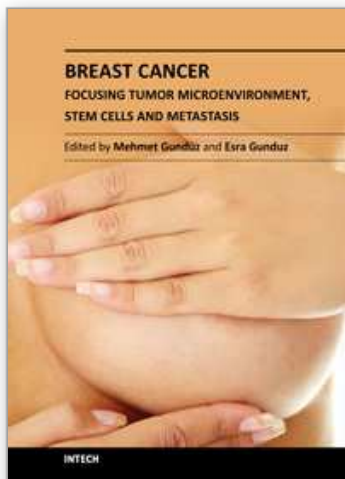
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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