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## Mesenchymal stem cell secretome and regenerative therapy after cancer

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### Abstract

Cancer treatment generally relies on tumor ablative techniques that can lead to major functional or disfiguring defects. These post-therapy impairments require the development of safe regenerative therapy strategies during cancer remission. Many current tissue repair approaches exploit paracrine (immunomodulatory, pro-angiogenic, anti-apoptotic and pro-survival effects) or restoring (functional or structural tissue repair) properties of mesenchymal stem/stromal cells (MSC). Yet, a major concern in the application of regenerative therapies during cancer remission remains the possible triggering of cancer recurrence. Tumor relapse implies the persistence of rare subsets of tumor-initiating cancer cells which can escape anti-cancer therapies and lie dormant in specific niches awaiting reactivation via unknown stimuli. Many of the components required for successful regenerative therapy (revascularization, immunosuppression, cellular homing, tissue growth promotion) are also critical for tumor progression and metastasis. While bidirectional crosstalk between tumorigenic cells (especially aggressive cancer cell lines) and MSC (including tumor stroma-resident populations) has been demonstrated in a variety of cancers, the effects of local or systemic MSC delivery for regenerative purposes on persisting cancer cells during remission remain controversial. Both pro- and anti-tumorigenic effects of MSC have been reported

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in the literature. Our own data using breast cancer clinical isolates have suggested that dormant-like tumor-initiating cells do not respond to MSC signals, unlike actively dividing cancer cells which benefited from the presence of supportive MSC. The secretome of MSC isolated from various tissues may partially diverge, but it includes a core of cytokines (i.e. CCL2, CCL5, IL-6, TGF $\beta$ , VEGF), which have been implicated in tumor growth and/or metastasis. This article reviews published models for studying interactions between MSC and cancer cells with a focus on the impact of MSC secretome on cancer cell activity, and discusses the implications for regenerative therapy after cancer.

## Keywords

Mesenchymal stem/stromal cells; regenerative therapy after cancer; cancer recurrence; tumor-initiating cells

## 1. Introduction

Cancer treatment often relies on non-selective tumor ablative techniques that can result into severe functional impairments or disfiguring damages. Cellular therapy using hematopoietic stem cells (HSC) is already well established to rescue the bone marrow from the massive cytotoxic effects associated with dose-intensive treatment of hematologic malignancies. The emergence of regenerative medicine strategies using non-HSC populations offers comparable alternatives to restore other organ functions and rebuild excised tissues after cancer surgery. Mesenchymal stem/stromal cells (MSC) exhibit a set of pro-regenerative features (multi-lineage differentiation capacity, homing to sites of injury and inflammation, and paracrine immunomodulatory, pro-angiogenic, anti-apoptotic and pro-proliferative effects, Figure 1) that make them an attractive candidate for modulation of immune disorders and regenerative therapy approaches [1–3]. Unfortunately, the tumor and wound microenvironments share a lot of similarities [4] and MSC have been shown to similarly respond to tumor-associated inflammatory signals and home to malignant sites [5]. While this MSC tumor tropism has been encouragingly exploited to develop tumor targeting strategies [6], it also indicates that caution is required when delivering MSC to cancer-surviving patients for regenerative purposes [7–9]. A number of studies have stressed the *in vivo* recruitment of MSC by pre- or co-injected cancer cell lines in a variety of animal models and the subsequent promotion (or inhibition) of either tumor growth or metastasis (Table 1). This review outlines the conflicting data currently available in the literature from *in vitro* and *in vivo* models of cancer cell-MSC interactions with an emphasis on MSC-secreted factors and their role on tumor development. We discuss the potential impact of these interactions under regenerating conditions.

## 2. MSC and regenerative therapy after cancer

The attractiveness of MSC for cell-based regenerative therapies relies not only on their capacity to differentiate into multiple mesenchymal lineages [10], but also on the delivery of various paracrine signals responsible for chemoattractant, immunomodulatory, angiogenic, anti-apoptotic, anti-scarring, and pro-survival effects [11]. Yet, the same MSC-secreted factors that accompany tissue regeneration and revascularization have also been linked to the promotion of cancer growth and metastasis (Figure 1) [7]. The safety of bone marrow (BM)-derived MSC (BM-MSC) was assessed in clinical trials in 1995 [12] and MSC-based strategies were subsequently introduced for regenerative trials for bone [13, 14] and cartilage [15] defects, or immunomodulation of graft versus host disease [16, 17], autoimmune disease [18] and stroke [19]. HSC transplantation was widely used in the 1990s to rescue the hematopoietic system of breast cancer patients undergoing intensive

chemotherapy [20]. This strategy was ultimately abandoned because no significant therapeutic effect could be demonstrated over conventional therapies. However, the co-administration of MSC and HSC in breast cancer patients significantly accelerated the restoration of the hematopoietic compartment [21]. Several studies have investigated the effects of BM-MSC and HSC co-transplantation to facilitate engraftment or reduce graft-versus-host disease into patients treated for hematopoietic malignancies [16, 22, 23]. Autologous BM-MSC were also delivered in a fibrin spray to accelerate wound healing in patients with acute wounds including skin cancer surgery-induced lesions [24], and our group has recently validated *in vitro* an analogous strategy using unpassaged adipose-derived MSC [25]. Intrabone and systemic delivery of MSC has been tested in a multiple myeloma animal model for simultaneous inhibition of tumor growth and regeneration of bone lesions [26].

Another MSC-based approach currently under consideration for regenerative therapy after cancer is cell-assisted soft tissue reconstruction for patients treated for head and neck or breast cancer [7]. Cosmetic restoration after disfiguring surgical tumor excision remains an important part of the treatment. Soft tissue reconstruction after breast cancer was pioneered in late 19<sup>th</sup> century by Czerny [27] and could provide satisfactory short-term cosmetic results, but remained flawed mainly due to poor long term volume retention [28, 29]. Recently, MSC-assisted autologous fat transfer approaches for soft tissue reconstruction have been developed and have been shown to enhance graft survival and local angiogenesis to sustain stable, functional and natural appearance [7].

### 3. Models of MSC-tumor cell interactions

A list of currently published studies examining interactions between MSC and cancer cells is summarized in Table 1. Most investigators relied on established cancer cell lines rather than clinical isolates to mimic tumor behavior in epithelial, hematopoietic and mesenchymal cancers. These studies exposed a variety of cell-cell and paracrine interactions (including both pro- and anti-tumor activities) relying primarily on breast cancer cell lines and MSC isolated mostly from human BM and adipose (Table 1). These studies are sometimes contradictory, and MSC can be shown to either promote or inhibit tumor progression within the same cancer model (Table 1), occasionally using identical cancer cell lines. For example, human adipose-derived MSC support proliferation of the glioma cell line U87MG *in vitro* and tumor growth *in vivo* [30], while human umbilical cord-derived MSC were shown to be cytotoxic to the same line in a separate publication [31]. Such discrepancies are even more evident in studies of MSC interactions with epithelial cancers. MSC interactions can vary tremendously depending on numerous factors, including MSC tissue of origin, cancer type and model, pre-treatment of MSC using cytokines or small molecules, and a variety of *in vitro* and *in vivo* system-related discrepancies, including the relative number of both MSC and cancer cells, simultaneous or individual injection of MSC and cancer cells, local versus systemic MSC delivery or the kinetics of tumorigenesis. Human BM- and adipose-derived MSC were demonstrated to respectively promote and inhibit the *in vitro* proliferation of the breast cancer cell line MCF7, as well as the *in vitro* survival or *in vivo* growth of the PC3 prostate cancer line [32–36]. BM-MSC and foreskin-derived MSC respectively promoted and inhibited SGC-7901 gastric cancer growth *in vivo* [37, 38]. Lung cancer models using the identical cancer cell line (A549) or similar Lewis tumors revealed diverging effects of MSC on either tumor *in vitro* proliferation or *in vivo* growth [38–41]. These inconsistencies can even be detected using both the same source of MSC and cancer cell line (BM-MSC pro- and anti-proliferative effects on breast cancer MDA-MB-231 line [32, 42] or pro- and anti-tumor growth *in vivo* with the prostate cancer PC3 line [35, 36]). Some authors preferred using immortalized MSC lines, which could also affect the outcomes, as mouse BM-MSC had no effect on the proliferation of the multiple myeloma cell line RPMI8226,

whereas the mouse C3H10T1/2 line exerted potent inhibitory activity [39, 43]. Co-implantation of rat BM-MSC with COS1NR osteosarcoma cells accelerated early onset of tumor growth, but not metastasis, whereas intravenous MSC injection did increase the number of metastatic nodules without affecting tumor growth [44]. Finally, some authors emphasized aberrant behavior of MSC isolated from cancer clinical isolates, compared with healthy BM- or adipose-derived MSC [45].

### 3.1. How to model regenerative therapy after cancer?

MSC selection techniques can vary in the literature, but plastic adherence is typical and considered axiomatic [46]. This crude selection method does not exclude heterogeneity of MSC sources within a single tissue (e.g. adipose) [47–49] or persistence of hematopoietic lineages at early passages (e.g. macrophages) [50, 51]. Although all MSC populations share basic similarities immunophenotypically and functionally, differences can be demonstrated using high resolution techniques [52, 53] and are reflected in variability within their secretome [7, 54]. A growing number of studies have developed models to study MSC-tumor interactions (Table 1). Only a few groups have investigated these interactions using clinical isolates [26, 45, 51] (including ours) which may be more relevant to the *in vivo* tumor heterogeneity than homogeneous cancer cell lines. The source of MSC in these studies can vary tremendously, including differences of species (human, mouse, rat, rabbit) and tissue of origin (i.e. normal bone marrow, umbilical cord, placenta, subcutaneous, omental and breast adipose, or cancer tissue). Some authors relied on immortalized MSC lines (mouse C3H10T1, human fetal derm Z3 and rat MCP1cE), but most studies employed the two most prevalent MSC currently used in clinical practice: human BM and subcutaneous adipose (SA) –derived MSC. Dissimilarities between BM-MSC and adipose-derived MSC (termed adipose-derived stem/stromal cells or ASC), have already been reviewed in [55].

**3.1.1. MSC variability**—Multipotent MSC were originally isolated from bone marrow [10] and have been defined as a plastic-adherent fibroblastic cell population, exhibiting a defined immunophenotype (e.g. expression of CD73, CD90, CD105 and lack of expression of hematopoietic/endothelial markers), and capable of clonal differentiation towards mesenchymal lineages (e.g., adipogenic, osteogenic and chondrogenic lineages) [46]. Similar mesenchymogenic populations have been isolated from the connective tissue of multiple tissues [56], including adipose [57]. Recent studies have unraveled transcriptomic, proteomic or epigenomic [53, 58–60] disparities between tissue-specific MSC, which may mark some degree of niche-associated bias. The inherent heterogeneity of the pool of mesenchymogenic progenitors participating in the MSC activity of each tissue can be reflected by some disparities measured at the secretome level [7, 54]. Yet, it seems that shared sources of MSC, such as the ubiquitous pericytes, retain functionality across discrete niches. CD146+ perivascular cells, or pericytes, represent a ubiquitous source of MSC throughout various organs [61, 62], whereas other more specialized progenitor populations may contribute to MSC activity in tissues such as fat [47–49]. CD146+ BM-resident subendothelial cells are *in vivo* precursors of BM-MSC and can organize the hematopoietic niche via their secretome (i.e. release of Angiopoietin-1) and support adult HSC [63]. This presumably BM-specific function is retained by non-medullar sources of MSC such as adipose [64], although this activity seems to be restricted to the CD146+ pericytic source of ASC [65]. Inversely, ASC secrete adipose-specific factors, such as leptin and adiponectin [7], which are not shared with BM-MSC, and may reflect heterogeneity and/or specialization within the pool of adipose progenitors [66]. The bulk of MSC-secreted factors comprises a common core, independently of their tissue of origin, including an overlapping set of anti-apoptotic, immunomodulatory, anti-scarring, supportive, angiogenic and chemoattractant factors such as interleukin-6 (IL6), chemokine C-C motif ligand 2 (CCL2), PAI-1,

transforming growth factor-beta1 (TGF  $\beta$ 1), CD106 and vascular endothelial growth factor (VEGF) [11, 67]. A few studies have compared the effects of distinct MSC populations in cancer models. Both BM-MSC and adipose-resident cells have been shown to be recruited to sites of ovarian tumors, where BM-MSC preferentially give rise to tumor-associated fibroblasts (TAF) while the adipose stroma contributes to vascular/fibrovascular lineages [68]. Yet, both BM-MSC and subcutaneous adipose-derived MSC can acquire a TAF phenotype in presence of ovarian cancer cells [69]. Breast-derived ASC are potent activator of basal-type breast cancer progression and invasiveness [70] via secretion of specific factors (Matrix metalloproteinase-1 (MMP1), MMP3) not expressed by BM-MSC. Adipose tissue is distributed in multiple depots, which may have distinct developmental origins and visceral fat possesses potent inflammatory activity. Klopp et al. compared the behavior of BM-MSC, visceral and subcutaneous ASC [54] in both *in vitro* and *in vivo* studies of endometrial cancer. Both BM-MSC and omental-ASC displayed robust tumor-homing, pro-angiogenic (including higher pericyte coverage), extra-cellular matrix (ECM)-remodeling and pro-proliferative activities *in vivo*. While the tumor proliferation enhancing effects of omental ASC were confirmed *in vitro*, BM-MSC seemed to display an opposite behavior in co-culture experiments. Surprisingly, subcutaneous ASC did not display any significant effect for all pro-tumoral activities [54]. Omental ASC were also the only MSC population to protect cancer cells from necrosis *in vivo*. Szebeni et al analyzed mouse BM-MSC and subcutaneous ASC interactions with breast cancer and melanoma *in vivo* models [71], but did not report any divergent effects on tumor growth, vascularity and metastasis support. In another study, human cord blood-derived MSC and breast-derived ASC exhibited a similar behavior when injected intravenously in a breast cancer model, including tumor tropism and inhibition of both tumor growth and metastasis [72]. A multiple myeloma model revealed minor differences between mouse and human BM-MSC in the presence of tumor cells, although both populations contributed to tumor growth augmentation [43]. Both mouse and human ASC have been shown to support the growth of breast cancer cell lines [73] and any direct distinction between species remains to be investigated.

**3.1.2. Tumor effects on MSC**—Some authors have also analyzed the effects of tumor-derived MSC populations [45, 74, 75] on cancer progression. Evidence has been accumulating concerning the existence of deranged tumor-resident MSC isolated from several cancers including multiple myeloma [76–80], breast cancer [81], liver cancer [74] and ovarian cancer [45, 75, 82]. The tumor-supporting properties of MSC (immunomodulation, angiogenesis, cell survival or migration) often seem to be enhanced in tumor-derived MSC populations [45, 74, 75]. For instance, human ovarian cancer-derived MSC showed higher pro-tumor growth activity than normal human BM-MSC and ASC, promoting the acquisition of a phenotype resembling putative cancer stem cells (CSC) [45], in support of local tumor-MSC crosstalk leading to specialized tumor-resident MSC populations. Both BM- and adipose-derived MSC display tumor tropism due to various tumor-released chemotactic factors including CCL25 [43], C-X-C motif chemokine-1 (CXCL1) [54], epidermal growth factor (EGF) [83, 84], hepatoma-derived growth factor (HDGF) [85], IL-8 [54], platelet-derived growth factor (PDGF) [84], stromal cell-derived factor-1 (SDF1, a.k.a. CXCL12) [86, 87], TGF  $\beta$  [88], and VEGF [84]. Recruited tumor-resident MSC populations or their direct progeny (i.e. TAF, myofibroblasts) often possess augmented ability to promote tumor growth [45, 75, 77, 82] and invasion [74, 75] compared with healthy donor MSC via superior angiogenesis [75, 77, 80, 82, 89], or abnormal immunomodulation [76, 79, 81], resulting in increased release of cytokines/growth factors including hepatocyte growth factor (HGF) [80, 82], IL-6 [76, 77, 79, 82], IL-10 [81], fibroblast-specific protein-1 (FSP1, a.k.a. S100A4) [74], TGF  $\beta$  [79, 81] and VEGF [75, 80, 82] by tumor-resident MSC.

**3.1.3. Tumor-initiating cells**—Hematopoietic rescue by autologous blood or bone marrow transplantation following high dose chemotherapy is possibly the most exploited strategy to treat hematologic malignancies and can achieve significant clinical responses, but does not invariably prelude future cancer relapse. Similarly, therapy for epithelial cancers such as breast cancer is rarely curative and cancer recurrence remains a significant cause of mortality after induction of successful and often durable remissions. Late recurrence is well documented and provides direct evidence for the persistence of tumor-initiating cells at a subclinical level, referred as cancer dormancy. The cell cycle state (quiescent or homeostatic) of dormant cancer cells and their reactivation after a symptom-free interval remain both poorly understood. Tumor-initiating cells, often referred as CSC, are restricted to specific tumor subsets within the heterogeneous bulk of malignant cells in several cancers, and are characterized by the expression of markers originally associated with normal stem/progenitor cells. These include CD44, CD90, CD117, and CD133 [90]. While cancer dormancy depends on the sub-clinical persistence of rare tumor-initiating cells, the CSC paradigm might offer clues to how tumor subsets may escape anti-cancer therapies [91, 92]. *In vitro* cellular models of cancer dormancy [93–96], CSC [97], or other tumor-initiating cells possibly involved during cancer relapse remain poorly established and only rare studies rely on the purification of resting subsets of tumorigenic cells akin to the cells involved during relapse [51]. Dormant and active breast cancer cells possess distinct genome-wide expression signature, especially angiogenesis-related genes [96] and our own published work support that resting and active tumor-initiating breast cancer cells respond differently to MSC signals [51]. Our *in vivo* xenograft approach relied on an animal model utilizing unpassaged sort-purified breast cancer clinical isolates injected in limited number and resulting in small (5–10mm<sup>3</sup>) tumors developing 6 or more months after injection. Breast tumor-initiating activity is enriched in the CD44+CD24-CD326+ fraction of breast cancer cells, which was originally shown to contain both quiescent and actively proliferating cells [98]. We previously refined the breast cancer tumor-initiating activity to a CD90+ subset of CD44+ cells [99], which is localized at the invasive front in breast cancer tumors [90]. Small (low light scatter) resting CD90+ breast cancer cells give rise to tumors with high efficiency (<100 cells/injection) [90, 99], independently of supportive stroma/ASC [51]. Large (high light scatter) CD90+ tumor-initiating cells include a large number of dividing/aneuploid cells and are only tumorigenic at higher dose (>600 cells) [90, 99], although co-injection with ASC can rescue their tumorigenic potential at lower dose (100 cells) [51]. Importantly, our *in vivo* mouse model displayed tumor growth kinetics and incidence similar to dormant cancer cell line models [93–96], in contrast to studies relying on aggressive cancer cell lines and resulting often into >100mm<sup>3</sup> tumors less than a month after implantation [7]. Models using aggressive cell lines have little relevance to regenerative therapy after cancer, but may be more appropriate for evaluating potential suppressive effects of MSC on rapidly growing high-grade therapy unresponsive tumors.

#### 4. The MSC secretome and cancer cells

MSC can be mobilized and recruited to active tumor sites, where they can incorporate into the tumor's microenvironment [5, 68, 100–103]. There they can potentiate further tumorigenesis via differentiation into tumor-nurturing stroma (TAF, myofibroblasts) [82, 104], direct cell contact interaction with cancer cells [105, 106] or release of paracrine factors (Table 2). Tumor-MSC interactions studies have revealed MSC tumor-supporting paracrine activities (local immunosuppression and angiogenesis, promotion of tumor growth and invasion (i.e. acquisition of epithelial-mesenchymal transition (EMT)/CSC phenotype or ECM remodeling), inhibition of tumor apoptosis or necrosis) in a large spectrum of cancers (Table 1). Table 2 summarizes published MSC-secreted factors that have been identified during MSC-cancer cell interactions and their reported effect on cancer cells. Several cytokines usually involved during MSC-mediated tissue regeneration (e.g. IL-6, TGF ,

VEGF) are secreted at elevated levels by MSC upon recruitment by cancer cells and support actively growth or invasion of cancer cells. As mentioned previously, the exact role(s) that MSC play in the modulation of tumor cell growth remains controversial [7–9] and release of some factors such as DKK1 can inhibit the proliferation of hematopoietic cancer cells [33, 43, 77]. Pro-tumorigenic effects of MSC can be inhibited by pretreatment of MSC with imatinib (PDGF-receptor inhibition) [107], gefitinib (EGFR inhibition) [83] or interferon-gamma (INF ) [108] while some preconditioning treatment (hypoxia, irradiation, genetic engineering) enhance MSC migratory and pro-tumoral activities [32, 109–111]. Obesity may also accelerate tumor growth, via an increased endogenous ASC reservoir, which directly contribute to sustain the tumor microenvironment [112]. IL-6 is an MSC-secreted inflammatory cytokine displaying pro-survival, pro-growth and pro-angiogenic activities [11], which has been implicated in tumor progression of various cancers including breast cancer [113, 114]. Secretion of elevated levels of IL-6 by MSC has been detected upon interaction with malignant cells in several epithelial, hematopoietic and mesenchymal cancers (Table 2) [43, 69, 76, 77, 82, 115–119]. In these studies, MSC-released IL-6 supported tumor growth by stimulating cancer cell proliferation and survival or protecting from apoptosis. BM-MSc and ASC could also potentiate cancer cell migration, invasion and metastasis via the release of IL-6 in the tumor microenvironment [116, 120]. BM-MSc and ASC can also secrete a combination of anti-apoptotic and angiogenic factors [121], including HGF, SDF-1/CXCL12, CD106 (sVCAM) and VEGF which can promote tumor growth, local angiogenesis and metastasis [42, 84, 122–127]. Secretion levels of some cytokines, such as VEGF, can vary depending on the tissue from which MSC are derived. Subcutaneous adipose-derived MSC populations seem to secrete lower level of VEGF than BM-MSc [7, 54] or visceral ASC [54]. The monocyte chemoattractant protein-1 (MCP1) or CCL2 is commonly detected among MSC secreted cytokines/chemokines [7, 128]. Although not reported in direct tumor cell-MSc interaction studies (Table 2), MCP1 can be secreted by stromal [129] or tumor cells (to recruit MSc [130] and macrophages). MCP1 is a critical chemoattractant responsible for the recruitment of macrophages into tumor and for angiogenesis in breast cancer [131, 132], and may contribute to indirect crosstalk between MSc and cancer cells via recruitment of tumor-resident macrophages. The immunosuppressive activity of MCP1 has been implicated in the progression and metastasis of cancer in animal models of skin papilloma [133], colon carcinoma [134], prostate cancer [135], breast cancer [136, 137] and lung cancer [138]. MSc-mediated immunosuppression activity has been shown to be modulated via tumor necrosis factor-alpha (TNF ) [139]. MSc have also been shown to release elevated levels of TGF upon interaction with breast and prostate cancer [32, 35, 81], resulting into stimulation of the proliferative and migratory capacities of the cancer cells. The implication of TGF signaling in promotion of tumor invasion and metastasis [140] via EMT [141] is well established. Another MSc-secreted pro-metastasis cytokine, CCL5 (RANTES), can be secreted upon interaction with cancer cells and is associated with tumor progression and invasion in various cancers [73, 87, 100, 142–144]. CCL5 can be secreted by both BM-MSc and ASC [100, 144] and displays pro-proliferative activities on breast cancer cell lines [145, 146]. Other MSc-secreted factors upregulated during interactions with cancer cells and exhibiting potent effect on tumor cells include BMP2, CXCL1, CXCL5, CXCL6, CXCL7, EGF, IL4, IL8, IL10, IL17b or S100A4.

## 5. Summary and conclusions

Early cancer recurrence following hematopoietic or epithelial cancer treatment is often characterized by very aggressive active disease [7], a clear contraindication to regenerative reconstructive therapy. On the other hand, patients with responsive disease who enter clinical remission are nonetheless at risk for late relapse, implying the persistence of a distinct population of dormant cancer-initiating cells. While bi-directional cross-talk between MSc and aggressive cancer cells is well documented, specific interactions between

MSC and dormant-like tumor-initiating cells remain poorly established. A non-obvious parallel comes from our experience in cellular reprogramming of myeloid progenitors to pluripotency [147]. Many of the same reprogramming elements are shared between pluripotency and tumorigenicity [148] and the most commonly used reprogramming factors for induced pluripotent stem cell (iPSC) technology are known oncogenes (MYC) or have been directly linked to tumorigenicity in a variety of human cancers (NANOG, SOX2, OCT4) [148]. Indeed, non-tumorigenic epithelial mammary cells have been shown to be induced with CSC activity via cellular reprogramming [149]. Interestingly, hematopoietic progenitors seem to be more amenable to cellular reprogramming than conventional stem cells [150] and we have demonstrated that MSC co-cultured with actively dividing myeloid progenitor cells facilitate their acquisition of induced pluripotency, via both cell-cell contacts and release of multiple cytokines and growth factors [147]. These studies illustrate differential reprogramming behavior of progenitor and stem cell populations and confirm that MSC cross-talk with progenitor populations can potentiate their cellular fate.

Cancer cells can display fluctuating levels of stem-like activities [151]. In fact, MSC may exert distinct effects on tumor-initiating cell populations according to their degree of stemness. This may result into promotion of a pro-resting CSC niche [152, 153] for the most therapy-resistant stem-like cells, or recruitment and promotion of tumorigenesis for more active progenitor cells. Our previously published *in vivo* breast cancer model provides the only available data on the interaction of adipose-derived MSC with tumor cell subsets sorted from unpassaged clinical isolates. A basic comparison of the major cytokines, chemokines and growth factors secreted by ASC revealed a close correspondence to the secretome of BM-ASC, including the major cytokines implicated in promotion of tumor growth, such as IL-6. Although levels of VEGF secreted by ASC were moderate, we could still detect the development of human blood vessels within tumor xenografts coinjected with human ASC. The effects of a few secreted factors unique to adipose derived MSC, such as leptin and adiponectin, remain unclear, although, leptin has been associated with tumor progression in breast cancer [154]. Engraftment and tumorigenesis of active tumor cells significantly benefited from the coinjection of ASC. Yet, resting cells were not responsive to local ASC signals, although they were consistently able to generate tumors from a limited number of injected cells. We could not detect differences (size, histology) between tumors generated by active and resting tumor-initiating cells.

Taken together, the secretome of MSC exert potent tissue remodeling effects. The results from multiple laboratories suggest that the effects of MSC on tumor cells are multiple and may depend on the state of the tumor cell, the properties of specific MSC populations, and interactions with other cell types, such as tumor infiltrating immune cells..

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## Abbreviations

**ASC** adipose-derived stem/stromal cells



<b>BA</b>	breast adipose
<b>BM</b>	bone marrow
<b>CCL</b>	chemokine C-C motif ligand
<b>CSC</b>	cancer stem cells
<b>CXCL</b>	C-X-C motif chemokine
<b>ECM</b>	extra-cellular matrix
<b>EGF</b>	epidermal growth factor
<b>EMT</b>	epithelial-mesenchymal transition
<b>FSP1</b>	fibroblast-specific protein-1
<b>HDGF</b>	hepatoma-derived growth factor
<b>HGF</b>	Hepatocyte growth factor
<b>HSC</b>	hematopoietic stem cells
<b>IL-6</b>	interleukin 6
<b>INF</b>	interferon-gamma
<b>IPSC</b>	induced pluripotent stem cell
<b>MCP1</b>	monocyte chemoattractant protein-1
<b>MMP</b>	matrix metalloproteinases
<b>MSC</b>	mesenchymal stromal/stem cells
<b>OA</b>	omental adipose
<b>PDGF</b>	platelet-derived growth factor
<b>SA</b>	subcutaneous adipose
<b>SDF1</b>	stromal cell-derived factor-1
<b>TAF</b>	tumor-associated fibroblasts
<b>TGF</b>	transforming growth factor-beta
<b>TNF</b>	Tumor necrosis factor-alpha
<b>UC</b>	umbilical cord
<b>VEGF</b>	vascular endothelial growth factor

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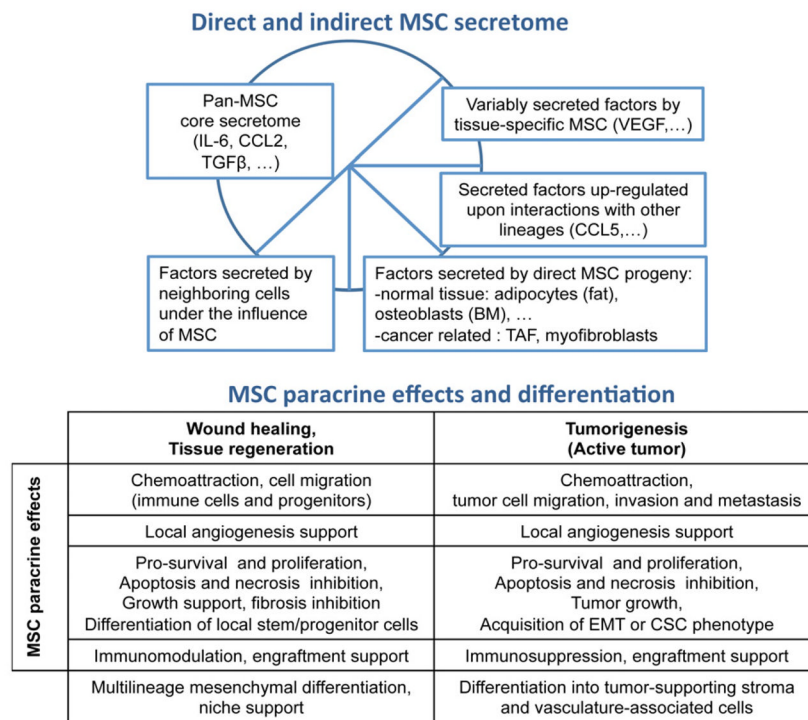
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### Highlights

- MSC regenerative potential relies in part on paracrine activities.
- MSC secretome can interact with tumor-initiating cancer cells.
- Same MSC signals are involved in regenerative and pro-cancer activities.
- Dormant cancer may not respond to the same signals as active malignant tumor.

**Figure 1.**

MSC paracrine activity and incidence on oncogenesis. MSC exert paracrine interactions by a combination of direct (MSC-secreted) and indirect (released by MSC differentiated progeny or neighboring cells) secreted factors. MSC can secrete a large array of cytokines, chemokines and growth factors natively or upon interactions with other cell types. According to the MSC tissue of isolation, levels of MSC secreted factors may vary. MSC secretome shares similar activities during wound healing and interactions with active tumor, including pro-migratory, pro-angiogenic, pro-proliferative, anti-apoptotic and immunosuppressive effects. MSC can also affect the cellular fate of surrounding cells (including tumor cells) and their state of differentiation. Upon interactions with cancer cells, MSC may promote acquisition of pro-tumorigenic CSC activity, or pro-invasion epithelial-to-mesenchymal transition. While MSC multilineage differentiation capacity is a great advantage for regenerative purposes, MSC may also directly support tumor progression by replenishing the local stroma (tumor-associated fibroblasts) or supporting the development of the tumor vasculature (pericytes/myofibroblasts). While the effects of MSC on active tumor seems to mimic wound healing activities, interactions with resting tumor-initiating cells involved during delayed cancer relapse is still poorly characterized.

Table 1

*In vitro* and *in vivo* studies of interactions between MSC and cancer cells.

	cancer	cell lines or clinical isolates	MSC source	<i>in vitro</i>	<i>in vivo</i>	references
	bladder cancer	VX2	rabbit BM		pro-growth, pro-angiogenic	[155]
	breast cancer	4t1, Eo771, HMLER, MCF7, MDA-MB-231, MDA-MB-435, SK-BR-3, SUM149, SUM159, T47D, spontaneous tumor, clinical isolates	human BM, human SA, human BA, human UC, mouse BM, mouse SA, rat BM	tumor tropism, anti- or pro-proliferation or no effect, pro-apoptotic or no effect on survival, anti- or pro-migration or no effect, pro-invasion, pro-CSC or EMT phenotype	tumor tropism, pro-engraftment or no effect, anti- or pro-growth, anti- or pro-proliferation or no effect, pro-apoptotic, pro-angiogenic, source of TAF, pro-invasion, anti- or pro-metastasis or no effect, pro-CSC phenotype	[32-34, 51, 68, 71-73, 85, 88, 100, 112, 115, 116, 144, 156-159]
	cervical cancer	HeLa	human SA	no effect on survival		[34]
	colon cancer	Caco-2, COLO 320DM (CC3), H1D2, KM12SM, MC38, SW480	human BM, human SA, mouse BM, rat BM MCP1cE line	tumor tropism, anti-proliferation or no effect, anti-survival, pro-angiogenic, pro-migration, pro-invasion	tumor tropism, pro-engraftment, anti- and pro-growth, pro-proliferation, anti-apoptotic, immunomodulation, pro-angiogenic, pro-invasion, pro-metastasis, pro-necrosis	[34, 38, 41, 160-163]
	endometrial cancer	Hec1a	human BM, human OA, human SA	tumor tropism, anti- or pro-proliferation or no effect	tumor tropism, pro-growth or no effect, pro-proliferation, pro-angiogenic, ECM remodeling, anti-necrosis	[54]
Epithelial	gastric cancer	SGC-7901, spontaneous tumor	human BM, human foreskin, mouse BM	anti-proliferation or no effect, pro-apoptotic, pro-angiogenic, pro-migration, pro-EMT	pro-engraftment, anti- and pro-growth, anti- and pro-proliferation, pro-apoptotic, pro-angiogenic	[37, 38, 89]
	liver cancer	H7402, HepG2, HuH7, MHCC97L, H22	human SA, human fetal derm Z3 line, human liver cancer, mouse BM	anti- or pro-proliferation, pro-apoptotic, anti-survival, pro-invasion	anti- or pro-growth, pro-metastatic	[34, 74, 164, 165]
	insulinoma	INS-1	mouse BM	anti-proliferation		[165]
	lung cancer	A549, H460, Lewis, UCH10 (small cell lung cancer)	human BM, human SA, mouse SA, mouse C3H10T1 line	anti- and pro-proliferation or no effect	anti- or pro-growth, anti-apoptotic, pro-angiogenic, anti-metastasis	[30, 38-41, 108, 112]
	melanoma	A375SM, B16	human BM, mouse BM, mouse SA, mouse C3H10T1 line	anti- or pro-proliferation, immunosuppression	tumor tropism, pro-growth, pro-engraftment, anti-metastasis	[39, 40, 71, 166, 167]
	ovarian cancer	A2780, Hey1, ID8, IGROV-1, OVCAR3, SKOV3, primary cultures	human BM, human SA, human ovarian cancer, mouse BM, mouse C3H10T1 line	pro-proliferation or no effect, pro-angiogenic, source of TAF, increase CSC phenotype, pro-migration, pro-invasion	pro-growth, pro-angiogenic, pro-invasion, pro-metastasis, source of TAF	[39, 45, 68, 69, 75, 82, 120]

	cancer	cell lines or clinical isolates	MSC source	<i>in vitro</i>	<i>in vivo</i>	references
Hematopoietic	pancreatic cancer	BxPC-3, Capan-1, Capan-2, Colo-357, MIA-Pa-Ca2, Panc-1	human BM, human SA	tumor tropism, anti-proliferation, anti-survival, pro-necrosis, no effect on apoptosis	tumor tropism, anti-growth, anti-proliferation, pro-angiogenic, pro-apoptotic	[34, 84, 168]
	prostate cancer	LNCaP, MDA-Pca-118b, PC3, TRAMP-C2	human BM, human SA, mouse BM, mouse C3H10T1 line	tumor tropism, anti- and pro-survival, pro-proliferation or no effect, pro-migration, pro-invasion, ECM remodeling, chemoresistance	tumor tropism, anti- or pro-growth or no effect, pro-angiogenesis, anti-metastasis, pro-necrosis	[34-36, 39, 86, 106, 119, 169, 170]
	renal cancer	Renca	mouse C3H10T1 line	no effect on proliferation	pro-engraftment, pro-proliferation, immunomodulation, no effect on metastasis	[39]
	AML	HL60, KG1a	human BM, human SA	anti-proliferation		[33, 41]
	CML	BV173	human BM	anti-proliferation, anti-apoptotic	pro-growth	[41]
	Erythroleukemia	K562	human BM, human SA	anti-proliferation	anti-proliferation	[33, 41]
	transformed B cell line	wS9-B-LCL	human BM	anti-proliferation		[41]
	lymphoma	BJAB, Daudi, EL-4, Raji, SKW6.4, U937, YAC-1	human BM, mouse BM, mouse C3H10T1 line	anti- or pro-proliferation, anti- or pro-apoptotic or no effect, pro-angiogenic	pro-engraftment, anti- or pro-growth, pro-proliferation, pro-angiogenic, pro-necrosis	[38, 39, 105, 165, 171, 172]
	Multiple Myeloma	5T33MM, ARPL H929, HLE, MMS.1, RPMI8226, U266, clinical isolates	human BM, human placenta, mouse BM, mouse C3H10T1 line	tumor tropism, anti- or pro-proliferation or no effect, anti- or pro-apoptotic	tumor tropism, anti- or pro-growth, anti- apoptotic	[26, 39, 43]
	T cell leukemia	Jurkat	human BM			[41]
Nervous system	glioma - glioblastoma	C6, Gli36, U87MG	human BM, human SA, human UC, mouse C3H10T1 line	pro-proliferation or no effect, anti-survival	pro-growth or no effect, anti-apoptotic	[30, 31, 39, 173]
	neuroblastoma	CHLA-255, NB-19	human BM	pro-proliferation or no effect, anti-apoptotic or no effect	pro-growth	[117]
	Kaposi's sarcoma	KSIMM	human BM	anti-proliferation	tumor tropism, anti-growth	[106]
Non-epithelial	osteosarcoma	COS 1NR, Saos-2	human BM, rat BM	tumor tropism, pro-proliferation, pro-migration	tumor tropism, pro-growth, pro-metastasis	[44, 87, 118]
	fetal MSC-derived	F6	human fetal, adult BM		pro-engraftment, pro-growth, pro-invasion, pro-angiogenic, pro-necrosis	[160]

BA= breast adipose, BM = bone marrow, CSC = cancer stem cell, EMT = epithelial-mesenchymal transition, ECM = extracellular matrix, OA = omental adipose, SA = subcutaneous adipose, TAF = tumor-associated fibroblast, UC = umbilical cord.



**Table 2**

MSC-secreted factors detected during studies of cancer cell-MSC interactions.

MSC-secreted factors	MSC source	cancer	reported MSC paracrine activities on cancer cells	references
IL-6	human BM, human SA, human BA, mouse BM	breast cancer, ovarian cancer, prostate cancer neuroblastoma, multiple myeloma, osteosarcoma	tumor tropism, pro-growth, pro-survival, pro-proliferation, anti-apoptosis, pro-migration, pro-invasion, pro-metastasis	[43, 69, 76, 77, 82, 115–120]
VEGF	human BM, human OA, human SA, ovarian cancer, mouse BM	endometrial cancer, gastric cancer, ovarian cancer, pancreas cancer, prostate cancer, multiple myeloma	tumor tropism, pro-angiogenesis	[43, 54, 69, 75, 80, 82, 84, 86, 89]
CCL5	human BM, human SA	breast cancer, osteosarcoma	pro-migration, pro-invasion, pro-metastasis	[73, 87, 100, 144]
TGF	human BM, human BA	breast cancer, prostate cancer	pro-survival, pro-proliferation, pro-migration, pro-invasion	[32, 35, 81]
DKK1	human BM, human SA, mouse BM	erythroleukemia, multiple myeloma	anti-proliferation	[33, 43, 77]
IL-17b	human BM	breast cancer	pro-migration, pro-metastasis	[88]
S100A4	human liver cancer	hepatocellular carcinoma	pro-proliferation, pro-invasion, pro-metastasis	[74]
BMP2 (BMP4, BMP6)	human BM, human SA, ovarian cancer	ovarian cancer	pro-growth, pro-proliferation, pro-CSC phenotype	[45]
IGF1	human BM, mouse BM	prostate cancer, multiple myeloma, osteosarcoma	pro-survival	[43, 118, 119]
SDF1	human BM, human SA, mouse SA	endometrial cancer, ovarian cancer	pro-migration, pro-metastasis	[54, 69, 73]
EGF	human BM	ovarian cancer	pro-proliferation	[82]
HGF	human BM	ovarian cancer, multiple myeloma	-	[80, 82]
IL-10	human BM, human BA, mouse BM	breast cancer, multiple myeloma	-	[43, 81]
IL-4	human breast cancer	breast cancer	-	[81]
IL-8, CXCL5, CXCL6, CXCL7, CXCL1	human BM	breast cancer	-	[115]
FGF	human BM, human OA, human SA	endometrial cancer, ovarian cancer, multiple myeloma	-	[54, 80, 82]
TSP1, TnC, SL1	human BM	ovarian cancer	-	[82]
Non-specified paracrine factors	human BM, human SA, human UC, human foreskin, mouse C3H10T1 line	breast cancer, gastric cancer, lung cancer, pancreatic cancer, prostate cancer, renal cancer	pro-engraftment, anti- or pro-growth, anti- or pro-proliferation or no effect, pro-apoptosis, pro-angiogenesis pro-EMT phenotype	[34, 36–40, 156, 157, 159]