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Review

Deepening a Simple Question: Can MSCs Be Used to Treat Cancer?

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Abstract. *In cancer, mesenchymal stem/stromal cells (MSCs) have been considered as vehicles for targeted delivery of drugs due to their inherent tropism toward primary and metastatic tumors. However, it is still unclear whether MSCs could be therapeutically explored without significant harm, since a great amound of evidence indicates that MSCs are able to exert both tumor-suppressive and pro-oncogenic effects. Here, we discuss how MSCs might adopt a pro- or anti-inflammatory profile in response to changes within the tumor microenvironment and how these features may lead to opposite outcomes in tumor development. Additionally, we address how differences in experimental design might impact interpretation and consistency of the current literature in this specific field. Finally, we point-out critical issues to be addressed at a pre-clinical stage, regarding safety and therapeutic effectiveness of MSCs application in cancer treatment.*

Mesenchymal stem/stromal cells (MSCs) are undifferentiated multipotent cells with the ability to self-renew and differentiate into several distinct cell lineages (1, 2). They are composed of a heterogeneous population of cells, involved in the maintenance and repair of tissues throughout life. Since their first isolation from bone marrow samples, MSCs are also obtainable from different biological sources such as adipose tissue, umbilical cord, dental pulp and fallopian tubes, among others (3-6). MSCs have been shown to derive from perivascular cells, known as pericytes, that are released from the basement membrane surrounding blood vessels upon injury or inflammation (7-9).

Pre-clinical studies support functional recovery after MSCs transplantation in diverse pathologies (10-15). Many of these studies show significant therapeutic benefits of cell transplantation even when exogenous cells are not present in the target tissues. This effect is predominantly associated with the release of soluble factors affecting diverse biological processes such as angiogenesis, apoptosis, and immune response (13, 16-22). Due to these paracrine effects, MSCs have been considered as "Medicinal Signaling Cells", delivering biological mediators to sites of injury or inflammation (7, 23).

MSCs are also emerging as promising targeted anti-cancer agents for the treatment of a number of different cancer types due to their inherent tumor-tropic migratory properties, which allow them to serve as vehicles for the effective delivery of drugs to primary tumors and metastatic sites. MSCs have already been engineered to express anti-proliferative, pro-apoptotic or anti-angiogenic agents that specifically target different cancer types (24, 25). For this purpose, transfection of MSCs using viral vectors is the most used strategy however, some new methods, such as the therapeutic ultrasound (TUS) are being proposed (26).

Although this engineered-MSCs approach may be promising, basic investigation of unmodified MSCs effects on tumor development is needed. MSCs from different biological sources have been evaluated in animal models of cancer, but discrepant results have been reported (27), either enhancing (28-30) or inhibiting tumor growth (31-33).

Therefore, in cancer, it is still unclear whether MSCs could be used in clinical studies without significant harm. In this review, we will focus on MSCs residents of the stroma and mainly on exogenous MSCs used as cell therapy.

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MSCs Activity Within the Tumor Microenvironment

It is known that MSCs can modulate their secretory profile depending on the composition of their microenvironment, *i.e.*, their biological behavior is modified according to the factors that they are exposed to (34-39). The tumor microenvironment (TME) is a functional ecosystem of tumor, stromal elements and signaling molecules (40). The stroma is a histological unit consisting of peri-tumoral cells, including fibroblasts and MSCs, that actively interact with the tumor cells (27, 40-49).

As reviewed by Ridge and coworkers (50), MSCs are key players in cancer progression, as they can act in tumor development at various stages of progression from growth of the primary tumor to the establishment of distant metastasis. It was recently pointed-out that the presence of MSCs in 3D cancer spheroids promotes the formation of a stroma-like tissue surrounding the tumor supporting growth and increasing resistance to chemotherapy of liver colorectal-tumor (51).

The bi-directional signaling between the cytokines secreted by malignant and non-malignant cells plays an important role in the establishment, progression, and metastatic dissemination of cancer (52-55).

TME is also rich in cytokines derived from immune system cells, such as tumor necrosis factor-alpha (TNF-α), tumor growth factor-beta (TGF-β), interleukin 1 (IL-1) and interleukin 6 (IL-6), angiogenic factors, such as vascular endothelial growth factor (VEGF), and chemokines. As it is reviewed by de Visser and coworkers (56), TNF-α is a key cytokine that is mobilized during acute inflammation mediating tumor development. Knockout mice for TNF-α and its receptors have less susceptibility to skin cancer and develop fewer metastases. As TNF-α receptors are expressed in both stromal and epithelial cells, TNF-α facilitates the development of cancer directly by regulating the proliferation and survival of neoplastic cells, and indirectly by exerting its effects on endothelial cells, fibroblasts, and immune cells in the tumor microenvironment (54, 56, 57). TNF-α was found to affect the permeability of the blood brain barrier and its increased expression was correlated with the development of brain metastasis in breast cancer patients (58).

TME can influence the activity of resident MSCs exchanging membrane proteins through nanotube structures and through soluble factor or exosomes containing micro RNA (40, 59-61). It has already been reported that in breast cancer, resident MSCs can migrate to the proximity of tumor foci, where they produce diverse cytokines such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and TGF-β, contributing to tumor growth (52). As reviewed by Bhome and coworkers (40), cancer-associated fibroblasts (CAFs) are responsible for the structural architecture of the tumor and at least 20% of CAFs originate from MSCs. MSCs differentiation to CAFs can be induced by either CAFs or tumor and recruitment is dependent on TGF-b and stromal cell-derived factor-1 (SDF-1), which stimulates growth, proliferation and invasion, angiogenesis and metastasis (40, 62).

The tumor cell mass is highly heterogeneous, which may be the key for its progression and adaptation to different treatment modalities, thus complicating personalized-medicine strategies (63, 64). Among the different tumor cell types, cancer stem cells (CSCs) deserve special attention since they possess unique properties that are crucial for cancer progression to a more malignant state, including high efficiency to initiate and propagate tumors (65-70), and increased resistance to many kinds of chemical or physical insults (71). Cellular components of the TME, including MSCs and pericytes, have a critical role in the maintenance of a stem-like state in tumor cells, as well as in CSC self-renewal (56).

MSCs and Immune Response Against Cancer Cells

The immune system has a natural capacity to detect and destroy abnormal cells, playing a major role in preventing tumor development. Despite that, tumor cells frequently adopt strategies to escape from immune cells, usually related to reduced antigen expression on their surface membrane and to induction of an immunosuppressive microenvironment (73-77).

In order to efficiently eliminate cancer cells, a great effort is being made to understand how cancer evades the immune system (78-82). In the past few years, significant progress has been made in immunotherapy strategies for cancer treatment. Different monoclonal antibodies, such as the MDX-010 (ipilimumab), which recognizes the cytotoxic T lymphocyte antigen-4 (CTLA-4), have been developed to boost the immune response against tumor cells. Treatment with MDX-010 was shown to increase T-cell function and antitumor responses in patients with advanced metastatic melanoma (83). Despite these positive results, significant toxicity was associated with this therapeutic approach, consisting mostly of inflammatory events in healthy body parts without cancerous cells (83).

Some cancerous cells also secrete programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), which are able to interact with PD-1 receptor on T-cell surface, thus inhibiting T-cell activation and promoting tumor immune escape. Recently, a treatment with a novel human IgG4 PD-1 antibody (Nivolumab) increased overall survival in patients with squamous-cell lung carcinoma, in comparison with the conventional chemotherapy treatment. Nivolumab was reported efficient in disrupting PD-1–

mediated signaling in T-cells, thereby restoring antitumor immunity (84-90).

MSCs possess immunosuppressive properties such as the ability to inhibit the differentiation of dendritic, B- and T-cells, attenuate natural killer (NK) cells, and also suppress regulatory T-cells (91-97). Therefore, possible oncogenic effects of MSCs have been considered in several MSC-based cell therapy protocols. The immunosuppressive potential of MSCs, however, is highly dependent on the composition of the microenvironment in which they are being stimulated. Waterman and coworkers (98) reported that stimulation of Toll-like receptors (TLR) TLR3 or TLR4 in MSCs may result in different secretory profiles, namely MSC1 and MSC2, mostly pro-inflammatory or immunosuppressive, respectively. These distinct profiles also support potential opposing effects of MSCs on cancer, either inhibiting (MSC1) or stimulating (MSC2) tumor growth (99).

The bi-modality of MSCs was also demonstrated by Chan and coworkers (100). It was reported that reduced levels of interferon-γ (IFN-γ) cause MSCs to express major histocompatibility complex class II (MHC-II) and ultimately act as antigen-presenting cells (APCs), stimulating inflammatory responses. When IFN-γ is present in high levels, MHC-II expression is reduced, preventing MSCs to act as APCs and consequently inducing an immunosuppressive MSC phenotype. In another *in vivo* study, administration of colon cancer cells along with MSCs pre-stimulated with inflammatory cytokines IFN-γ and TNF-α, accelerated tumor growth in mice, compared to MSCs without pre-stimulation (101). Pre-treated MSCs showed higher expression levels of VEGF regulated *via* the hypoxia-inducible factor 1-alpha (HIF-1α) signaling pathway that enhanced tumor angiogenesis, finally leading to increased colon cancer growth (101, 102).

MSCs' Pro-Cancer Effect

The cancer-associated stromal cells promote and regulate tumor growth, invasion and metastasis by the secretion of extracellular matrix components and growth factors (29, 103, 104). Mi and coworkers (105) observed that even MSCs' conditioned media, due to IL-6 presence, was responsible to promote metastasis in hepatocellular carcinoma.

In a cell therapy context, transplanted MSCs might integrate within the cancer stroma and influence tumor development. The formation of new blood vessels is an important hallmark for tumor development (106). Following intravenous injections, it was observed that MSCs were able to home to tumor sites and assist the production of new tumor vessels (107, 108). It was also observed that MSCs were able to increase the proportion of CSCs in gastric carcinoma *in vitro* through activation of the WNT and TGF-β signaling pathways (109, 110).

Besides other immune cells, lymphocytes are also being investigated in cancer physiopathology. Recently, a correlation of high lymphocytic reaction with better prognosis in patients with solid colorectal cancer was reported (111). Therefore, when MSCs act as immunosuppressants, inhibiting T-cell proliferation, they might enhance cancer progression (111-116).

It was demonstrated that autologous or allogeneic MSCs might suppress the proliferation of naïve and memory T lymphocytes stimulated by alloantigen, mitogens, or T-cell co-receptors CD3 and CD28, in a mechanism independent of MHC recognition (117-123). This immunosuppressive property is maintained when MSCs and lymphocytes are separated by a semi-permeable membrane, pointing out the involvement of soluble factors that might vary according to the stimulating agent and the lymphocyte population used (whether full or sorted) (121, 124-131). Nevertheless, isolated extracellular vesicles derived from MSCs failed to suppress lymphocyte proliferation, suggesting that cell–cell contact also plays an important role on the immunosuppressive potential of MSCs (132) or indicating that the factors related to lymphocyte proliferation are not secreted through vesicles.

Similarly, MSCs inhibit the differentiation of naive and memory $CD4^+$ T-cells into Th17 precursors and might also inhibit naturally-occurring Th17 cells (133, 134). Human memory Th17 cells were found to suppress T-cell activation in breast cancer, suggesting that intratumoral Th17 cells contribute to cancer development and compromise anticancer therapy in breast cancer patients (135). Knockdown of interleukin-25 (IL-25) expression in MSCs abrogated Th17 suppression both *in vitro* and *in vivo* (136), highlighting the cytokine involvement in this process.

Epigenetic changes are also implicated in this process. It was previously observed that MSCs induced the production of IL-10 and the trimethylation of histone H3 lysine 4 at *FOXP3* promoter in Th17 cells, leading to a higher capacity of these cells to inhibit *in vitro* proliferation of activated $CD4^+$ T-cells (137). Also, MSCs provide maximal enhancement of regulatory T-cell function through direct cell-to-cell interaction mediated by the MSC membrane-expressed CD80 molecule (138).

Regarding B lymphocytes, some contradictory results are observed. It has been shown that MSCs could both increase or decrease proliferation and survival of these cells (139-144). The mechanisms of action involve both contact-dependent factors, such as PD-L1 and PD-L2, and soluble factors such as matrix metalloproteases. Though, these results depend on the source of B lymphocyte and the experimental conditions used.

The effect of MSCs is also observed in elements of the innate immune system. MSCs have an inhibitory effect on NK cells, affecting different aspects of their function, such as proliferation, cytotoxicity, and cytokine production (145,

146). Maturation and differentiation of dendritic cells (DC) are also influenced after co-culture with MSCs, mainly through prostaglandin E2 (PGE-2) action. Additionally, DC previously co-cultured with MSCs impaired allostimulation of T cells (147, 148).

MSCs' Anticancer Effects

Conversely, many studies have also shown that MSCs can suppress tumor growth (149, 150) (Figure 1). Despite low expression of MHC or costimulatory molecules by MSCs, it was hypothesized that allotransplantation of MSCs could elicit an immune response that would ultimately inhibit tumor growth (149, 151). Nevertheless, Khakoo and coworkers (32) showed that the inhibitory effect on tumor growth is due to an active role of MSCs: when human umbilical vein endothelial cells (HUVECs) were injected in a Kaposi's sarcoma model, no significant effect on tumor size was observed, while a significant tumor inhibition was observed in the same model after injection of MSCs.

MSCs may also suppress tumor growth due to an anti-angiogenic effect (152, 153). MSCs migrate to the capillaries and position themselves between endothelial cells, resulting in defects in gap junctions. As a consequence, there is an increased production of reactive oxygen species, leading to endothelial cell apoptosis and subsequent degeneration of the capillaries. Thus, without the necessary supply of oxygen, the tumor stops growing.

Finally, some components of the MSCs' secretome can actively impair tumor growth. It has already been demonstrated that MSCs' conditioned medium can cause inhibition of tumor proliferation and induction of tumor cell death by cell cycle arrest and necrosis (31). Lu and coworkers (22) also reported induction of tumor cell death, but in this case, through apoptosis mediated by caspases and p21, instead of necrosis.

Divergences on Experimental Design

Studies aiming the evaluation of MSCs as a therapeutic approach for cancer use highly divergent methodologies, which might hinder a precise scientific understanding of the subject. In this section we discuss these differences and their implications. Selection of the appropriate MSC source, time and route of injection, experimental models, and number of injected cells are elements that must be taken into consideration when analyzing results.

Source of MSCs

Countless organs and tissues are now recognized as potential sources of MSCs. Each one provides a different microenvironment for its resident cells, acting on MSCs characteristics and regulating their migration and differentiation abilities. Therefore, MSCs obtained from different sources might have distinct biological properties and secretome patterns (154).

What is referred to as "mesenchymal stromal cells" is in fact a combination of different subpopulations of cells that possess similar immunophenotypic profiles and share the ability to differentiate into the three mesenchymal lineages. Most pre-clinical and clinical studies have been performed using a heterogeneous population of stromal cells (NCT02530047; NCT01983709; NCT02181478; NCT01275612), which could partly explain some contradictory results or even the lack of reproducibility.

In addition, allotransplantation or even xenotransplantation of MSCs in cancer animal models have shown inhibition of tumor development. It is imperative to determine if these results are due to the native pro-inflammatory effect of transplanted cells or if they are merely due to a non-self origin effect, with the exogenous cells eliciting an immune response and ultimately enhancing the activity of the host immune system to fight the tumor cells. On the other hand, *in vitro* and *in vivo* studies using syngeneic MSCs and tumor lineages showed important results in cancer inhibition in immunocompetent mice (152). Also, an active and straight role of MSCs might occur even if transplanted into immunodeficient mice (32). Nevertheless, some studies showed increased tumor growth after MSCs perfusion in immunocompetent or athymic mice (28, 155).

Time and Route of Injection

One of the most frequent procedures aiming to verify the effect of MSCs in tumor growth includes co-injection of both MSCs and tumor cells. In this regimen, distinct proportions of tumor cells and MSCs might interfere in the experiment outcome. Other experimental designs include injection of MSCs after the tumor establishment.

The impact of different timing of MSCs infusion was evaluated by Jazedje and coworkers (156). When MSCs were co-injected with murine breast cancer cells, the animals had a more severe course of the disease and displayed a reduced survival, while MSCs injected in mice already at the initial stage of mammary adenocarcinoma resulted in significant reduced tumor growth and also increased lifespan, as compared with control animals.

Moreover, MSCs can be transplanted through many routes such as subcutaneous or intravenous, and this variable might also impact the final outcome.

Experimental Models

Another issue to be considered is the species that tumor cells and MSCs are derived from. Many groups use human

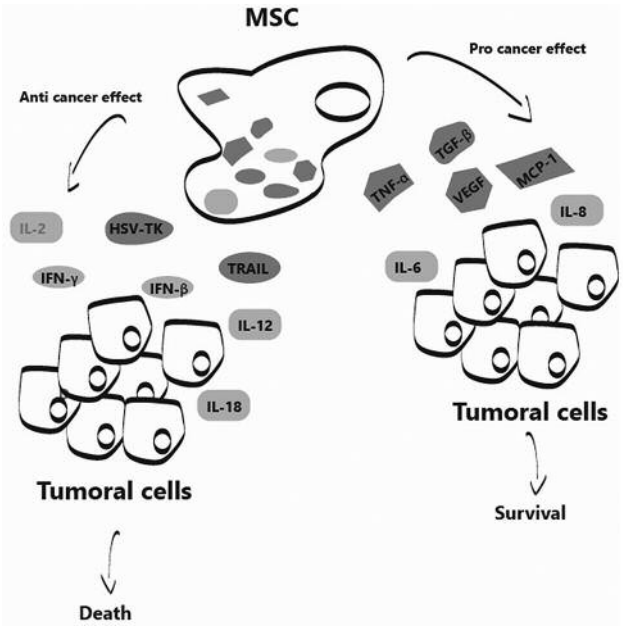

Figure 1. *Pro and anti-cancer effect of mesenchymal stem stromal cells (MSCs). MSCs can produce pro or anti-cancer molecules, in response to the tumoral microenvironment, which can directly or indirectly affect the survival of cancer cells. MSCs have also been engineered to produce high amounts of anti-tumoral molecules (24). IL-6, interleukin 6; IL-8, interleukin 8; TNF-α, tumor necrosis factor-alpha; TGF-β, tumor growth factor-beta; MCP-1, monocyte chemoattractant protein-1; IFN-γ, Interferon-γ; IL-2, Interleukin-2; IL-12, Interleukin-12; IL-18, Interleukin-18; VEGF, Vascular Endothelial Growth Factor; TRAIL, TNF-Related Apoptosis-Inducing Ligand; HSV-TK, Herpes Simplex Virus-Thymidine Kinase.*

tumoral cell lineages that consequently require an immunodeficient mouse model, otherwise, cancer cells could be recognized and destroyed by the host immune system. Since there is a lack of effective immune response, when MSCs are injected there are no proper interactions between these two components. Such studies are useful to understand the direct effect of MSCs on cancer but it is not sufficient to answer the question about MSCs' effects in cancer patients with a functional immune system.

There are also murine cell lineages of different tumors, which may have variability in their establishment or aggressiveness, thus responding differently to treatments. Cousin and coworkers (31) treated diverse tumor cell lines with adipose-derived stromal cells conditioned medium *in vitro*. Except for the cervical and breast cancer cell lines, MSCs-conditioned medium was able to inhibit tumor cell proliferation in pancreatic and other epithelial cancer-derived cell lines (liver, colon, prostate). These results demonstrated that different tumoral lineages may respond differently to a given treatment (31).

Dose-dependence

The effect of MSCs on cancer therapy also depends on the number of cells used. Long and coworkers (157), demonstrated by *in vitro* co-cultures that MSCs can generate a stimulatory or inhibitory effect on tumor growth, depending on the ratio between MSCs and cancer cells. When the proportion of MSCs was lower than the number of cancer cells, the later cells were able to proliferate. Respectively, when the proportion of MSCs was increased, the proliferation of cancer cells was reduced. Using fibroblasts, Delinasios and coworkers (46) studied early interactions, *i.e.* not fully-grown tumor, of stromal cells and cancer cells. It was shown the influence of cell confluence and also the HeLa: Fibroblasts ratio on *in vitro* cancer establishment.

These observations suggest that, in order to achieve successful results with MSC therapy, not only the amount of injected cells is important, but also the frequency of the injections. Khakoo and coworkers (32) demonstrated that, when a single dose of MSCs was injected intravenously concomitant to the subcutaneous injection of tumoral cells (day zero), tumor size was reduced. In the same study, three additional injections of MSCs were able to potentiate their effect on tumor growth inhibition. A similar effect was also observed when three MSCs injections were administered after tumor establishment.

Concluding Remarks

Despite the difficulty in comparing existing studies about the use of MSCs for cancer therapy, there is convincing evidence of both, tumor suppression and pro-oncogenic effects of MSCs. In any case, studies that investigate MSCs as anti-cancer agents should take into account real-life situations that cancer patients may experience. For instance, co-injection of tumoral cells and MSCs does not mimic a real clinical scenario. Instead, dose escalation studies of MSCs delivered systemically in tumor-bearing mice seem more suitable. In this pre-clinical setting, other important variables should be tested, including the frequency of MSCs injections and the type of MSCs. In the latter case, potency tests should also be developed to discriminate MSCs populations with the appropriate activity for a desirable anti-tumor effect. It has been observed that MSCs secrete different proteins even when they are obtained from the same tissue of different donors or from different tissues of the same donor (158). Additionally, MSCs activity is known to decline with donor's age (159). It would be interesting to determine a secretome profile of MSCs that best suits cancer therapy purposes, as Ranganath and coworkers (160) reviewed for ischemic heart failure.

Similarly, for the investigation of possible pro-oncogenic effects of MSCs, different MSCs/tumor cell ratios should be

evaluated, mimicking different stages of tumor development. Moreover, orthotopic tumor models using MSCs of corresponding biological residence are more informative, given the differences in the tumor microenvironment among tissues. Noteworthy, variations in the constitution of the tumor microenvironment occur along the disease progression (63, 161), and the effects of such variations on the activity of MSCs should be clarified. The use of the appropriate cellular controls is another important issue to be considered. Injection of differentiated cells from the same biological source, such as fibroblasts, would indicate whether the effect on tumor development is a specific property of MSCs. Likewise, when human MSCs are used in murine models, injections of syngeneic murine MSCs would provide evidence that observed effects are not due to an interspecies artifact.

Besides the risk of increasing tumor size and tumorigenicity, there is the risk of MSCs injection itself. Safety of MSCs transplantation has already been reported by several studies, using MSCs from various sources in different diseases (162-165), but others have shown side effect, such as fibrosis, nausea, vomiting, increase of respiratory rate and pulmonary edema (166-168). Therefore, these reports highlight the importance of using well characterized MSCs.

Overall, studies addressing the role of MSCs in tumor development are equally important and the ensuing complementary knowledge is critical to evaluate possible applications of MSCs to treat cancer patients. The approach hereby proposed for pre-clinical studies should yield valuable information to support the elaboration of future clinical protocols.

Disclosures

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