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Mesenchymal stem cells in the tumor microenvironment (Review)

JIAN GUAN and JIE CHEN

Department of Pathology, Peking Union Medical College Hospital, Beijing 100730, P.R. China

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Abstract. Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent cells, which are able to differentiate to bone, adipose and cartilage tissue. MSCs have the characteristic of migration to injured areas or tumor microenvironment following induction by chemokines or inflammatory factors. An increasing number of studies have reported that MSCs recruited to the tumor microenvironment play various roles in tumor cell development and tumor progression. In this study, we reviewed the studies related to the tumor-promoting roles of MSCs from several aspects, such as increasing stemness of tumor cells, mediating migration, promoting angiogenesis, suppressing immune response and inducing drug resistance.

Contents

1. Introduction

Mesenchymal stem cells (MSCs) are pluripotent cells that give rise to a variety of connective tissue cell types (1,2). They are considered to be non-hematopoietic, multipotent cells, characterized by the expression of stromal cell markers (CD73, CD105, CD44, CD29 and CD90) in the absence of hematopoietic markers (CD34, CD45 and CD14) and endothelial markers (CD34, CD31 and vWF) (3). MSCs have the potential to differentiate along osteogenic, adipogenic and chondrogenic lineages when placed in the appropriate environments (4). An increasing number of studies have demonstrated that MSCs play complicated roles in carcinogenesis and tumor development by differentiating into more mature mesenchymal cells to support tumor parts and by playing special roles as a resident component in the tumor microenvironment. Therefore, comprehensive knowledge on the mechanism of interaction between MSCs and cancers is vital.

MSCs may be extractable from the bone marrow but may also be isolated from other mature tissues, such as skeletal muscle, umbilical cord, amniotic fluid, fetal liver and adipose tissue (5-7). MSCs are characteristically recruited to injured areas or hypoxic tumor microenvironments. Following intravenous administration, MSCs were identified mainly in tumors and had been cleared from normal tissue (8). Therefore, MSCs may serve as a platform for the delivery of biological agents to tumors. During the progression of carcinogenesis, when induced by chemokines of tumor cells to migrate to the area surrounding the tumor, MSCs are involved in supporting the neoplastic properties of cancer cells.

2. Homing to the tumor microenvironment

During the progression of carcinogenesis, recruitment of MSCs to tumors is reportedly due to the presence of soluble factors secreted by tumor cells, as well as the inflammation background or the hypoxic condition in the tumor microenvironment. Tumor cells secrete growth factors, cytokines and chemokines, such as IL-6 (9), IL-1β (10), transforming growth factor-β1 (TGF-β1) and SDF-1α (11,12). Signaling events promote MSC migration and survival. Additionally, several tumors exhibit hypoxia, a state of reduced oxygen that often parallels inflammation. Hypoxia plays an important role in perpetuating the inflammatory process in tumors, resulting in the generation of chemokines that are involved in immune cell and likely MSC migration to tumors. It was reported that, under hypoxic conditions (1.5% O_2), breast cancer cells secrete high levels of IL-6, which serve to activate and attract MSCs (9).

3. Differentiation of MSCs

When MSCs arrive at the area surrounding the tumor, they may differentiate into more mature mesenchymal cells, such as cancer-associated fibroblasts (CAF) (13), macrophages (14) or endothelial cells (15,16). It was reported that, when treated with tumor-conditioned media, MSCs exhibited

Correspondence to: Professor Jie Chen, Department of Pathology, Peking Union Medical College Hospital, 1 Shuai Fu Yuan Hu Tong, Beijing 100730, P.R. China
E-mail: xhblk@163.com

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upregulation of cancer-associated fibroblast-associated genes and expression of markers specific to the myofibroblast lineage, such as α-SMA, vimentin and fibroblast-specific protein 1 (FSP1/S100A4) (17). Previous studies on the origin of fibroblasts in the tumor microenvironment demonstrated that the bone marrow and the adipose tissue surrounding tumor areas are the most common sources (18,19). In a study conducted by Quante *et al* (11), bone marrow-MSCs were labeled with EGFP, following which >70% of CAFs detected in the tumor microenvironment were identified as EGFP-positive, indicating their bone marrow origin. The majority of FSP-positive and fibroblast activation protein-positive CAFs originate from MSCs located in the bone marrow, whereas adipose-derived MSCs tend to differentiate into vascular and fibrovascular stromal cells (20). In addition, α-SMA-positive myofibroblasts originate from MSCs in the bone marrow (11,13). Other molecular markers, such as platelet-derived growth factor (PDGFR)-β was found to be positive in CAFs in the area surrounding the tumor, originating from pericyte progenitors in the bone marrow, which are responsible for regulating vascular stability and survival (21).

Following differentiation, MSCs exhibited a series of morphological changes, including elongated phenotype, reduced adhesion, cytoskeletal stiffening and increased migration (22). TGF-β participates in the process of differentiation from MSCs to CAFs, and coordinates the increase of α-SMA and the decrease of gelsolin to promote MSC differentiation (23). Under the stimulation of TGF-β, MSCs are hypomethylated and exhibit alterations in their gene expression profiles towards myofibroblast signature-expressing markers, such as α-SMA, tenascin-C and fibroblast surface protein (FSP), as well as an increased expression and secretion of growth-stimulating factors such as CCL5 and stromal cell-derived factor-1 (SDF-1) (11,17). The pathway involved is reportedly dependent on TGF-β signaling via Smad3 in MSCs (24). Adipose-derived MSCs may differentiate into α-SMA-expressing CAFs by expression of periostin, an extracellular matrix (ECM) protein, induced by A549 human lung adenocarcinoma cells (25). Under tumor conditions, MSCs may differentiate into hematopoietic cells, more precisely into macrophages, through reduced Ca^{2+} influx (14), or PDGFR-positive CAFs (26). In addition, it was reported that the exosome secreted by tumor cells may induce MSCs to express α-SMA and tumor-promoting factors SDF-1, VEGF, CCL5 and TGF-β (27).

4. Functions in the tumor microenvironment

In the tumor microenvironment, MSCs promote tumor cell development and progression. The tumor-MSCs crosstalk is complex. When stimulated by tumor cells, MSCs exhibit certain changes at the gene level. Data from a recent study demonstrated that following co-culture with MSCs and analysis by transcriptomic methods, tumor cells exhibited altered biological function of certain gene clusters, such as those related to the increase of metastatic ability, proliferation and chemoresistance (28). Therefore, upon interaction with MSCs, tumor cell functions are significantly supported on multiple levels.

Stemness. MSCs have multilineage potentials and also provide a beneficial microenvironment for tumor cells and enhance the stemness of tumor cells through multiple pathways. For example, in breast cancer, co-culture of MSCs and tumor cells promoted mammosphere formation, which is the three-dimensional culture morphology of cancer-initiating cells (29,30). MSCs regulate breast cancer stem cell self-renewal through cytokine loops involving IL-6 and CXCL7 (31). Carcinoma-associated MSCs (CA-MSCs) promoted tumor growth by increasing the number of cancer stem cells through bone morphogenetic protein signaling (32). Other pathways include the WNT, TGF-β (33) and the IL-6/JAK2/STAT3 signaling pathways (34,35). In addition, a pathway may be induced by tumor cells, which results in the enhancement of the stemness of tumor cells. Tumor cells may induce MSCs to express greatly elevated levels of PGE2 which, in combination with the cytokines that are also induced in the MSCs, contribute to the increase of the ALDH-positive fraction of cancer cells (36).

Migration. Epithelial-mesenchymal transition (EMT) is the early event of tumor cell migration. EMT renders podocytes motile, leading to their detachment from the basement membrane. Increased expression of the zinc finger proteins Snail and Slug, fibroblast-specific protein 1 (FSP1/S100A4), fibronectin and vimentin are correlated with mesenchymal phenotype and prometastatic behavior (37,38). MSCs actively recruited to the tumor stromal microenvironment may induce EMT in numerous tumors and actively increase the metastatic potential of tumor cells. When co-cultured with MSCs, breast cancer cells exhibited an enhanced expression of vimentin, Snail and Slug and a decreased expression of E-cadherin and β-catenin (30). MSCs promoted the production of lysyl oxidase from breast cancer cells, which in turn stimulated the Twist transcription factor, which mediates the MSCs-triggered EMT of carcinoma cells. Thus, MSCs enhance metastasis of cancer cells to the lungs and bones (39). It was also reported that paracrine transforming growth factor-β1 (TGF-β1) secreted by MSCs regulated the establishment of EMT in MCF7 cells by targeting the ZEB/miR-200 regulatory loop (40). The same phenomenon may be observed in hepatic carcinoma cells. In addition, when co-cultured with tumor cells, MSCs acquired the CAF markers tenascin-c and SDF-1 (41,42). During a study on pancreatic cancer, MSCs were found to regulate EMT and sphere formation in pancreatic cancer cells through a Notch-dependent mechanism (43).

In addition to EMT, MSCs may affect the migration of tumor cells through a variety of mechanisms, such as via the CXCL1/CXCL5-CXCR2 pathway (44), the ER and CXCR4 pathways (45) or the regulation of RANTES and IL-6 (46) in breast tumors. Breast cancer cells may also induce CCL5 expression in MSCs, which in turn enhances motility and the invasive potential of cancer cells (47). A previous study demonstrated that MSCs promote prostate cancer invasion and migration by upregulating MMP2/9 expression (48).

Angiogenesis. One of the effects of MSCs on tumor cells is angiogenesis. A previous study reported that the conditioned media from MSCs may increase sprouting of human umbilical vein endothelial cells due to VEGF production by MSCs (49).

In vivo, co-injected MSCs directly supported the tumor vasculature by localizing close to the vascular walls and expressing CD31 (50). *In vitro*, when co-cultured with tumor cells, MSCs exhibited a distinct tendency to organize in clusters and form capillary-like structures (51). The soluble molecular factors secreted by MSCs, such as LIF, M-CSF, MIP-2, VEGF (50), IFN-γ and TNFα (52) promote angiogenesis. A previous study demonstrated that exosomes, which are 40-100 nm diameter vesicles secreted by MSCs, may enhance angiogenesis of tumors by VEGF and CXCR4 expression in tumor cells through the ERK1/2 and p38 MAPK pathways (53).

Immunosuppression. MSCs may affect the proliferation and maturation of T cells (54), B cells (55), dendritic cells (DCs) (56,57) and natural killer (NK) cells (58,59). Recent studies have focused on MSC-based immune therapy in allogeneic cell and organ transplantation (60-62). Cytokines secreted by MSCs, such as IL-10 (60), TGF-β (63), nitric oxide (64), indoleamine 2,3-dioxygenase (65) and prostaglandin E2 (66) are involved in immunosuppression.

Furthermore, MSCs-mediated immunosuppression has been variously demonstrated in tumor development and progression. MSCs may protect breast cancer cells by increasing Tregs and reducing the activity of natural killer cells and cytotoxic T lymphocytes (67). In melanoma, the immunosuppressive function of MSCs was elicited by IFN-γ and TNF-α. These cytokine combinations led to the expression of inducible nitric oxide synthase by MSCs (68). The inflammatory background in prostate cancer elicited the upregulation of TGF-β in MSCs, which enabled prostate cancer cells to escape from immune surveillance (69).

Chemotherapy resistance. The mechanisms involved in classic chemotherapy resistance include enhanced activity of positive regulators of cell proliferation, such as oncogenes, loss of tumor suppressor gene function, inactivation of cell death or enhancement of survival functions and activation of telomerase. Besides the classically defined causes of drug resistance, environment mediated-drug resistance (EMDR) arises from an adaptive, reciprocal signaling dialogue between tumor cells and the surrounding microenvironment. EMDR may be subdivided into two categories: soluble factor-mediated drug resistance, which is induced by cytokines, chemokines and growth factors secreted by fibroblast-like tumor stroma; and cell adhesion-mediated drug resistance, which is mediated by the adhesion of tumor cell integrins to stromal fibroblasts or to components of the ECM, such as fibronectin, laminin and collagen (70). MSCs are associated with EMDR by secreting soluble molecular factors such as SDF-1, IL-6, NO, IL-3, G-CSF, M-CSF and GM-CSF and by activating proliferation pathways in tumor cells and producing ECM to protect tumor cells against chemotherapy drugs. MSCs utilize autophagy to recycle macromolecules and synthesize antiapoptotic factors to facilitate the survival and growth of surrounding tumor cells (71). In colorectal carcinoma, MSCs stimulated survival of tumor cells through the release of soluble NRG1, activating the HER2/HER3-dependent PI3K/AKT signaling cascade (72). Platinum-based chemotherapy in breast cancer may induce MSCs to secrete two unique fatty acids that confer resistance to chemotherapy (73).

10. Conclusion

MSCs exert multiple effects on tumor development and progression, by increasing stemness of tumor cells, mediating migration, promoting angiogenesis, suppressing immune response and inducing drug resistance. In-depth understanding of these actions may provide information regarding the biological behavior of tumors and set the basis for the design of an MSCs-based therapeutic method for carcinomas and immunological diseases. The tumor-promoting molecules secreted by MSCs or the pathway activated by MSCs in tumor cells may enrich the list of potential targets for molecular therapy.

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