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Review

Recent discoveries concerning the tumor - mesenchymal stem cell interactions

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ABSTRACT

Tumor microenvironment plays a crucial role in coordination with cancer cells in the establishment, growth and dissemination of the tumor. Among cells of the microenvironment, mesenchymal stem cells (MSCs) and their ability to evolve into cancer associated fibroblasts (CAFs) have recently generated a major interest in the field. Numerous studies have described the potential pro- or anti-tumorigenic action of MSCs. The goal of this review is to synthesize recent and emerging discoveries concerning the mechanisms by which MSCs can be attracted to tumor sites, how they can generate CAFs and by which way MSCs are able to modulate the growth, response to treatments, angiogenesis, invasion and metastasis of tumors. The understanding of the role of MSCs in tumor development has potential and clinical applications in terms of cancer management.

Contents

Abbreviations: ADSC, Adipose stromal cells; Akt, protein kinase B; BM-MSC, bone marrow mesenchymal stem cells; CAF, cancer associated fibroblast; CRC, colorectal cancer; CSC, cancer stem cell; HCC, hepatocellular carcinoma; IGF, insulin-like-growth factor; IL-1, interleukin-1; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; MMP, metalloproteinase; NK, natural killer; PCa, prostate cancer; PGE2, prostaglandin E2; TAM, tumor associated macrophage; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor.

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1. Introduction

MSCs are defined as mesenchymal stem cells or mesenchymal stromal cells, but represent commonly a large set of different types of cells. Indeed, MSCs have been isolated from different types of tissues, including in particular the bone marrow (BM-MSC), umbilical cord blood, adipose tissue (we will define them as adipose derived stromal cells), but also peripheral blood, fetal liver, lung, amniotic fluid, or placenta (for a review, [1]). All these types of MSCs retain similar characteristics with the ability to adhere strongly to plastic surfaces, are characterized by surface markers (CD14− or CD11b−, CD19− or CD79α−, CD34−, CD45−, HLA-DR−, CD73+, CD90+, CD105+) and with the potential to be differentiated into chondrocytes, osteoblasts and adipocytes under standard in vitro differentiating conditions [1]. Despite some common features with regard to the immunophenotype and differentiation potential of MSCs, these cells do vary in accordance with their direct interaction with other cells or via a paracrine fashion to the surrounding microenvironment.

The field of MSCs in tumor development has progressed tremendously since the early 2000s (for a review, [1]). In the setting of cancer therapy, the TREAT-ME1 is the first clinical trial worldwide using genetically altered MSCs for the treatment of advanced gastrointestinal tumors [2]. In this study, MSCs have been engineered to express the thymidine kinase of the herpes simplex virus (HSV-Tk) under the control of RANTES (CCL5) promoter, which is highly active in MSCs in the tumor context [3]. The RANTES/CCL5 promoter should allow tumor stroma-targeted expression of the thymidine kinase gene, which when phosphorylated by the prodrug, ganciclovir, can be incorporated into replicating DNA leading to cell death.

Although this trial has demonstrated the safety usage of modified MSCs, it is nevertheless important to execute caution since the biological properties of MSC in the tumor microenvironment have been complicated by the limited lineage-specific markers and the inter- and intra-clonal heterogeneity of MSCs. Thus, the main focus of this review is to provide an updated review of the current understanding of MSCs and its interaction with tumor cells. Apart from the unique feature of MSCs migrating toward injured and pathological lesion tissues, we will focus on the role of MSCs during the development of cancer, emphasizing on the six hallmarks of cancers, i.e. how MSCs aid in (i) enabling replicative immortality to cancer cells (ii) sustaining proliferative signal of cancer cells and cancer stem cells (iii) its action on epithelial and mesenchymal transition and metabolism of cancer cells (iv) how MSCs can evade growth suppressor (v) resist cell death and (vi) induce angiogenesis.

2. Homing of MSCs to tumor sites

Chemokines or more generally cytokines are amongst the major players responsible for MSC migration to tumors (Fig. 1), which is not surprising since chemokines are abundantly produced in tumor sites [4–6]. In addition, treatment of tumor could also promote the migration of MSCs toward tumors. Irradiation of breast tumor cells has been shown to enhance the release of TGFβ1, VEGF and platelet-derived growth factor BB (PDGF-BB) by tumor cells, which enhance the migration of MSCs towards cancer cells [7]. Furthermore, the migratory event was dependent on the upregulation of CCR2 on MSCs following exposure to irradiated cancer cells.

Using rat MSCs, Menon et al. have shown that the migration of MSCs towards cancer cells involved the up-regulation of CXCL12 in MSCs [8]. CXCL8 has been implicated for the migration of MSCs derived from human umbilical cord blood and human bone marrow [9] towards gliomas. Interestingly, even when MSCs are isolated from the same source, i.e. BM-MSCs, different cytokines have been implicated to provide the signaling cues to the migration of MSCs toward cancer cells. For example, CCL2 and CCL25 are the major chemokine responsible for stimulation human BM-MSC to migrate towards breast cancer [10] and multiple myeloma (MM) [11] respectively. Migration of human BM-MSCs towards hepatoma cells involves the release of CCL15 and CCL20 by cancer cells [12] and the chemokine macrophage inhibitory factor secreted by various cancer types can attract human BM-MSCs in a CXCR4-dependent manner [13]. Thus, the type of cytokine released that are crucial for mediating MSC migration is, in part, dependent on the tumor cell type and its niche as illustrated in Fig. 1.

Another way MSC can mediate tumor tropism is via secretion of extracellular vesicles such as the exosomes. Exosomes are small membrane vesicles secreted from cells that are important mediators of

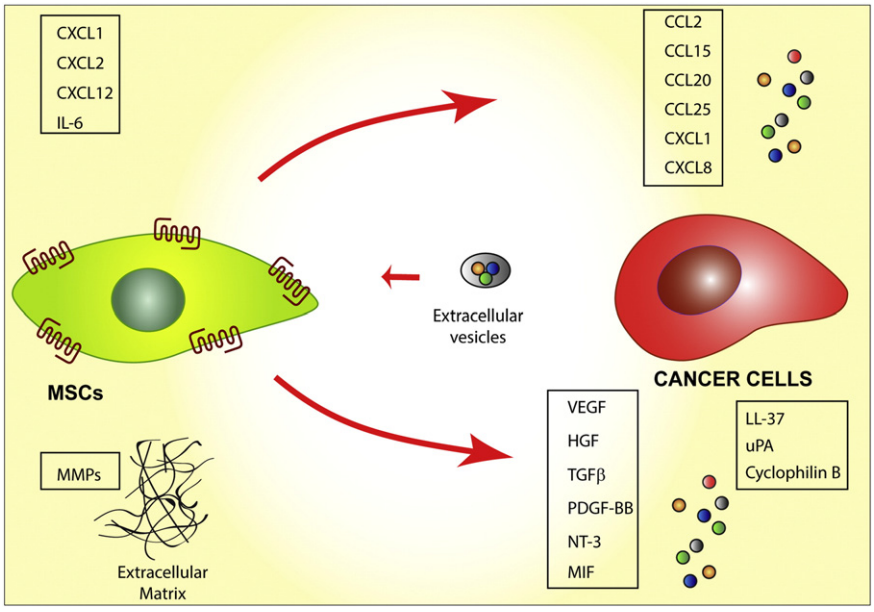

Fig. 1. Factors favoring MSc homing towards tumor cells. Cancer cells secrete a number of chemokines (CCL2, CCL15, CCL20, CCL25, CXCL1, CXCL8) which attract MSC through specific chemokine receptors at their surface. Chemokines can be directly released in the extracellular medium or incorporated into vesicles. Other cytokines including VEGF, HGF, TGFβ, PDGFF-BB, NT-3, MIF and factors such as LL-37, uPA and cyclophilin B released by tumor cells will affect the tropism of MSCs. Moreover, upon interaction with cancer cells, MSCs will secrete cytokines such as CXCL1, CXCL2, CXCL12 or IL-6 and metalloproteinases (MMPs), the latter with the ability to degrade extracellular matrix and favor migration.