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Review

Mechanisms of tumor escape from immune system: Role of mesenchymal stromal cells

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ABSTRACT

Tumor microenvironment represents the site where the tumor tries to survive and escape from immune system-mediated recognition. Indeed, to proliferate tumor cells can divert the immune response inducing the generation of myeloid derived suppressor cells and regulatory T cells which can limit the efficiency of effector antitumor lymphocytes in eliminating neoplastic cells. Many components of the tumor microenvironment can serve as a double sword for the tumor and the host. Several types of fibroblast-like cells, which herein we define mesenchymal stromal cells (MSC), secrete extracellular matrix components and surrounding the tumor mass can limit the expansion of the tumor. On the other hand, MSC can interfere with the immune recognition of tumor cells producing immunoregulatory cytokines as transforming growth factor (TGF)β, releasing soluble ligands of the activating receptors expressed on cytolytic effector cells as decoy molecules, affecting the correct interaction among lymphocytes and tumor cells. MSC can also serve as target for the same anti-tumor effector lymphocytes or simply impede the interaction between these lymphocytes and neoplastic cells. Thus, several evidences point out the role of MSC, both in epithelial solid tumors and hematological malignancies, in regulating tumor cell growth and immune response. Herein, we review these evidences and suggest that MSC can be a suitable target for a more efficient anti-tumor therapy.

Abbreviations: ADCC, antibody dependent cellular cytotoxicity; CDC, complement dependent cytotoxicity; AICD, activation-induced cell death; APC, antigen presenting cells; ARG_{1-2}, arginase 1-2; ATRA, all trans retinoic acid; BAFF, B cell activating factor belonging to TNF superfamily; BM, bone marrow; CAF, carcinoma associated fibroblasts; CCL22, chemokine ligand 22; CEACAM1, carcinoembrionic epithelial antigen cell adhesion molecule 1; CLIR, C-lectin type inhibitory receptors; CLL, chronic lymphocytic leukemia; CTLA-4, cytotoxic T lymphocyte antigen 4; COX_2, cyclooxigenase 2; CTL, cytotoxic T lymphocytes; DC, dendritic cells; DLBCL, diffuse large B cell lymphoma; DL, diffuse lymphoma; DNAM1, DNAX accessory molecule 1; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMC, extracellular matrix component; EMT, epithelial mesenchymal transition; Her2b, epidermal growth receptor 2b; FAP, fibroblasts associated protein; FL, follicular lymphoma; FDC, follicular dendritic cells; GM-CSF, granulocyte-monocyte colony stimulating factor; GIST, gastrointestinal stromal tumor; HDAC, hystone deacetylase; HLA, human class I leukocyte antigen; HL, Hodgkin lymphoma; HSC, hematopoietic stem cells; KIR, killer Ig-like Inhibitory Receptor; ICAM1, intercellular adhesion molecule 1; IDO, indoleamine 2,3, dioxygenase; IL, inteleukin-2, 6, 10, 12, 15, 18; IFNγ, interferon γ; LAIR-1, leucocyte associated Ig-like inhibiting receptor-1; LNMSC, lymph node MSC; LSC, leukemic stem cell; M-CSF, monocyte-colony stimulating factor; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MICA/B, MHC class I polypeptide related sequence A/B; MM, multiple myeloma; MSC, mesenchymal stromal cells; N-BPs, aminobisphosphonates; NK, natural killer; NHL, non-Hodgkin lymphoma; NKG2D, natural-killer group 2 member D; NKG2DL, NKG2D ligand; NKT, natural killer-like T cells; NOS_2, nitric oxide synthase 2; NSCLC, non-small cell lung cancer; PDC, pancreatic ductal carcinoma; PGE_2, prostaglandin E2; PD1, programmed death 1; PD2, programmed death 2; PDL, programmed death ligand; TSC, tumor stem cells; P4H, prolyl-4-hydroxylase; SLAM, signaling lymphocyte molecule family; TAA, tumor associated antigen; TLR, toll like receptor; SMA, smooth muscle actin; TAF, tumor associated fibroblast; Th, T helper; TNFα, tumor necrosis factor α; TGFβ, transforming growth factor β; Treg, regulatory T cells; ULBP1-6, UL16 binding protein 1-6; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VPA, valproic acid.

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1. Introduction

It is thought that immune system controls the survival and proliferation of cancer cells [1–19]. Several anti-tumor effector lymphocytes can be detected within the tumor microenvironment where they exert anti-tumor activity through a direct interaction with tumor cells or releasing soluble factors as cytokines which influence the fate of cancer cells and regulate tumor mass [3–5,7,8,11]. Among anti-tumor effector lymphocytes two main groups can be distinguished: (a) innate cells as natural killer (NK) cells, γδT cells and T cells with the so called NK-like activity [3]; and (b) antigen specific cytotoxic T cells (CTL) reacting with tumor associated antigens (TAA) expressed on tumor cells [3]. Both CTL and innate cells express surface receptors which bind to corresponding ligands bored on tumor cells [3]. This interaction leads to the activation of anti-tumor lymphocytes which try to eliminate tumor cells killing them through the secretion of perforins, granzymes and Fas ligand or different cytokines as IFNγ and TNFα [3]. Antitumor immune cells display a functional behavior typical of Th1 or Th1-Th17 cells [3]. Within the microenvironment several molecular mechanisms can be switched on in order to favor tumor cell growth and escape from the immune-mediated control [7,10,12,13]. Different cells are involved in this regulation: tumor cells, endothelial cells, mesenchymal stromal cells (MSC), regulatory T cells (Treg), antigen presenting cells (APC) including dendritic cells (DC) and myeloid-derived suppressor cells (MDSC) [7,12,14,15,19–21]. Altogether, these cell populations interact one to each other giving positive and negative signals, thus influencing survival, expansion of tumor cells and the anti-tumor effector lymphocyte activities [7,18–21]. This situation is different from what happens during the reparation of a tissue where the same players, except for tumor cells, work in the same direction to establish and maintain the homeostasis [20]. MSC are fibroblast-like cells able to produce the extracellular matrix components (EMC) that are involved in the expansion of tumor mass [19]. MSC together with myeloid-derived cells such as fibrocytes are the players present both during tumor cell expansion and tissue reparation [7], thus it is conceivable that they are relevant in regulating tumor microenvironment and tissue repair [22,20]. Herein, we review the literature on the role of MSC in regulating tumor cell growth and anti-tumor immune response focusing on the phenotypic and functional characteristics, molecular surface structures and biochemical mechanisms involved in MSC interaction with anti-tumor effector lymphocytes. Importantly, we collect under the denomination of MSC several types of fibroblast-like cells as myofibroblasts expressing α-smooth muscle actin, tissue α-smooth muscle actin negative fibroblasts, lymph node MSC, bone marrow-derived MSC migrated to the tumor due to inflammation fibrocytes and pericytes that can differentiate, like epithelial cells, into MSC with a prominent role in angiogenesis [23]. All these types of mesenchymal cells, with an evident intrinsic differentiation plasticity, are able to regulate innate and adaptive immune responses, thus they may play a key role in regulating the fate of tumor growth [24].

2. MSC and tumor microenvironment

Microenvironment is the place where several different cell types interact with EMC influencing both resident cells and cells located in other organs [25–27]. Tissue microenvironment is composed of blood and lymphoid vessels with MSC involved in defining tissue architecture and integrity through the production of EMC usually disposed as fibers of collagen, fibronectin, laminin, heparan sulphate, proteoglycans and several others [25–27]. On this matrix and in the free space among fibers, cells typical of that organ interact and interplay with the MSC [25–27]. We can consider three different tumor microenvironments related to tumor histotype: (a) carcinoma microenvironment, (b) lymph node (LN) in lymphomas and (c) bone marrow (BM) niche in hematological malignancies (Fig. 1).

2.1. MSC in carcinomas

In epithelial solid tumors the microenvironment is composed of cancer cells, endothelial cells, immune cells, myeloid cells, EMC and different types of MSC (Table 1) which are located within mucosa or under this layer relating to the stage of the carcinoma. All these components play an important role in regulating tumor cell growth, host response against tumor and more remarkably the response to cancer therapy [25–27]; thus it is artificial to separate the effects elicited by one type of cell from another without taking into account that the outcome of a given cell-to-cell interaction can be influenced by several types of cells at the same time [25–28]. We now focus our attention on MSC, taking them into account in any kind of microenvironment. They have a fibroblast-like fuse shaped morphology and secrete EMC; furthermore, under appropriate conditions, MSC can differentiate into more specialized stromal cells producing few kinds of EMC. Indeed, MSC derived from any kind of tissue may generate osteoblasts, adipocytes, chondrocytes and smooth muscle cells characterized by specific EMC [25–28]. It is worth to underline that within the tumor MSC can be derived from different cell types: resident fibroblasts, BM- or tissue-derived mesenchymal stem cells, endothelial- and epithelial-derived trans-differentiated cells and pericytes [25–28]. Fibroblasts-like cells in the tumor are often called tumor associated fibroblast (TAF, also named carcinoma associated fibroblasts, CAF, in the case of epithelial tumors) [25–27] (Fig. 1). TAF are the paradigmatic example of MSC involved in the maintenance of survival and proliferation of small cancer cell populations, including tumor stem cells, which allow the escape from anti-cancer therapy [29]. Table 1 is a rough list of the phenotypic characteristics of the different MSC that can be present within a tumor [26]. We should point out that it is difficult to identify peculiar markers of a given MSC and only the expression of several receptors can aid in the classification (Table 1 and Fig. 1). MSC do not generally express leukocyte lineage specific cell markers; on the other hand, they bear markers shared by epithelial cells (several members of epidermal growth factor receptor (EGFR) family) and monocyte/macrophages [30,31]. It makes their characterization quite difficult. The characteristic spindle-shaped cell appearance can change depending on the tissue specific context to a stellate or to a polygonal epithelial-like morphology [30,31]. Thus, we consider MSC as fibroblast-like cells with an intermediate phenotype between epithelial cells and monocytes (Table 1). To complicate this scenario, it is known that epithelial cells can undergo epithelial-mesenchymal transition (EMT) and also mesenchymal cells can assume some epithelial characteristics [25–28,30,31]. Furthermore, fibrocytes are derived from $CD34^+CD45^+$ cells (thus they would be considered as leukocytes) that produce EMC, as collagen I, III and fibronectin, express some markers of MSC and can differentiate to myofibroblasts and pericytes [32–37]. Also, fibrocytes can show immunosuppressive effects and this cell population increases in the peripheral blood of patients suffering from sarcomas [32] (see also the specific Section 3.1 on fibrocytes).

A critical role in the interaction between TAF and tumor cells is played by transforming growth factor (TGF)β [1,2]. In murine models, it has been shown that TGFβ can have opposite effects on tumor cells, depending on the stage of the tumor [38–41]. Indeed, at early stages TGFβ has usually an inhibiting effect while later, it favors tumor cell selection and expansion [38–41]. In particular,