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Review

An overlooked tumor promoting immunoregulation by non-hematopoietic stromal cells

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ABSTRACT

Multidirectional complex communication between tumor-residing hematopoietic and non-hematopoietic stromal cells (NHSCs) decisively regulates cancer development, progression and therapeutic responses. HSCs predominantly participate in the immune regulations, while, NHSCs, provide parenchymal support or serve as a conduit for other cells or support angiogenesis. However, recent reports suggest NHSCs can additionally participate in ongoing tumor promoting immune reactions within tumor-microenvironment (TME). In this review, based on the state-of-art knowledge and accumulated evidence by us, we discuss the role of quite a few NHSCs in tumor from immunological perspectives. Understanding such consequence of NHSCs will surely pave the way in crafting effective cancer management.

Contents

1. Introduction

Despite having the full power of the immune system to eliminate completely the residual tumor cells after surgery and to develop tumor specific memory response to combat the disease recurrence, cancer continues to escape cure. Several brilliant researches show promises but desired success is yet to be achieved. In addition to the biological/biochemical alterations, extensive changes within associated immune components make the cancer more complex and un-responsive to therapy but surely hold the clues for its remission [1]. To unravel these complexicity, recent studies have focused to the tumor microenvironment (TME) rather than cancer cells. The disease supporting microenvironment contains transformed cells, non-transformed stromal (hematopoetic and non-hematopoetic) cells, extracellular matrix, soluble factors, tumor vasculature and lymphatics [2]. These non-transformed recruited immune cells (hematopoetic stromal components) interact with tumor and predominantly regulate the immune response in a complex manner. While non-hematopoietic stromal cells (NHSCs), e.g., fibroblasts/myofibroblasts, endothelial

Abbreviations: TME, tumor microenvironment; NHSC, non hematopoietic stromal cells; MSC, mesenchymal stem cells; MF, myofibroblasts; CAF, cancer associated fibroblasts PGE2 prostaglandin E2; VEC, vascular endothelial cells; LEC, lymphatic endothelial cells; PDGFR, platelet derived growth factor receptor; FAP, fibroblast activator protein; LN, lymph node; TKI, tyrosine kinase inhibitors; IMiDs, immunomodulatory drugs.

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cells, pericytes etc., are primarily provide organizational support, supply nutrients, regulates hemodynamic and entry/exit of immune cells. Most of these NHSCs directly participate in tumor growth promoting cascade within TME by producing growth factors and by (over)expressing receptor tyrosine kinases. However, their role in ongoing immune responses is received least attention till date.

Under the inflammatory conditions within TME, NHSCs acquire additional novel feature (immune signature), critical for the development of pathological processes and disease progression. Classically primary immunity begins in the secondary lymphoid organs, where naive T cells encounter antigen through professional antigen presenting cells, and then these effector/memory cells emigrate to the peripheral (inflammatory/tumor) sites via blood stream, where re-encounter of antigen may be possible via tissue resident immune cells or occasionally via NHSCs. In this context, role of hematopoietic stromal cells (classical immune cells) is well studied, however, Immunomodulatory role of NHSCs is recently gained special interest. For better understanding of the complex and unnoticed role played by different NHSCs from immunological perspectives, this review will focus mesenchymal stem cells (MSCs), fibroblasts/myofibroblasts, endothelial cells, pericytes and adipocytes in relation to their immunoregulatory functions to promote tumor growth (Fig. 1).

2. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are a group of heterogeneous, non-hematopoietic, multipotent precursor cells generated from $Sox1^+$ neuroepithelium during embryogenesis and in later phases (during postnatal development) from other origins [3]. As a multipotent stromal cells, it retains the potential to differentiate into osteoblasts, chondrocytes, neurons, muscle, endothelium, and more [3,4] as well as can trans-differentiate into cells of ecto-/endodermal origin. MSCs mainly reside within hypoxic bone marrow, but can also be found in most tissues. The primary cellular function is to repair injured tissues by providing angiogenic growth factors and structural support including tissue reorganization and cell differentiation.

Within tumor, MSCs are recruited in a large number from distant sites via inflammatory mediators (primarily via CXCL16). Unlike normal MSCs, tumor-MSCs promote tumor cell survival and inhibit apoptosis either by releasing anti-apoptotic/pro-survival factors or by inducing autophagy [5]. MSCs in a paracrine way enhance cancer cell motility, invasion and metastasis. Furthermore, MSCs played important role in tumor vasculogenesis either by secreting pro-angiogenic factors or by differentiating into cancer associated fibroblasts, pericytes and endothelial-like cells [6]. Other important tumor growth and recurrence promoting events such as epithelial-mesenchymal transition, cancer stem cell (CSC) proliferation and shifting of mesenchymal niches are also directly influenced by MSCs [7,8].

In spite of the low immunogenicity of MSCs, as a bone marrow resident cell, it essentially interacts with immune cells and their progenitors. MSC can influence both adaptive and innate immune responses, like inhibition of T and NK cell proliferation, recruitment and support of regulatory T cells, suppression of Th17 lymphocytes, inhibition of dendritic cell (DC) maturation and immunoglobulin production by plasma cells, etc [9,10]. As MSCs lack expression of most of the co-stimulatory molecules and MHC-II, T cell suppression is crucially regulated by MSC-secreted soluble factors including TGFβ, hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), soluble HLA-G5, heme oxygenase-1, indolamine-2,3-dioxygenase (IDO), inducible nitric-oxide synthase (iNOS), leukemia-inhibitory factor and IL-10 [11,12]. Furthermore, few studies demonstrated role of TLR–TLR ligand in MSC’s immunomodulatory activity and in this line Nemeth et al., reported that MSCs activated by a TLR4 ligand could reprogram macrophages by releasing PGE2 [13]. MSC hamper differentiation and functions of DC by releasing IL-6, TGFβ and PGE2. Recent studies demonstrated that constitutively expressed galectin 1 and 3 on MSCs act as another major negative regulator for T cells [14].

Although the role of MSCs in constructing TME and its potential mechanisms are still controversial, immunoregulatory properties (including several side effects related to systemic immunosuppression) are thought to be attributed for MSC mediated pro-tumor functions. Han et al. implanted B16 melanoma cells in allogenic mice and demonstrated that MSCs help tumor establishment by promoting immune evasion [15]. In this line, Prevosto et al., also reported that immunosuppressive effect of MSCs is mediated by regulatory $CD8^+$T cells [16]. In a recent study, we found that under tumor conditions MSC recruited not only in tumor site but also in lymph nodes and predominantly target DC-induced expansion and late phase effector functions of both $CD4^+$ and $CD8^+$ T cells via IL-10-STAT3 signaling (Ghosh et al., Ms under revision, *Int. J. Cancer*). More importantly, MSC secretes higher amount of IL-10 than classical immunoregulatory cells. Overall data suggested MSCs within tumor acquire more 'immunosuppressive signature' to support tumor growth.

3. Fibroblasts-myofibroblasts

Fibroblasts, the principal cell of connective tissues, synthesize extracellular matrix and collagen to form structural tissue framework, hence, play an important role in wound healing and act as a regulatory cell for developmental processes. Morphologically, these heterogeneous cells show diverse appearance depending on their location and activity. During wound healing and fibrosis, quiescent fibroblasts undergo transformation to activated myofibroblasts (MFs) [17].

In aggressive tumor, frequency of fibroblasts or myofibroblasts is found to be increased along with scar-like collagen deposition [18]. This altered fibroblast or cancer associated fibroblasts (CAFs) exhibited a spatio-temporal abnormal phenotype and is identified by their expression of PDGFRα, vimentin, α-Smooth muscle antigen and Fibroblast Activator Protein (FAP) [19] and serves as a main source of ECM components and modulators [20]. CAF can be derived from pericytes, endothelial cells, myoepithelial cells or MSCs. More importantly by providing multi-faceted functions fibroblast play a crucial role in cancer progression towards more invasive phenotype and help in the preparation of metastatic niche by maintaining stemness [21]. Similar to the immune cells, CAFs inhibit early stages of tumor progression [22] and later on promote tumor progression by secreting soluble factors like PDGFs, EGF, IGF-I/II and TGFβ [21,23]. It also plays an important role in hypoxia-induced angiogenesis by secreting VEGF and direct modulation of ECs functions [24]. Moreover, in metastatic tumor, by exploiting oxidative stress and activating cyclooxygenase 2, NFκB and HIF-1, fibroblast-drive EMT [21]. Unlike other tumor-resident NHSCs, modulatory role of fibroblasts on immune cells (macrophages or DCs or T cells) are considered as important as its other tumor promoting functions. Being most primitive cells, fibroblasts can interact with immune cells as an alternative APC and can modulate functions of various leucocytes linked with pathophysiology of several diseases [25]. At the site of chronic inflammation, fibroblast plays an important role in lodging and retention of lymphocytes and interacts through cell adhesion molecules [26]. In different disease settings, fibroblasts suppress inflammation, induce type 2 immune response and modulate monocyte/macrophage functions [27]. Molecular studies suggest that two important transcription factors, NFκB and