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State-of-the-art of regulatory dendritic cells in cancer

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ABSTRACT

Dendritic cells (DCs) with robust immunosuppressive activity are commonly found in the microenvironment of advanced solid tumors. These innate immune cells are generically termed regulatory DCs and include various subsets such as plasmacytoid, conventional and monocyte-derived/inflammatory populations whose normal function is subverted by tumor-derived signals. This review summarizes recent findings on the nature and function of regulatory DCs, their relationship with other myeloid subsets and unique therapeutic opportunities to abrogate malignant progression through their targeting.

Contents

1. Introduction

In the tumor microenvironment, DCs have a pivotal role for the activation of T cell-mediated anti-tumor immunity. However, in individuals with advanced cancer, tumor-derived extracellular inflammatory signals alter hematopoietic differentiation within the bone marrow, resulting in an increase in myeloid output, termed "emergency" myelopoiesis. Altered myelopoiesis progressively impairs the capacity of DCs to prime and sustain immune protection against tumor growth, resulting in significantly accelerated malignant progression.

Recent mechanistic insight from different groups has unveiled important clues on how tumor-induced signals block the generation of mature, immunocompetent DCs in some tumors, while also transforming tumor-associated DCs (tDCs) from a potentially immunostimulatory to an immunosuppressive (regulatory) cell type in others. This review will focus on the role of regulatory DCs in advanced malignancies and how a better understanding of their activities and the immunosuppressive mechanisms that they elicit could lead to the design of more effective therapeutic interventions to restore anti-tumor immunity.

2. The nature of regulatory dendritic cells in the tumor microenvironment

Although terminal differentiation of at least murine myeloid cells is impaired by tumor-derived factors, including VEGF-A (Gabrilovich

Abbreviations: DC, dendritic cell; ER, endoplasmic reticulum; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; iNOS, inducible nitric oxide synthase; IRE1α, inositol-requiring enzyme 1 alpha; MAPK, mitogen-activated protein kinase; PD1, programmed death 1; PD-L1, programmed death-ligand 1; PEI, polyethylenimine; PERK, PRKR-like endoplasmic reticulum kinase; PGE2, prostaglandin E 2; RNA, ribonucleic acid; ROS, reactive oxygen species; siRNA, small interfering RNA; tDC, tumor-associated DC; TGFβ, transforming growth factor beta; TLR, toll-like receptor; TME, tumor microenvironment.; VEGF-A, vascular endothelial growth factor; UPR, unfolded protein response; XBP1, X-box binding protein 1.

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et al., 1998), rare populations of DCs with significant antigen-presenting capabilities have been identified in a variety of tumors for both humans and mice (Broz et al., 2014). However, DCs spontaneously lacking the capacity to effectively stimulate T cells are a more common occurrence in the microenvironment of advanced solid tumors (Shurin et al., 2013). Besides losing their immunostimulatory function, tDCs also acquire direct inhibitory activities against tumor-reactive T cells and/or the ability to promote the generation of regulatory T cells (Treg). These DCs are generically termed regulatory DCs and include very diverse myeloid subsets of different origins and activities. Although the abundance and phenotype of regulatory DCs reported in different tumors varies, immunosuppressive attributes have been associated with DCs representing the major DC subsets in mice and humans: Plasmacytoid, conventional and inflammatory DCs (Bachem et al., 2010; Haniffa et al., 2012; Manh et al., 2013; Merad et al., 2013; Segura & Amigorena, 2013, 2014; Segura et al., 2013).

Plasmacytoid DCs ($B220^+CD11c^{low}MHC\text{-}II^+$ leukocytes co-expressing CD303 in humans and CD317 in mice) represent a rare DC subset specialized in the production of type I IFN in inflammatory conditions. They have been found to promote immunosuppression by enhancing IL-10 secretion by $CD4^+Foxp3^-$ T cells in human hepatocarcinoma (Pedroza-Gonzalez et al., 2015), while their presence is associated with regulatory Th2 responses in breast cancer patients (Ghirelli et al., 2015) and human melanoma (Aspord et al., 2013), as well as Treg activity in human breast cancer (Sisirak et al., 2013). Finally, plasmacytoid DCs contribute to tumor-induced immunosuppression by inducing $CD8^+$ regulatory T cells in the human ovarian cancer microenvironment (Wei et al., 2005).

Besides plasmacytoid DCs, other authors have identified tumor-induced regulatory DCs in preclinical mouse models as conventional DCs (recently identified as *Zbtb46*$^+$ cells (Meredith et al., 2012; Satpathy et al., 2012)) co-expressing CD11c, MHC class II and co-stimulatory CD80 and CD86 molecules and high levels of CD11b (Liu et al., 2009; Norian et al., 2009). $Lin^-ZBTB46^+MHC\text{-}II^+CD141^+$ conventional DCs (or their $CD8a^+CD4^-$ murine counterparts) typically cross-present extracellular antigens to $CD8^+$ T cells, while $Lin^-ZBTB46^+MHC\text{-}II^+CD1c^+$ conventional DCs (or their $CD8a^-$ counterparts in mice) express a distinct TLR pattern (Said & Weindl, 2015) and are particularly effective at inducing Th2 responses (O'Keeffe et al., 2015). In cancer, however, $CD11b^+$ conventional DCs have been found to suppress $CD8^+$ T cell function in tumor-bearing mice, among other potential mechanisms, via L-Arginine metabolism (Norian et al., 2009).

The phenotypic diversity of tumor microenvironmental DCs, however, cannot be understood without considering the pathological nature of myelopoiesis in cancer-bearing hosts. Thus, tumors are not only promoting inflammation at tumor beds, but also systemically, activating emergency myelopoiesis in bone marrow precursors. tDCs therefore include not only the short-lived leukocytes that typically arise from a hematopoietic lineage distinct from other leukocytes (Merad et al., 2013; Schraml et al., 2013), but also inflammatory cells derived from monocytes or DCs exhibiting markers differing from DCs generated during steady-state conditions, such as FcεRI and CCR7 (Fig. 1). Exhaustive studies by Amigorena and colleagues have characterized inflammatory DCs as human $CD11c^+CD115^+CD1c^+CD1a^+Fc\varepsilon RI^+CD206^+CD172a^+CD14^+CD11b^+$ leukocytes and $CD11c^+MHC\text{-}II^+CD11b^+F4/80^+Ly6C^+CD206^+CD115^+CD107b^+Fc\varepsilon RI^+CD64^+$ cells in mice (Segura & Amigorena, 2013, 2014). Although their precise ontogeny in inflammatory conditions remains unclear, inflammatory DCs can certainly arise from monocytes, and produce high levels of the pro-inflammatory cytokines TNF, IL-6, and IL-12 (O'Keeffe et al., 2015).

Distinguishing macrophages and DCs in the tumor microenvironment (TME), however, is more complex than in the steady-state conditions because they arise from a continuum of pathological myelopoietic

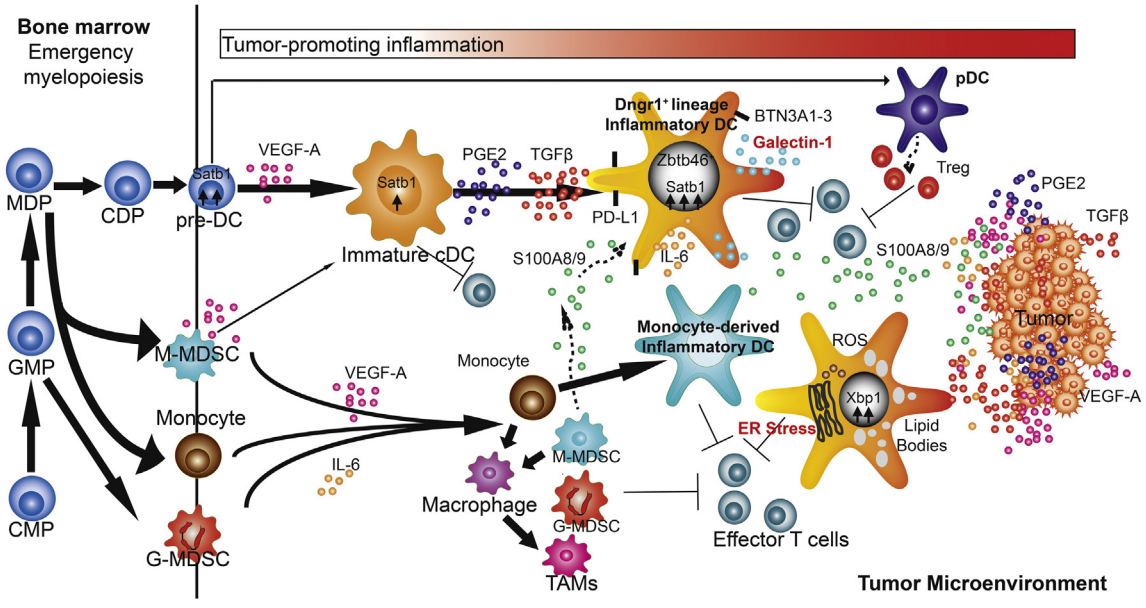

Fig. 1. Pathological myelopoiesis, ER stress and Satb1 overexpression converge to transform DCs from an immunostimulatory to an immunosuppressive, tumor-promoting cell type. During emergency myelopoiesis, myeloid differentiation is dysregulated by tumor-promoting factors such as S100A8/A9, IL-6 and VEGF-A, resulting in the expansion of immature myeloid subsets and their mobilization to lymphatic locations and tumor beds. Pathological myelopoiesis involves disruption in the differentiation program of common myeloid progenitors (CMP) into granulocyte–macrophage progenitors (GMP), which give rise to PMN-MDSCs. Differentiation of macrophages and DCs is also subverted, resulting in the generation of monocytic MDSC (M-MDSC), which turn into macrophages and DCs in the TME. DC maturation is impaired by tumor-derived factors, including VEGF-A, promoting anergy and ineffective priming of T cells and, eventually T cell exhaustion. Inflammatory DCs originating from both monocytes and true DC precursors due to inflammatory stimuli undergo oxidative stress at tumor beds. Generation of reactive oxygen species (ROS) in inflammatory DCs results in ER stress and subsequent upregulation of XBP1, inducing inflammatory DCs to abnormally accumulate lipids, resulting in an inhibitory phenotype and diminished ability to induce robust anti-tumor T cell responses. In addition, inflammatory DCs acquire profound suppressive activity in the TME under the influence of tumor-derived PGE2 and TGFβ. Furthermore, tumor- and myeloid cell-derived S100A8/9 drives unremitting expression of the genomic organizer SatB1 in pre-DC-derived inflammatory DCs, driving hyper-secretion of IL-6 and galectin-1, which has a strong direct immunosuppressive activity on T cells. Plasmacytoid DCs (pDCs) also drive Treg differentiation at tumor beds, further contributing to the suppression of anti-tumor immunity. The immunosuppressive activity of tDCs derived from M-MDSCs remains to be determined.

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