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Myeloid cells in cancer-related inflammation

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ABSTRACT

Myeloid cells are key elements of the cancer-related inflammation with the potential to support not only tumor growth but also invasion and metastasis. Tumor-derived factors affect myeloid cell differentiation inducing a phenotype that supports tumor growth, inducing immunosuppression, angiogenesis and tissue remodeling. Soluble mediators, produced at primary tumor site, can also act in a remote mode inducing the release from bone marrow of myeloid cells that have immunosuppressive activities in tumor-draining lymphoid organs and can predispose to colonization when migrate to metastatic organs. We will here review current knowledge on the contribution of tumor-derived signals that affect polarized activation of myeloid cells, their bone marrow release and recruitment to metastatic sites with a particular focus on the role of chemokines.

Introduction

Chronic inflammation is one of the consistent features of the tumor microenvironment and is now recognized as an enabling characteristic of cancer (Elinav et al. 2013). Inflammation can fuel cancer in two ways: inflammatory conditions caused by extrinsic stimuli can promote cancer insurgence or oncogenes can activate the expression of inflammation-related programs that sustain tumor growth (Mantovani et al. 2008). Myeloid cells are major players in cancer-related inflammation (CRI). These cells have the potential to develop an antitumoral immune response but they are often instructed by the tumor to favor tumor growth stimulating tumor cell proliferation and angiogenesis, malignant progression, metastasis and resistance to therapy.

Myeloid cells at tumor site include different cell types: inflammatory monocytes, macrophages (called tumor-associated macrophages-TAM), neutrophils (tumor-associated neutrophils-TAN), dendritic cells and a population functionally identified as myeloid-derived suppressor cells (MDSC) that have been classified in mice as monocytic CD11b+/Ly6C+ MDSC (Mo-MDSC) and granulocytic CD11b+/Ly6G+ MDSC (G-MDSC) on the basis of the expression on their surface of the Ly6C or Ly6G antigen, respectively. Mo- and G-MDSC are not fully separated cell subsets and share functional and phenotypical similarities with TAM and TAN (Youn and Gabrilovich 2010). Thus far, the differential role of tissue-resident versus newly recruited myeloid cells in tumor progression remains unsolved due to a lack of clear knowledge on primitive precursors (Schulz et al. 2012; Guilliams et al. 2013; Ginhoux et al. 2010) and the use of few markers not entirely restricted to particular myeloid cell types that composed tumor (Van Overmeire et al. 2014). In this review we will focus our attention on common emerging cytokines and chemokines that are implicated in myeloid cell recruitment and instruction by tumor cells to promote its own growth (Fig. 1).

Myeloid cell mobilization from the bone marrow

Stromal and tumor cells produce a wide spectrum of chemokines and growth factors that determine recruitment of myeloid cells to tumor sites from the bone marrow and from splenic reservoir (Swirski et al. 2009) as demonstrated by Cortez-Retamozo et al. (2012).

Abbreviations: CRI, cancer-related inflammation; TAM, tumor-associated macrophages; TAN, tumor-associated neutrophils; MDSC, myeloid-derived suppressor cells; TADC, tumor-associated dendritic cells; BMDC, bone marrow-derived haematopoietic progenitor cells; ACKR2, atypical chemokine receptor 2; M-CSF, macrophage colony stimulating factor; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor beta; bFGF, basic fibroblast growth factor; PGE2, prostaglandin E2; Treg, T regulatory cells; VEGFR1, vascular endothelial growth factor receptor 1; MMP9, matrix metalloproteinase-9; MMP2, matrix metalloproteinase-2; LOX, lysyl oxidase; TEN, tumor-entrained neutrophils; MET, mesenchymal to epithelial transition; EMT, epithelial to mesenchymal transition.

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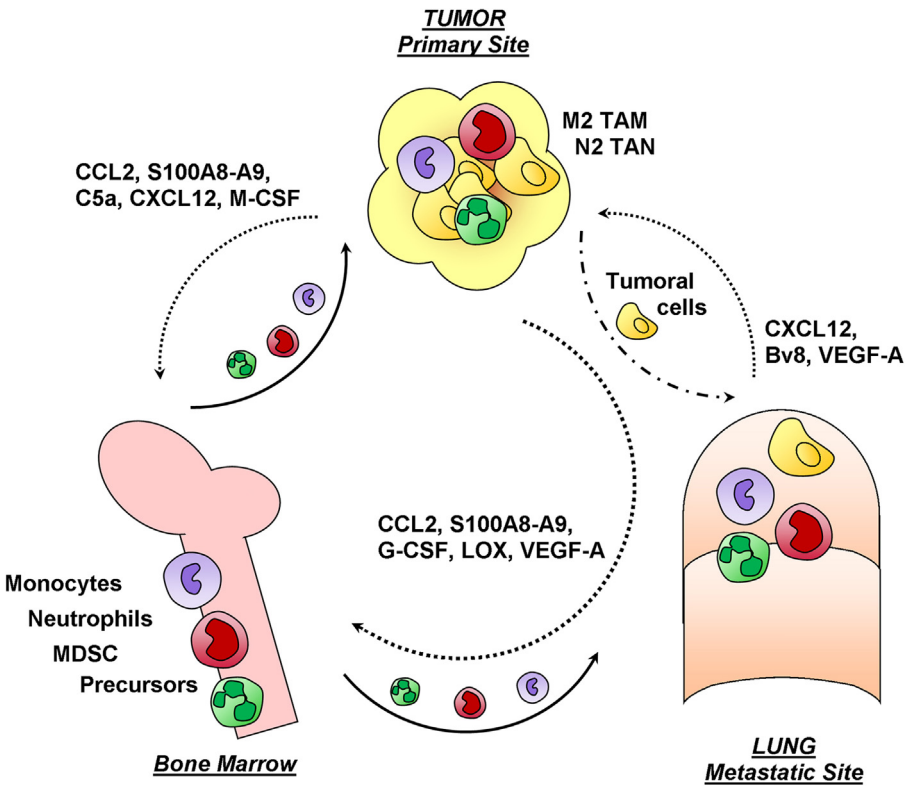

Fig. 1. Role of tumor-derived factors in tumor growth and metastatization. Myeloid cell polarization toward a type 2 protumoral phenotype is dictated by tumor-derived signals in the local microenvironment. Tumor derived factors also influence bone marrow myeloid cell mobilization. In this way they can enter into the bloodstream and home at tumor site or in the premetastatic niche, predisposing the tissue for successful tumor colonization.

The key players of monocyte egression from the bone marrow in inflammatory conditions are notoriously the chemokines CCL2 and CCL7 and their receptor CCR2 (Tsou et al. 2007; Tacke et al. 2007; Shi et al. 2011; Shi and Pamer 2011; Martin et al. 2008). CCL2 is the first tumor-derived chemotactic factor identified (Bottazzi et al. 1983) being expressed in a huge number of tumors, like glioma (Leung et al. 1997), melanoma (Graves et al. 1992), ovarian carcinoma (Negus et al. 1995) squamous cell carcinoma of the uterine cervix (Riethdorf et al. 1996), breast (Soria and Ben-Baruch 2008) and prostate cancer (Lu et al. 2006). In patients with breast cancer (Feng et al. 2011), pancreatic cancer (Sanford et al. 2013) and melanoma (Schmidt et al. 2005), high levels of CCL2 correlate with increased monocyte mobilization and poor survival. In particular, in pancreatic cancer patients, the reduced numbers of monocytes in the peripheral blood is predictive of increased survival (Sanford et al. 2013). In a murine model of pancreatic cancer, the CCR2 inhibition promotes anti-tumor immunity and prevents liver metastasis. On the basis of these data, a phase Ib/II clinical trial using PF-04136309, a novel CCR2 inhibitor, combined with standard chemotherapy, is started in patients with pancreatic cancer with locally advanced, non-metastatic disease (Sanford et al. 2013). The relevance of CCL2/CCR2 axis in the tumor infiltration of monocytes has been also demonstrated in Kaposi's sarcoma, where the expression of the atypical chemokine receptor 2 (ACKR2), a CCL2 scavenger receptor, inversely correlates with tumor aggressiveness (Savino et al. 2014).

Another important chemokine axis in monocytes, but also neutrophil egress from bone marrow and recruitment at tumor site is the CXCL12/CXCR4 axis. The treatment of tumor-bearing mice with a CXCR4 antagonist is sufficient to significantly impair the monocyte recruitment in different tumor models (Gabrilovich et al. 2012; Yang et al. 2008; Schmid et al. 2011). One of the understood mechanism by which CXCL12 promote leukocyte recruitment inside the tumor is by promoting changes in integrin affinity and avidity. In fact, in a model of subcutaneous injection of Lewis lung carcinoma, CXCL12 was reported to activate $\alpha 4\beta 1$ integrin on monocytes, improving integrin clustering and monocyte attachment to VCAM-1, expressed by endothelial cells (Schmid et al. 2011).

Chemokines and chemokine receptors are also critical for the dynamic turnover of MDSC in tumor bearing mice. In fact, CCR2 absence caused striking conversion of infiltrating MDSC from Mo-MDSC to G-MDSC in the tumor, associated with the excessive production of CXCR2 ligands and G-CSF at tumor site, without affecting tumor growth (Sawanobori et al. 2008). MDSC traffic is also regulated by other chemoattractants present at tumor site, such as the C5a complement component. It has been reported to recruit MDSC into tumors and to increase their T cell-directed suppressive abilities through modulation of the production of reactive oxygen and nitrogen species. Moreover, pharmacological blockade of the C5a receptor considerably impaired tumor growth in mice (Markiewski et al. 2008).

Neutrophils mainly migrate toward CXCR2 ligands not only in physiological and pathological conditions but also in the tumor setting. Tumor-derived CXCL5 recruited TAN that promote tumor growth and metastasis (Zhou et al. 2014). In addition, in murine models, CXCR2 deficiency or neutrophil depletion suppressed inflammation-related tumorigenesis and the onset of spontaneous tumors (Jamieson et al. 2012).

Beyond chemokines, monocyte recruitment at tumor site is sustained by noncanonical chemotactic peptides, such as macrophage colony stimulating factor (M-CSF/CSF-1), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF).

M-CSF is the subject of intense research and inhibitors are in clinical trials for cancer therapy (Hume and MacDonald 2012). Genetic depletion of M-CSF in a spontaneous model of breast