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Mini-review

Cancer related inflammation: The macrophage connection

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Abstract

Tumor-associated macrophages (TAM) are key regulators of the link between inflammation and cancer. In the tumor microenvironment neoplastic cells shape the differentiation and functional orientation of TAM which, in turn, express several protumoral functions, including secretion of growth factors and matrix-proteases, promotion of angiogenesis and suppression of adaptive immunity. This review analyzes our current knowledge of TAM and their involvement in tumor development and progression. The interplay between TAM and neoplastic cells represents a promising target of future therapeutic approaches.

Keywords: Tumor-associated macrophages; Macrophage polarization; Tumor promotion; Therapeutic targets; Inflammation; Cancer; Chemokines; Cytokines; Angiogenesis

1. Origin of TAM

Solid tumors are infiltrated with leukocytes and the cross-talk between neoplastic and blood-borne cells have profound effects on tumor progression. Leukocytes account for up to 50% of the tumor mass, the most represented subsets being lymphocytes and macrophages. The presence of immunocompetent cells within human tumors has been considered as a proof of an immunological anti-tumor response. Indeed, the density of T lymphocytes has been significantly associated with a more favourable clinical outcome in some tumor types, including for instance colorectal and ovarian cancer, melanoma [1–5]. In contrast, the density of macrophages is correlated in most – though not all – tumors with increased angiogenesis, tumor invasion and poor prognosis [6–9].

The presence of TAM at the tumor site represents one of the hallmarks of cancer-associated inflammation. [10–13]. TAM derive from circulating monocytes which are selectively attracted within the tumor microenvironment by locally produced chemotactic factors. Historically, a tumor-derived chemotactic factor (lately identified as CCL2) was described 25 years ago [14]. Experimental and human studies have confirmed that the levels of tumor-derived CCL2 significantly

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correlate with TAM density in ovarian, breast, pancreatic and other tumors [6,13]. Other chemokines (e.g. CCL5, CCL7, CCL8, CXCL12) or cytokines e.g.: vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and macrophage colony stimulating factor (M-CSF) have been shown to attract blood monocytes at the tumor site [15]. TAM accumulate into necrotic regions of tumors, characterized by low oxygen tension [16]. This preferential localization is regulated to a large degree by tumor hypoxia which induces the expression of hypoxia inducible factor (HIF-1)-dependent factors, like for instance VEGF, the chemokine CXCL12 and its receptor CXCR4, which modulate TAM migration in avascular regions [17–19].

Incoming monocytes differentiate in the tumor microenvironment to tissue resident macrophages mainly due to the effects of tumor-derived growth factors, especially M-CSF. Functional plasticity is a well known characteristic of the mononuclear phagocyte system and the paradigm of M1 and M2 polarization identifies the two extremes of the whole spectrum of macrophage functional activities (see for review 20) Briefly, while M1 macrophages have immunostimulatory Th1-orienting properties, M2 cells have an IL-12^{low}, IL-10^{high} profile, poor antigen-presenting capacity and suppress Th1 adaptive immunity. In addition, M2 macrophages actively scavenge debris, promote wound healing, angiogenesis and tissue remodeling. Microenvironmental signals expressed at the tumor microenvironment play a central role in the orientation of differentiating macrophages and recent studies have clarified that TAM represent a distinct M2-polarized macrophage population [21]. Among the factors having the potential to promote the polarization of M2 macrophages are PGE2, TGFβ, IL-6 and IL-10 [22,23]. The immunosuppressive cytokines IL-10 and TGFβ are produced by many types of cancer cells and by TAM themselves. IL-10 promotes the differentiation of monocytes to mature macrophages and blocks their differentiation to DC. Thus, a gradient of tumor-derived IL-10 may preferentially push incoming monocytes toward macrophage differentiation, in different micro-anatomical localizations of a tumor. Such situation was observed in breast cancer and in papillary carcinoma of the thyroid, where TAM were evenly distributed throughout the tissue, in contrast to DC which were present only in the periphery [24].

2. Protumoral role of TAM

The pro-tumorigenic activities of TAM cover several crucial features of neoplastic cells: proliferation, migration and metastasis; survival in hypoxic conditions due to stimulated angiogenesis; immune evasion due to suppression of anti-tumor immunity.

Already in the late '70s it was clear that in the absence of M1-orienting signals (LPS and IFNγ) TAM rather promoted tumor cell growth in vitro [13,25–27]. Studies in experimental murine models showed that tumors producing CCL2 and harboring higher numbers of TAM had more spontaneous lung metastases compared to parental non-producing tumors. In turn, genetic studies in mice have shown decreased rates of tumor growth and metastasis to be associated with decreased TAM number [6,28].

Intercross of transgenic mice susceptible to mammary cancer (PyMT), with mice containing a recessive null mutation in the M-CSF gene (Csf^{op}) demonstrated that TAM recruitment is an absolute requirement for productive metastatic growth [29]. Lin and colleagues [30] demonstrated a slower rate of progression to malignancy and fewer pulmonary metastases in macrophage-deficient *CSF-1* null mutant mice bearing spontaneous mammary carcinoma than in *CSF-1* wild-type mice. In this mouse model, they also showed that TAM play a crucial role in the "angiogenic switch" when hyperplastic lesions develop into early stage mammary carcinomas [30]. It is interesting to note that SHIP1-deficient mice, which exhibit a spontaneous drift towards M2 macrophages polarization, experience increased growth of transplanted tumors [31].

The protumoral role of TAM in human cancer is supported by many clinical studies that found – in most tumors – a correlation between the high macrophage content and poor patient prognosis [6–9,11]. Accordingly, genes associated to macrophage infiltration (e.g. CD68) or differentiation (M-CSF) are part of recent molecular signatures which herald poor prognosis in lymphoma and breast cancer [32,33].

Many macrophage products released in the tumor stroma can directly stimulate the growth of tumor cells and/or promote tumor cell migration and metastasis (Fig. 1). These include epidermal growth factor (EGF), members of the FGF family, TGFβ, VEGF, chemokines and cytokines. It is well established that IL-1β augments metastasis [34–37].