Macrophages and Cancer Development

Subjects: Immunology

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Macrophages are innate immune cells pivotal for tissue homeostasis, removal of superfluous cells, and inflammatory responses to infections. Macrophages also play diverse roles in cancer development, ranging from antitumor activity in early progression stages to, most commonly, tumor-promoting roles in established cancer. Notably, macrophages are highly plastic cells and, depending on the microenvironmental cues in the Tumor Microenvironment (TME), can undergo marked changes in their function. In established cancers, high macrophage infiltration often strongly associates with poor prognosis or tumor progression in many types of solid tumors, including breast, bladder, head and neck, glioma, melanoma, and prostate cancer. Conversely, in colorectal and gastric cancers, high macrophage infiltration correlates with a better prognosis. These apparently opposite effects are likely related to macrophage plasticity and resultant heterogeneity of phenotype and functions in various cancers.

tumor-associated macrophages immunotherapy tumor microenvironment tumor immune suppression macrophage

1. The Role of Macrophages in the Tumor-Promoting Inflammation

In a physiological context, inflammation is initiated to restore homeostasis after the disturbance caused by external factors [1]. However, not every type of inflammation is advantageous, and chronic inflammation increases the chances for the transformation into a malignant cell. Tumor-promoting inflammation could be induced long before tumor formation and can support tumor growth by encouraging neoangiogenesis, immune suppression, and oncogenic mutations [2]. Cell death is frequent in tumors and leads to the release of damage-associated molecular patterns (DAMPs), like High Mobility Group Box 1 (HMGB1), Heat Shock Proteins (HSPs), or ATP [3][4]. This stimulation can lead to the promotion of anti-tumor immunity, e.g., by activation of dendritic cells and macrophages. However, chronic stimulation will lead to immunosuppression mediated by increased production of IL-10, which inhibits the expression of proinflammatory cytokines and induces the formation of regulatory T lymphocytes (Tregs) [5] (Figure 1).

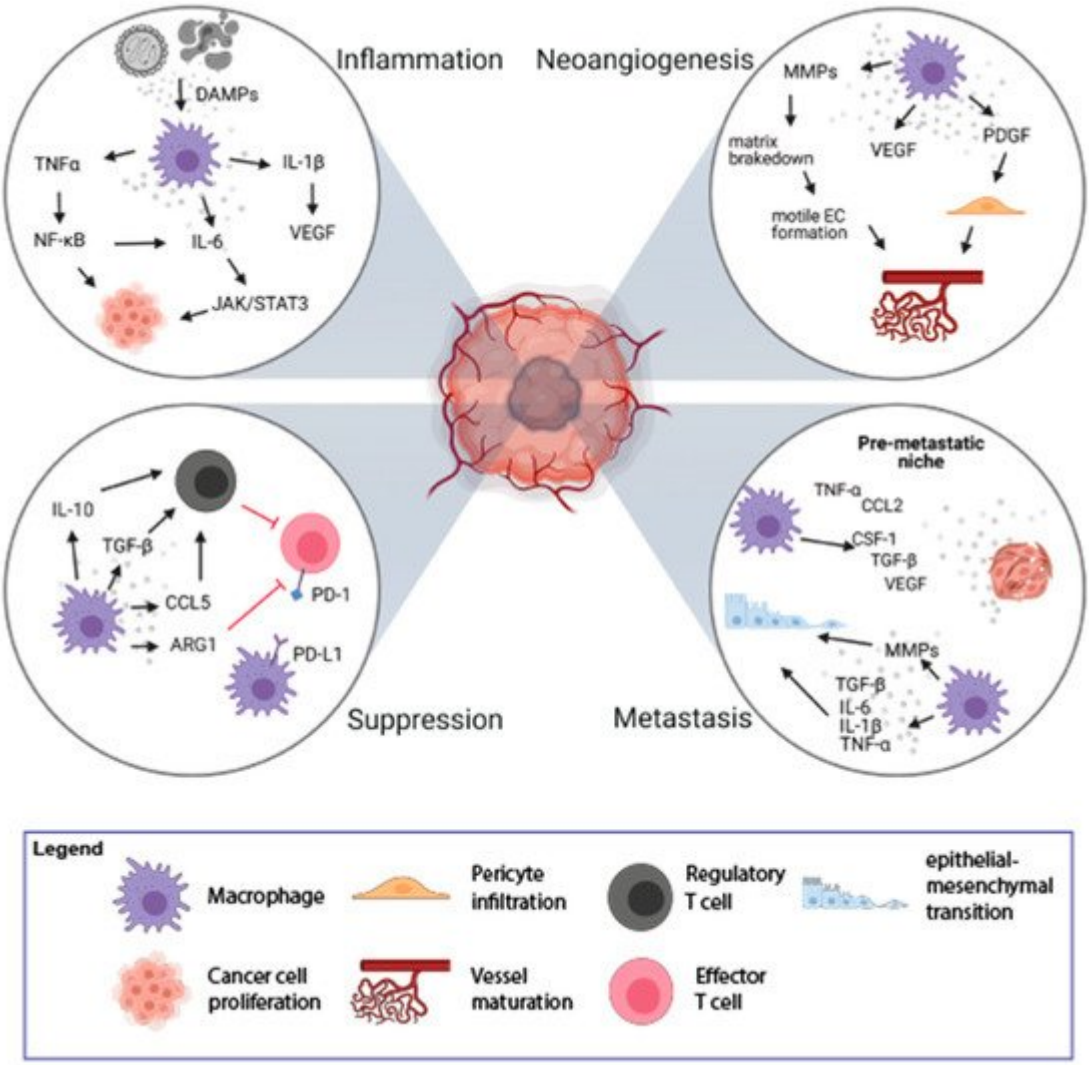

Figure 1. Mechanisms of tumorigenesis stimulation by Tumor-Associated Macrophages (TAMs). TAMs play an important role in the process of tumorigenesis by induction of inflammation (top left loop), stimulation of neoangiogenesis (top right loop), immune suppression (bottom left loop), and induction of metastasis (bottom right loop). The figure was created with Biorender.com.

Macrophages can contribute to tumor-promoting inflammation, e.g., by secretion of proinflammatory cytokines, like IL-6, IL-1β, TNFα. On the one hand, it can induce immune response but it can also support tumor growth and survival of malignant cells. TNFα, upon binding to its receptors (TNFR1/2), activates the nuclear factor -κB (NF-κB) pathway. NF-κB further mediates cancer cell proliferation and survival by controlling the expression of target genes (e.g., VEGF, IL-6) and stimulation of neoangiogenesis [6]. The proinflammatory effect of IL-6, mediated by the JAK/STAT3 pathway, leads to cell proliferation, differentiation, and apoptosis [1][7]. Proinflammatory cytokine, IL-1β, activates endothelial cells to produce VEGF, which supports angiogenesis, contributing to tumor invasiveness and metastasis. It also drives the expression of downstream pro-tumorigenic cytokines such as IL-6, TNFα, and TGFβ [8]. TGFβ is also produced by activated macrophages and plays a dual, pro-, or anti-inflammatory role [9][10]. In the early stages of tumor development, TGFβ promotes apoptosis and inhibits the progression of the cell cycle. In the later stages, TGFβ induces epithelial-mesenchymal transition (EMT), which enhances tumor invasion and

metastasis. Increased TGFβ concentrations have an inhibitory effect on anti-tumor T-cell response [1][11]. Thus, TAMs could enhance tumor formation and progression by their inflammatory activity, particularly a chronic low-grade inflammatory state.

2. Macrophages and Neoangiogenesis

The rapid proliferation of cancer cells results in the fast growth of tumor mass and increased demand for nutrients and oxygen. Essential nutrients are delivered to the tumor by a capillary network formed in the process of neoangiogenesis. The formation of new vessels is regulated by the growth factors released by cells in the TME [12]. Due to poor regulation, the structure and function of newly formed vessels are abnormal with increased vessel permeability, which contributes to disease progression [13]. Hypoxic regions of tumor tissue are formed due to the rapid and uncontrolled cell growth and are accompanied by an increased rate of cancer cell death. TAMs infiltrate these hypoxic regions to regain homeostasis through stimulation of new blood vessel formation. The process of neoangiogenesis is modulated by many factors produced by TAMs, including VEGF, matrix metalloproteinases (MMPs), platelet-derived growth factor (PDGF), and angiopoietin-1 (Figure 1) [14][15]. VEGF induces proliferation and maturation of endothelial cells by engaging the VEGF Receptor 2 (VEGFR2) expressed on the endothelial cells (ECs) [16]. VEGF also stimulates the chemotaxis of macrophages and ECs. This process is promoted by MMP-2, MMP-7, MMP-9, which are also secreted by TAMs. The main role of MMPs is to break down the extracellular matrix, which allows migration of ECs and the formation of new vascular sprouts [16]. Additionally, it facilitates the infiltration and invasion of adjacent tissues, which may also promote the formation of metastases [13].

TAMs and platelets are also the main sources of PDGF, which induces infiltration of pericytes [17]. The interaction between pericytes and ECs is crucial for vessel maturation and remodeling, which affects vascular permeability [18]. The angiopoietin-1 released from pericytes binds to Tie-2 receptor on ECs, leading to tightening of ECs' cell-cell junctions and stabilization of newly formed vessels (Figure 1) [19].

It has been shown that a specific subset of monocytes expressing the Tie-2 receptor (Tie-2 receptor-expressing monocytes—TEMs) account for most of the proangiogenic activity of macrophages in both spontaneous and orthotopic tumors. TEMs are present in peripheral blood and are responsible for early angiogenic responses. Thus, it is thought that TEMs can be precursors of proangiogenic TAMs [20].

3. Immune Suppression and Orchestration of the Tumor Microenvironment by TAMs

The TME is infiltrated with various immune cells, out of which TAMs are the most abundant cell population. TAMs play a significant role in immunosuppression and tumor progression by releasing immunomodulatory factors such as PGE2, IL-10, and TGFβ, which inhibit cytotoxic activity of T lymphocytes and NK cells (Figure 1) [2][11]. Upon secretion of IL-10 and TGFβ, TAMs induce Tregs that suppress the activity of effector T lymphocytes. Moreover, TAMs recruit Tregs to the TME by secretion of chemokines CCL5, CCL20, and CCL22 [21]. Additionally, TAMs are

involved in the conversion of Th cells into Tregs, which further inhibit the immune response in an antigen-specific manner [22].

The other mechanism of the suppression of the immune response can be mediated by direct cell-to-cell contact between macrophages and other immune cells. TAMs could directly inhibit the immune response by expression of surface proteins, PD-L1, CD80/CD86, or death receptor ligands, FasL or TRAIL, that function as agonists for inhibitory receptors, PD-1, CTLA-4, FAS, and TRAIL-RI/-RII, respectively, that are present on the immune effector cells [23][23]. The stimulation of PD-1 and CTLA-4 receptors leads to the inhibition of the signaling pathway from the T cell receptor (TCR) and causes a decrease in the production of cytokines and proteins that promote cell survival. PD-L1 expression has been observed on macrophages and dendritic cells in many cancer types [24] as well as on macrophages and myeloid-derived suppressor cells isolated from the hypoxic tumor regions [25]. Therefore, macrophages may modulate lymphocyte function and inhibit the antitumor immune response via PD-1/PD-L1 interaction [26]. TAMs also express CD80 and CD86, that upon binding to CTLA-4 on T lymphocytes, inhibit their activation [27]. Moreover, TAMs produce arginase-1—an enzyme degrading L-arginine, which is necessary for the expression of TCR complex, lymphocyte proliferation, development of the immunological memory [28], and T cell-mediated antitumor response [29]. L-arginine starvation leads to inhibition of T cell proliferation via G_0–G_1 phase blockade [30]. Thus, TAMs have pleiotropic immunosuppressive abilities that quench adaptive antitumor immunity.

4. TAMs in Tissue Invasion and Distant Metastasis

Colonization of distant organs by neoplastic cells is a multistep process. First, cancer cells acquire the ability to grow invasively; second, they penetrate the vasculature; third, they survive in the circulation; and last effectively settle in the new metastatic location [31]. TAMs are important players in almost every step of metastasis formation [31]. Activation of Toll-like receptor 4 (TLR-4) on the surface of M2-like macrophages increases the level of IL-10, which promotes the EMT program, which plays an important role in the first steps of metastases [32]. EMT can also be induced by proinflammatory cytokines (IL-6, IL-1β, TNFα) [33] and TGFβ [34] released by TAMs (Figure 1). During the EMT, epithelial cells lose cell-cell junction and acquire motile and invasive mesenchymal cell phenotype facilitating the passage through dismounted basement membranes. TAMs are also involved in the breakdown of the extracellular membrane around endothelium by the release of MMP9 and cathepsins, which results in vascular intravasation of tumor cells. Additionally, there is a positive feedback loop between macrophages and tumor cells: CSF-1 produced by tumor cells stimulates macrophage motility and secretion of EGF, which in turn supports chemotaxis of tumor cells into blood vessels [35]. TAMs support the survival of cancer cells in the circulation by the interaction of α4 integrin with vascular cell adhesion molecule-1 (VCAM-1) on the surface of cancer cells. This interaction activates the PI3K/Akt survival pathway protecting cancer cells from the pro-apoptotic activity of molecules such as TRAIL [36]. It was observed that tumor cells are in direct interaction with TAMs when crossing the endothelial cell layer into the blood vessel [37]. Interaction of macrophages with tumor cells enhances extravasation. Before metastasis is formed, local changes occur in the target tissue leading to the creation of a premetastatic niche. Increased influx of macrophages into healthy tissue is an important step preceding the formation of metastases. Macrophages are attracted to the circulation by various agents released from tumor cells,

including CSF-1, CCL-2, VEGF, TNFα, or TGFβ, and accumulate at pre-metastatic sites [38]. Macrophages that appear in the site of future metastasis form migration tracks for cancer cells by remodeling of collagen fibers, which facilitates the invasion of cancer cells [39]. TAMs shape the extracellular matrix by releasing growth factors deposited in the extracellular matrix, which results in the stimulation of neoangiogenesis, extravasation, and EMT [31]. The above-mentioned processes show the role of TAMs in the enhancement of local tumor cell migration and distant metastasis formation.

5. The Role of M1 TAMs in the Elimination of Cancer Cells

Although the M2 TAMs play an important role in tumor development, M1 TAMs have been shown to effectively eliminate cancer cells. M1 polarized macrophages drive Th responses via antigen presentation more efficiently than M2 macrophages, including T cell proliferation and IFNγ secretion [40]. IFNγ-stimulated macrophages secrete IL-12 [41], which is a proinflammatory cytokine with potent antitumor activity [42] and the ability to recover costimulatory properties of TAMs for T cells [41]. M1 macrophages also secrete less VEGF, MMPs, and CCL18 than M2 macrophages [41]. What is more, TLR ligands (e.g., LPS) either alone or together with IFNγ drive M1 polarization, which further leads to the inhibition of cancer cell growth [43]. Therefore, M1 TAMs are considered tumor-suppressive, and M2 TAMs are considered tumor-promoting macrophages [44].

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