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Mini-review

Tumor microenvironment and therapeutic response

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ABSTRACT

The tumor microenvironment significantly influences therapeutic response and clinical outcome. Microenvironment-mediated drug resistance can be induced by soluble factors secreted by tumor or stromal cells. The adhesion of tumor cells to stromal fibroblasts or to components of the extracellular matrix can also blunt therapeutic response. Microenvironment-targeted therapy strategies include inhibition of the extracellular ligand–receptor interactions and downstream pathways. Immune cells can both improve and obstruct therapeutic efficacy and may vary in their activation status within the tumor microenvironment; thus, re-programme of the immune response would be substantially more beneficial. The development of rational drug combinations that can simultaneously target tumor cells and the microenvironment may represent a solution to overcome therapeutic resistance.

The tumor microenvironment (TME) comprises various cell types (endothelial cells, fibroblasts, immune cells, *etc.*) and extracellular components (cytokines, growth factors, hormones, extracellular matrix, *etc.*) that are surrounding tumor cells and nourished by a vascular network. The TME not only plays a pivotal role during tumor initiation, progression, and metastasis but also has profound effects on therapeutic efficacy. The environment-mediated drug resistance is a result of continuous crosstalk between the tumor cells and their surrounding stroma. While the role of the TME during tumorigenesis has recently been reviewed in detail elsewhere [1,2], in this review, we focus on how the TME regulates therapeutic response and discuss potential strategies to improve the effectiveness of drug treatment by modifying factors relating to the TME.

Major constituents of the tumor microenvironment

Vasculature

Angiogenesis plays a crucial role in tumor growth and metastasis, considered to be a hallmark of cancer [3]. Compared with normal blood vessels, the vasculature within a tumor exhibits altered structural and functional properties and results in areas of hypoxia and limited nutrient supply. The presence of hypoxia in the tumor could change gene expression of tumor cells, thereby increasing cell survival and resistance to apoptosis induction. Moreover, distance from vascular beds has been shown to be crucial for the distribution of drugs to all cells in the tumor [4]. Such variations in vascular networks generate distinct TME and ultimately influence therapeutic response. Although a number of growth factors regulate the process of angiogenesis, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor α (TGFα), vascular endothelial growth factor (VEGF) is often considered to be the prototypical angiogenic molecule in malignancy. While tumor cells are major sources of VEGF, stromal cells within TME are additional contributors [5]. Accordingly, microvessel density and VEGF expression are reported to be significant prognostic factors for poor outcome in various cancers [6,7].

Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) constitute a large proportion of the stromal cells within the TME and have been shown to provide critical signals that support tumor progression and allow minor populations of cancer cells to evade therapy [8]. The presence of a larger number of CAFs in the tumor stroma is shown to be associated with poor clinical prognosis in breast, lung, and

Abbreviations: AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; bFGF, basic fibroblast growth factor; CAFs, cancer-associated fibroblasts; CAM-DR, cell adhesion-mediated drug resistance; CCL2, chemokine (C-C motif) ligand 2; CLL, chronic lymphocytic leukemia; CSF1, colony-stimulating factor 1; CXCL1/2, chemokine (C-X-C motif) ligand 1/2; CXCR4, chemokine (C-X-C motif) receptor 4; ECM, extracellular matrix; EM-DR, environment-mediated drug resistance; ERK1/2, extracellular signal-regulated kinase 1/2; FGF, fibroblast growth factor; FGFR3, fibroblast growth factor receptor 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IFNγ, interferon γ; IGF1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; MDSCs, myeloid-derived suppressor cells; MM, multiple myeloma; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; PI3K, phosphoinositol 3 kinase; PKC, protein kinase C; SDF1, stromal cell-derived factor 1; SFM-DR, soluble factor-mediated drug resistance; TAMs, tumor-associated macrophages; TECs, tumor-associated endothelial cells; TNFα, tumor necrosis factor α; TGF, transforming growth factor; TKIs, tyrosine kinase inhibitors; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.

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pancreatic cancer [9,10]. The majority of activated CAFs are derived from resident fibroblasts that recruit and activate in response to many growth factors and cytokines such as TGFβ, FGF2, and PDGF that are abundant in the TME [10]. CAFs may also originate from bone marrow-derived mesenchymal stem cells and can be derived from resident epithelial or endothelial cells within the tumor stroma through epithelial-mesenchymal transition (EMT) or endothelial-mesenchymal transition (EndMT) [11]. Following activation, CAFs perform functions including the synthesis and secretion of extracellular matrix (ECM) and the release of proteolytic enzymes such as the matrix metalloproteinases (MMPs) and heparanase resulting in ECM remodeling [8]. Additionally, CAFs constitute an important source of growth factors and cytokines (including stromal cell-derived factor 1 (SDF1), hepatocyte growth factor (HGF), VEGF, PDGF, *etc.*), which all together promote tumor growth, angiogenesis and contribute to therapeutic resistance [5,12–14].

Immune cells

Both innate immune cells (macrophages, mast cells, neutrophils, dendritic cells, myeloid derived suppressor cells, and natural killer cells) and adaptive immune cells (T and B lymphocytes) are present and interact with the tumor cells *via* direct contact or through chemokine and cytokine signaling which shapes the behavior of the tumor and its response to therapy. Importantly, immune cells can both support and obstruct therapeutic efficacy and can vary in their activation status and localization within the TME.

It is well established that tumor-associated macrophages (TAMs) are key regulators of therapeutic response in the TME. In solid tumors, the main source of TAMs is circulating monocytes rather than proliferating resident macrophages inside tumors. Monocytes in bone marrow are derived from myeloid progenitors, and they can enter tumors through blood circulation and subsequently differentiate into macrophages. Macrophages can be categorized into M1 and M2 subtypes based on their polarization status. M1 macrophages can be activated by Th1 cytokine interferon γ (IFNγ) and microbial products. In contrast, M2 macrophages differentiate in response to Th2 cytokines, such as IL-4, IL-10 and IL-13 [15,16]. In the context of TAMs, M1 macrophages are considered to exert tumoricidal effects, whereas M2 macrophages promote tumorigenesis. Both M1 and M2 TAMs are plastic and reversible, and the TME plays a major role in the regulation of functional polarization of TAMs [17–19]. During cancer therapy, chemotherapeutic agents can elicit a misdirected tissue repair response orchestrated by TAMs [20], which may result in promotion of tumor growth and limitation of anti-tumor efficacy. *In vitro* and *in vivo* evidences have showed that TAMs mediate resistance to some chemotherapeutic agents (5-fluorouracil, doxorubicin, gemcitabine, paclitaxel, platinum compounds, *etc.*) as well as anti-VEGF treatment [21–26]. Moreover, TAMs acquire the ability to produce several suppressive cytokines such as IL-1β, IL-6, IL-10 and TGFβ, thus contributing to T-cell suppression in the TME [15].

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of myeloid origin cells that comprise myeloid progenitor cells and immature macrophages, immature granulocytes and immature dendritic cells. These cells expand during tumorigenesis and have a remarkable ability to suppress various T-cell responses [27]. MDSCs can also actively migrate to the tumor site, where they rapidly differentiate into TAMs. Together with TAMs, MDSCs have been shown to mediate resistance to anti-VEGF treatment by secreting factors compensating for VEGF loss to support angiogenesis [25,28]. Moreover, MDSCs play a critical role in refractoriness against some anti-cancer drugs such as cyclophosphamide, anthracycline, and sunitinib [29,30].

Tumor-associated endothelial cells

Tumor-associated endothelial cells (TECs) differ from normal endothelial cells in characteristics including proliferation, migration and responses to growth factors (i.e., EGF, VEGF) and chemotherapeutic drugs [31–33]. Growing evidences have shown that tumor cells trigger the immunosuppressive activities of TECs that influence anti-tumor immunity and therapeutic response [34]. Tumor vessels exhibit chaotic blood flow and impaired leukocyte extravasation, which have been associated with the structural abnormalities of the vasculature and aberrations of the adhesive properties of TECs. Reduced expression of E-selectin, intercellular adhesion molecule 1 (ICAM1), ICAM2 and vascular cell adhesion molecule 1 (VCAM1) by TECs leads to disrupted recruitment of tumor-specific cytotoxic T cells into the tumor lesion [35]. Moreover, TECs selectively permit transmigration of immunosuppressive myeloid cells from the blood into tumor and therefore impair the anti-tumor immune responses [36]. In addition to modulating immune cell infiltration, TECs in the TME may also suppress T cell function through expression of inhibitory molecules, such as programmed cell death ligand 1 (PDL1) and PDL2 [37]. TECs can also release soluble factors that influence T cell responses and the outcome of treatment, including prostaglandin E2, IL-6, TGFβ, and VEGF [38,39].

Extracellular matrix

Compared with normal tissue, the tumor stroma is associated with an altered ECM, that is produced by all of the cell types within the TME, resulting in an intricate fiber network that not only plays an important role in the ability of tumor cells to invade and metastasize [40] but also affects the sensitivity to drug treatment. The ECM comprises various components, including collagen, fibronectin, laminin, vitronectin, tenascin-C, SPARC, *etc*. In solid tumor, collagens and fibronectin provide mechanical strength, and proteoglycans contribute growth factors and cytokine-binding properties [41]. The composition and organization of the ECM, cell–cell interactions, and the tumor cell architecture constitute a physical barrier for drug delivery. Tumors that have a well organized interconnected collagen network and a reduced volume of the ECM display lower drug penetration [42,43]. On the other hand, sequestration of drugs by their binding to components of the ECM inhibits drug penetration to deeper regions of the tumor [44].

Mechanisms of the microenvironment-mediated therapeutic resistance

The multitude reciprocal interactions between tumor cells and the TME allow minor populations of tumor cells to evade apoptosis and to develop resistance. Importantly, the environment-mediated drug resistance (EM-DR) is usually transient, appearing only while the tumor cells are in contact with the microenvironment, and they can revert to drug sensitivity when removed from the microenvironment [45].

Soluble factor-mediated drug resistance

The TME is rich in cytokines and growth factors, which are secreted by either tumor cells or stromal cells and contribute to the aberrant growth, angiogenesis, metastasis and drug resistance. Some of the critical molecular signaling events involved in the soluble factor-mediated drug resistance (SFM-DR) have been identified. One example involves SDF1 and its membrane-bound receptor chemokine (C-X-C motif) receptor 4 (CXCR4). In chronic lymphocytic leukemia (CLL) cells, SDF1 produced by stromal cells can interact with CXCR4 and activate extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt pathways, leading to anti-apoptotic responses and