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BIOLOGY OF TUMOR MICROENVIRONMENT: A REVIEW

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ABSTRACT
Cancer is a systemic disease, and it is not a solo production but rather an ensemble performance. The tumor microenvironment (TME) is being increasingly recognized as a key factor in multiple stages of disease progression, particularly local resistance, immune-escaping, and distant metastasis, thereby substantially impacting the future development of frontline interventions in clinical oncology. As benign cells in TME niches actively modulate response of cancer cells to a broad range of standard chemotherapies and targeted agents, cancer-oriented therapeutics should be combined with TME-targeting treatments to achieve optimal clinical outcomes.

INTRODUCTION

Cancer is a systemic disease, and it is not a solo production but rather an ensemble performance [1]. The disease is usually initiated as a result of the stepwise accumulation of genetic and epigenetic changes in the epithelial compartment; however, increasing evidence indicates that the tumor microenvironment (TME) can dictate aberrant tissue function and play a critical role in the subsequent development of more advanced and refractory malignancies [2]. Physiologically, the stroma in healthy individuals is a physical barrier against tumorigenesis; however, neoplastic cells elicit various changes to convert the adjacent TME into a pathological entity. The orchestration of such an event implicates migration of stromal cells, remodeling of matrix, and expansion of vasculature [3]. In this review, we define the biological landscapes of neoplastic cell extrinsic environment, branded the TME.

Review of literature

The structurally and functionally essential elements in the stroma of a typical TME include fibroblasts, myofibroblasts, neuroendocrine cells, adipose cells, immune and inflammatory cells, the blood and lymphatic vascular networks, and the extracellular matrix (ECM). The naive stroma is a critical compartment in maintaining physiological homeostasis of normal tissue, and recent studies strengthened the concept that some stromal components have anticancer activities by regulating immunosuppression and restraining carcinogenesis, which is particularly the case of pancreatic ductal adenocarcinoma [4,5]. Thus, normal stroma possesses an inherent plasticity to respond rapidly to neoplastic situations, and act in concert with the adjacent epithelium in eliciting the emergence of "reactive stroma". The active stroma of solid tumors is not only composed of carcinoma-associated fibroblasts (CAFs) and myofibroblasts, but characterized with remodeled matrix, reprogrammed metabolism, activated transcription, and altered synthesis of repair-associated proteins [6,7]. Further, the physical or biological protection provided by the stromal part of the TME limits the effective delivery of anticancer agents to tumor foci and represents a favorable milieu that allows cancer cells to circumvent programmed cell death triggered by cytotoxicity and to develop acquired resistance as a preliminary step towards more malignant phenotypes.

Progression of organ-specific tumors is also reliant on infiltration of immune cells and occurrence of angiogenesis, which generates a stash for cancer stem cells (CSCs) and provides a complex signaling environment. CSCs, also known as tumor-initiating cells, have been

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intensively explored within the recent decade. Many tumor types involve CSCs in the TME milieu, which are characterized with the potential to cause resistance against various cytotoxicities due to intrinsic mechanisms, including genetic changes and epigenetic alterations. Both CAFs and CSCs are implicated in the TME-mediated signaling to remodel cancer cells; for instance, CAFs express high levels of extracellular factors including chemokine CXC motif ligand (CXCL)12, chemokine CC motif ligand (CCL)2, CCL8, and insulin-like growth factor binding protein 7, thereby forming an inflammatory niche [8,9] . Further, CSCs are highly responsive to immune modulation, and an immune signature is present in human prostate $CD133^+$ CSCs, including interleukin (IL)-6 and interferon-γ receptor 1 [10].

Under *in vivo* conditions both the innate and adaptive immune systems influence homeostasis, in particular the recruitment of immune cells into the tumor-adjacent milieu is active and forms distinct immune contextures, thereby exerting profound impacts on clinical outcome. For example, T cell activation involves both positive and negative checkpoint signals to finely tune responses to prevent excessive pathological changes [11,12]. The myeloid-derived suppressor cell (MDSC) population which encompasses immature dendritic cells, neutrophils, monocytes, and early myeloid progenitors implicates tumor-initiated endocrine signaling to the immune system through multiple chemokines such as granulocyte-macrophage colony stimulating factor [13,14]. Some immunosuppressive myeloid lineages not only inhibit adaptive immunity, but promote angiogenesis through secretion of soluble molecules like vascular endothelial growth factor (VEGF) A, basic fibroblast growth factor (FGF), and transforming growth factor β (TGF-β) [15]. Independent of T cell activities, B cells are able to facilitate disease progression by fostering pro-tumoral inflammation [16]. Furthermore, type II tumor-associated macrophages (TAMs) drastically affect tumorigenesis, angiogenesis, and intravasation, and can prevent immune attack by natural killer (NK) and T cells during tumor development and after recovery from chemo- and/or immunotherapy [17]. TME-mediated resistance can be initiated by multiple cell lineages and structural components in the stroma, including but not limited to fibroblasts, endothelial cells, pericytes, smooth muscle cells, neutrophils, macrophages, integrins, fibronectins, and collagens [18,19].

Particularly, resistance to chemotherapy frequently results from cell extrinsic factors such as cytokines, growth factors, and even proteases derived from a TME that is structurally and functionally modified by drug-induced cytotoxicity [20,21]. In such cases, CSCs represent the potential source of eventual tumor relapse following therapy, which are typically therapy-resistant due to decreased oxidative stress response, increased genomic stability, and expression of multiple drug resistance transporters [22].

Although dominant anticancer regimens, including chemotherapy and targeted therapy, provide major options for cancer patients, so far, mounting data pinpoints to an intricate link between epithelial-mesenchymal transition (EMT) and therapeutic resistance. Gain of function as resistance for cancer cells can be regulated by diverse mechanisms, and it may arise as a direct consequence of EMT triggered by a large array of the TME-derived molecules through activation of intracellular networks that cover hepatocyte growth factor/c-met, epidermal growth factor (EGF)/EGF receptor (EGFR), Wnt/beta-catenin axes, and several cytokine/chemokine-mediated pathways such as TGF-β/Smad signaling [23,24]. In this regard, most treatment-resistant cancers harbor a subgroup of cells with stem-like or mesenchymal features that are resistant to cancer therapies [25].

Throughout the course of tumor evolution, a vast group of host cells, ranging from fibroblasts to macrophages, sustain a supportive TME for disease progression, specifically by interfering immunosurveillance against cancer cells [26]. Among these disease-favorable stromal cells, several subpopulations are virtually bone marrow-derived cells (BMDCs) and frequently implicated in tumor expansion via homing to the primary site as active components of the local TME. Being a typical representative of BMDCs but still keeping differentiation potential, MSCs mainly derive from the bone marrow but are indeed resident in virtually all organs and mature tissues, receiving much interest in recent years particularly in cancer biology. In contrast to TAMs, which compose a terminal lineage, MSCs remain primitive and can generate adipocytes, pericytes, chondrocytes, neurons, osteocytes, and mainstay stromal cells, including fibroblasts and endothelial cells, and can also transdifferentiate into both ectodermal and endodermal cells, thereby displaying a high plasticity and contributing to tissue regeneration [27,28]. MSCs are capable of modulating immune status; however, the immunoregulatory function of MSCs is not intrinsic but depends on their cytokine milieu [29].

MSCs isolated from spontaneous lymphomas have a strikingly high expression of CCL2 compared with bone marrow-derived MSCs (BM-MSCs), and promote tumor growth by recruiting type 2 like TAMs to tumor site, a phenomenon that can be mimicked by treating BM-MSCs with tumor necrosis factor alpha (TNF-α) [30]. The MSC-mediated immunosuppression may interfere with the anti-tumor immunity and help the tumor escape immunological surveillance. Interestingly, MSCs derived from p53-deficient mice express more iNOS and exhibited greater immunosuppressive capacity in the presence of inflammatory cytokines. When inoculated with B16F0 melanoma in mice, p53-deficient MSCs resulted in tumors larger than those harboring wild type MSCs, and such a tumor promoting effect could be abolished by administration of the iNOS inhibitor, S-

Methylisothiourea [31]. Chemotherapy to leukemia elicits resistance by rebuilding an microenvironmental niche that allows cancer-propagating cells to evade apoptosis, and MSCs generate replatable mesenspheres and express CD29, CD51, and chemokine receptor CCR1 [32]. In ovarian cancer, MSC secretions promote phosphatidylinositol 3-kinase (PI3K)/Akt signaling and the X-linked inhibitor of apoptosis protein phosphorylation, inducing carboplatin-specific resistance through trogocytosis [33]. Metastasis accounts for approximately 90% of overall mortality among solid tumor patients [34]. The metastatic journey of cancer cells from original site to distant organs comprises several distinct stages, including local invasion, intravasation, circulationary survival, extravasation, and ectopic recolonization. Tumors not only preferentially select proclivity sites for metastasis, but exhibit variable dormancy length in temporary course. [35]

DISCUSSION

Local invasion is the physical entry of cancer cells resident within a well-confined primary tumor into the surrounding stroma. Cancer cells first breach the basement membrane, a specialized ECM structure in the TME, by co-opting the EMT program, which allows dissolution of tight junctions, loss of cell polarity, and acquisition of multiple mesenchymal attributes [36]. Intravasation is a critical step that allows cancer cells to cross pericyte and endothelial cell barriers before they gain access to other organs [37,38]. Either at primary sites or in vasculature vessels, cancer cells can release microvesicles or soluble factors to adapt incipient metastatic sites into 'pre-metastatic niches'; for example, systemic factors attract bone marrow-derived macrophages and hematopoietic progenitor cells that are accompanied by CAFs and endothelial cells to remodel tissue and eventually cause lung metastasis [39]. However, metastasis-incompetent cancer cells can foster a metastasis-compatible TME by secreting extracellular factors including thrombospondin 1 to promote niche formation at metastatic sites [40]. Unfortunately, tumors are prone to be awakened by various stimuli such as acquired mutations arising from of cancer cell genomic instability, which allow them to exit dormancy for resumed metastatic progression, while more events of tumor awakening and distant outgrowth are driven by the TME constituents. A novel mechanism of triple-negative breast cancer metastasis was recently delineated, and involves the TME factors as peripheral signals, including EGF and insulin-like growth factor-I (IGF-I), at distant indolent tumor sites [41]. Micro RNAs (miRNAs) are circulated in cancer patient serum and can serve as important biomarkers for many cancer types [42]. New studies presented mechanistic evidence that some miRNAs directly regulate metastasis by mediating tumor–TME interactions. Particularly, miR-210 is released from metastatic breast cancer cells via nSMase2-dependent exosomal secretion, which once transported to endothelial cells can enhance cell migration and capillary formation, thereby enhancing angiogenesis and metastasis [43]. The miRNAs can also be transmitted from stroma cells to cancer cells as exemplified by microvesicle-delivered miR-223, which is highly expressed in IL-4-activated TAMs but not in breast cancer cells and which, upon transmission from TAMs to cocultured cancer cells, promotes tumor invasion and metastasis [44]. The transmission of miRNAs between different cell types provides an additional mechanism of TME-regulated metastasis.

Altogether, it is increasingly evident that distinct stages of tumor advancing are subject to continuous and comprehensive influence of the TME in a special and temporal manner.

CONCLUSION

When defining predictive markers that will eventually aid in the selection of patients who most likely benefit from intervention, analysis based on the entire TME is an essential step of utmost importance to determine specific therapies to employ [45,46]. To this end, gene expression profiling has been proposed as predictive for response to a given therapy, while in the coming years a panel of markers will become available to achieve the predicted goal. More importantly, cancer cell-directed agents should be combined with the TME-targeting therapies as it is increasingly clear that stromal cells modulate the efficacy of a broad range of standard chemotherapies and targeted agents.

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