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Microenvironment of Tumor and its Role in Tumor Progression and Metastasise

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Abstract

Humans are continuously exposed to a wide of carcinogenic and mutagenic stimuli, including environmental toxins, radiation and viruses as well as other infections. Tumor metastasis is responsible for approximately 9% of all cancer-related deaths. The tumor microenvironment (TME) contains many distinct cell types, including endothelial cells and their precursors, pericytes, smooth muscle cells, fibroblasts, carcinoma-associated fibroblasts, myofibroblasts, neutrophils, eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells and antigen presenting cells (APC) such as macrophages and dendritic cells. Recent evidence has shown that stromal tissue is much more than a passive bystander in the development and progression of cancers. None the lese,the clinical therapy for many types of human cancers has mainly focused on the malignant cancer cell itself, and have made great achievements, yet cancer therapy still remains a great challenge. This review highlights the evidence for the crucial role of the tumor microenvironment in tumor progression and metastasis.

INTRODUCTION

Humans are continuously exposed to a wide of carcinogenic and mutagenic stimuli, including environmental toxins, radiation and viruses as well as other infections (1). These stimuli results in cells bearing abnormal characteristics reported in a relatively important number of otherwise healthy persons. Cancer has been long viewed as a disease consisting of transformed cells acquiring cell autonomous hyper proliferative, invasive and limitless survival capacities (2).

Tumor metastasis is responsible for approximately 9% of all cancer-related deaths (3). Metastasis, on the other hand, is a multistage process that requires cancer cells to escape from the primary tumor, survive in the circulation while hiding from tumor surveillance mechanisms, seed at distant sites, establish themselves and grow (4, 5). It is well established that to form a metastasis from a primary tumor, the cancer cells need to acquire additional properties that enable invasion of the extracellular matrix (ECM), intravasation, travel via the blood vessels, migration to and invasion into a secondary site, and finally the formation of metastatic nodules (6). As a solid tumor grows, the rate of cancer cell proliferation surpasses the ability of the existing vasculature to supply growth factors, nutrients, and oxygen and to remove the catabolites produced by the cells. The result of this imbalance between supply and demand is regions of hypoxia, low glucose levels and low pH. The development of metastasis is complex, requiring multiple individual steps to successfully establish a tumor at a secondary site (7).

The tumor microenvironment (TME) contains many distinct cell types, including endothelial cells and their precursors, pericytes, smooth muscle cells, fibroblasts, carcinoma-associated fibroblasts, myofibroblasts, neutrophils, eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells and antigen presenting cells (APC) such as macrophages and dendritic cells (8). Bidirectional communication between cells and their microenvironment is critical for both normal tissue homeostasis, and for tumor growth (9). In particular, interactions between tumor cells and the associated stroma represent a powerful relationship that influences disease initiation, progression and patient prognosis (10, 11). A major mechanism for carcinoma cell dissemination from the primary tumor to distant organs is hematogenous

spread (12). Multiphoton-based intravital imaging has demonstrated that invasive carcinoma cells in mouse and rat mammary tumors comigrate and intravasate when associated with perivascular macrophages (13). Specifically, intravasation occurs at sites where a macrophage, a tumor cell, and an endothelial cell are in direct contact. The TME comprises the ECM and basement membrane (BM), endothelial cells, adipose cells, tumor-infiltrating immune cells, cancer-associated fibroblasts (CAFs), neuroendocrine cells, pericytes, as well as a plethora of signalling molecules that regulate tumor progression (14). Cancer cells secrete growth factors and cytokines (including IL-6, IL-1, TGF- 1, TGF- 2, FGF-2, and PDGF) that recruit and reprogram stromal cells, such as immune cells and fibroblasts, as well as enzymes that degrade and remodel the surrounding ECM and BM, such as matrix metalloproteinases (MMPs) (15).

Instead, there is a bidirectional, dynamic and intricate complex of interactions between the cells of the stromal tissue and the cancer cells (16, 17). The first evidence that non-cancerous tissue elements might affect tumor formation and growth came from the weld of inflammation (9). A link between inflammation and cancer has been recognized already in 1863 by Rudolf Virchow, when he reported the presence of leucocytes in tumor tissues. Based on this observation he proposed the idea that cancer originates at sites of chronic inflammation. The presence of leukocytes in tumors was subsequently interpreted as an aborted attempt of the immune system to reject the tumor (18).

Another integral factor in tumor proliferation and protection from immune destruction is the establishment of adequate blood supply, through angiogenesis and the provision of tumor growth factors (4, 15). Platelets and, potentially, platelet derived micro particles [PMPs] fulfill this role and may contribute to immunosuppression (19). Finally, many tumors are hormone-sensitive, by virtue of their cells of origin or by their potential to express hormonal receptors that modulate their growth and spread. In this review, we summarize the latest findings in the efforts for understanding the complex roles of TME constituents in various stages of metastatic progression and discuss about strategies as well as future challenges for targeting TME components to battle the most aggressive forms of the disease (18, 19).

Roles of Cellular TME Components in Regulating the Metastatic Cascade:

Immune Regulation of Tumor Growth and Propagation

Most of the immune cell populations in the tumor microenvironment play distinct roles in the modulation of the tumor milieu, favoring or inhibiting tumorigenesis (20). It is unambiguously accepted that immune cells exert pivotal effects in the properties of cancer cells at different stages of the invasion-metastasis cascade, either by infiltrating the tumor or by affecting the systemic environment (21). It is nowadays considered that the main mechanism of tumor immunity is due to an antitumoral T cell response. This antitumor response can be due to the direct killing of tumor cells by CD8 cytotoxic T lymphocytes (CTL) recognizing major histocompatibility complex (MHC) class I restricted antigens expressed on the surface of tumor cells (22). IL-10 has pleiotropic effects on T cell functions, including the suppression of GM-CSF, IFN-gama and IL-2 production by T helper cells, inhibition of T cell proliferation, downregulation of expression of adhesion molecules and MHC class I and class II antigens (23, 24). Patients with ovarian carcinoma frequently present abundant levels of this cytokines in serum, in the peritoneal exudate and in the tumor tissue (25). Some cytokines inhibit the expression of immune activating cytokines, such as IL-2 and IL-4. This can inhibit the natural homeostatic mechanisms that control the specific cellular immunity and could be responsible for the signaling defects in T lymphocytes, routinely observed in late stage cancer patients, rendering them ineffective in mounting tumor associated antigen (TAA) specific effector activity (26).

Myeloid cells. Macrophages, often referred to tumor associated macrophages (TAMs) when present in the tumor milieu, are either recruited from the bone marrow or reside in the original stromal environment (8, 27). They interact with a wide range of growth factors, cytokines and chemokines, which are thought to educate the TAMs and determine their specific phenotype and, hence, functional role as tumoricidal/static or tumor promoters (28). They present foreign antigens to helper T cells and can prime naïve T cells. TAMs can act in two opposing functions depending on their polarization subtype: M1-type TAMs have pro-inflammatory and anti-tumoral properties and activate the immune system by releasing interferon (IFN)- and IL-12 (29). On the other hand, M2-type TAMs are pro-tumorigenic, and exert immunosuppressive functions by producing IL-10, induce angiogenesis and stimulate tumor cells to release MMPs that favor cancer progression by disrupting the ECM and BM (30, 31). Myeloid-derived-suppressor cells [MDSCs] arising in the context of aberrant myelopoiesis in cancer patients are a heterogeneous population of immune cells from the myeloid lineage that execute strong immunosuppressive activities (32). They are mobilized to the tumor milieu, where they infiltrate the growing tumor, favoring neovascularization and interfering significantly with the different mechanisms of immune surveillance (33).

Mast cells are resident granulocytes in most tissue, are recruited to the tumor milieu and act as reservoirs,

releasing tumor promoter cytokines (30).

The various components of the immune system seem to interplay with the stromal factors, regulating tumor growth and dissemination. It seems therefore evident that immune modulation should be a crucial component in the fight against cancer (34).

Inflammation

The link between inflammation and cancer was first proposed by Virchow, who observed leukocytes infiltrating tumor sites (35). Statistically, tissues subjected to chronic inflammation generally exhibit a higher cancer incidence, reflecting a deregulated microenvironment (36). It is becoming increasingly evident that inflammatory cells recruited in the tumor stroma play a pivotal role in triggering tumor angiogenesis. It has been proposed that inflammatory cells might in fact be responsible for a substantial portion of tumor angiogenesis by acting as initiator of vascularization. It has been hypothesized that the balance between the tumor antagonizing inflammatory cells and the tumor promoting inflammatory cells modulates tumor progression (35). The tumor-promoting inflammatory cells include macrophage subtypes, mast cells and neutrophils, as well as T and B lymphocytes. These cells can secrete several signaling molecules that serve as effectors of their tumor-promoting actions (37).

At the molecular level, free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and posttranslational modifications of key cancer-related proteins. Innate immune (i.e. macrophages, neutrophils) release a number of factors that able to stimulate and activate endothelial cells, such as VEGF, HGF, MMP-2, MMP-9 and IL-8 (37, 38). Neutrophils were largely ignored for a long time in the context of tumor angiogenesis but recent studies have shown their important role in this process (39). Within the tumor mass, in addition to fully differentiated immune cells, a variety of partially differentiated myeloid progenitors have been identified. These cells are intermediates between the circulating cells of bone marrow origin and the fully differentiated immune cells in normal and inflamed tissues, and they show tumor-promoting activities (40).

Other products of inflammation include cytokines, growth factors, and transcription factors such as nuclear factor-kappa B. These control the expression of cancer genes (e.g., suppressor genes and oncogenes) and key inflammatory enzymes such as inducible nitric oxide synthase and cyclo-oxygenase (40, 41). Chronic inflammation is also associated with immunosuppression, which is a general risk factor for cancer. In addition, to classical inflammatory cells, bone marrow-derived cells (BMDC) has been recently shown to be mobilized from the bone marrow in response to stimuli originating form the growing tumor, and to recruit at tumor sites to promote tumor angiogenesis and tumor invasion (4,25,26). Of the 12.7 million new cancer cases that occurred in 2008 worldwide, 16.1% (around 2 million) were associated with infections and their ensuing inflammation. Finally, exposure to radiation is also an important determinant of the stromal response to tumorigenesis as it induces both inflammation and tissue-specific dysfunction in repair processes with deregulated tissue homeostasis (42).

Stromal cells

The tumor margin is an important meeting place in the TME where recruited immune and stromal cells are highly active and interactive with the tumor (43). Immature myeloid cells accumulate in this region, and prevent differentiation of antigen-presenting DCs, thus supporting tumor immune evasion. Macrophages are another major cell type at the invasive edge of tumors, and are recruited by tumor-derived chemoattractants (44). Upon their arrival, TAMs promote invasion of tumor cells by supplying pro-migratory factors such as EGF, by regulating the production of fibrillar collagen to accelerate tumor motility, and by promoting ECM proteolytic remodeling. CAFs are similarly abundant at the tumor margin where they release pro-invasive factors for tumor cells; in hepatocellular carcinoma, CAFs participate in a TGF-β/PDGF signaling crosstalk with tumor cells to support EMT and the acquisition of an invasive phenotype (45).

Matrix metalloproteinases, or matrixins, are endopeptidases that belong to a family of zinc-dependent proteases with more than 21 human forms. Their main substrates are matrix molecules such as collagen, but many non-matrix substrates have also recently been identified (32, 46). They are important in many aspects of invasion and metastasis, and play a part in remodeling the ECM. Finally, stem cells are a key factor in tissue homeostasis. Their activity is tightly regulated during development and in adult tissues through the combined action of local and systemic effectors. Stem cells may also contribute to the establishment and continuous growth of tumors when tissue homeostasis is unbalanced (47).

Cancer-Associated Fibroblasts in Promoting Metastasis

Fibroblasts are a predominant, multi-functional cell type in connective tissue, depositing ECM and basement membrane components, regulating differentiation events in associated epithelial cells, modulating immune responses, and mediating homeostasis (48). In the tumor stroma, together with the other stroma cells, the fibroblasts are a source of S100A4, a calcium binding protein of the S100 protein

family, as well as the members of which have important roles in metastasis. High levels of S100A4 expression correlate with negative prognosis in several types of cancer (49).

CAFs constitute one of the most abundant stromal components in solid tumors (50). CAFs are distinguished from different cell subtypes based on the presence of several stromal markers, including integrin 1 (CD29), fibroblast activation protein (FAP), and α-smooth muscle actin (50, 51). In the TME, CAFs are present in aberrantly high numbers and are distinct from normal fibroblasts. For example, normal prostate epithelial cells give rise to intraepithelial neoplasia in mice when co-injected with CAFs, but not when co-injected with normal fibroblasts. Similarly in breast cancer, CAFs confer a mesenchymal-like phenotype and enhance metastasis of both premalignant and malignant mammary epithelial cells, whereas normal fibroblasts promote an epithelial-like phenotype and suppress metastasis (52). In addition, in women with primary tumors smaller than 2 cm without lymph node metastasis, the presence of CAF-S1 cells favors breast cancer metastasis to the bone via CDH11/osteoblast cadherin (47).

Cancer cells can activate fibroblasts in a three-step process: recruitment, transformation to CAFs, and maintenance in the TME. The presence of a specific subset of CAFs in the microenvironment and CAF-S1 were recently shown to suppress the immune system by attracting and promoting the survival, differentiation, and activation of CD4+CD25+ T lymphocytes (53). Interestingly, CAFs in the breast TME can select for bone-specific metastatic traits in primary tumor cells, due in part to a selective interaction between breast cancer cells with high Src activity, and primary CAFs that secrete CXCL12 and IGF1. This raises the intriguing possibility that heterotypic signaling in the primary TME enriches for metastatic cells primed to flourish in specific foreign microenvironments, providing further evidence for the interdependency of multiple cell types within the TME (3, 22, and 54).

Hypoxia in tumors

Solid stress and tumor stiffening contribute to metastasis not only by increasing directly the invasive and metastatic potential of cancer cells but also by inducing hypoxia (55). The development of tumor hypoxia is intrinsically linked to the formation of neovasculature by the process of angiogenesis, which involves the expansion of vascular endothelial cells, degradation of the local extracellular matrix, and migration of the endothelial cells towards the tumor (56). This requires a series of complex molecular events resulting in the simultaneous up-regulation of proangiogenic factors and down-regulation of angiogenic inhibitors (57).

During hypoxia, cancer cells change their metabolic activities by switching from oxidative phosphorylation to aerobic glycolysis which causes acidification of the extracellular space (26, 57, and 58). Acidosis is a major physiological parameter of TME linked to hypoxia which allows the survival of selected cells that can adapt to these acidic conditions. Experimental studies that clearly define the absolute oxygen level and duration of hypoxic exposure are needed to further elucidate the effects of temporal fluctuations in oxygen concentrations that occur within solid tumors (59). Induction of hypoxia activates a vicious circle of downstream signaling cascades to promote responses that define cancer hallmarks, including metabolic reprogramming, mesenchymal transformation of cells, proliferation, survival, angiogenesis, migration, invasion, immunosuppression, and metastasis. Approximately 50–60% of solid tumors exhibit hypoxic regions where O2 tension can be low (<10 mmHg) and heterogeneously distributed within the tumor (60). Hypoxia affects the TME and puts selective pressure on cancer cells that develop genetic and/or epigenetic adaptive changes in order to survive and in combination with the formation of new vessels, mainly at the tumor periphery, eventually metastasize to distant sites (61).

Therapeutic implication

Cancer cells require an enormous variety of genetic changes to elicit tumorigenesis (62). The clinical therapy for many types of human cancers has mainly focused on the malignant cancer cell itself, and have made great achievements, yet cancer therapy still remain a great challenge. Most therapeutic strategies against cancer have focused on targeting various aspects of tumor cells directly; however, stromal cells within the TME are genetically stable compared to tumor cells, and are thus likely to be less susceptible to classical mechanisms of therapeutic resistance (63). Various therapies attempt to block mechanisms of immune evasion by tumors, many of which are currently focused on advanced melanoma patients given their high numbers of lymphocytes (64). Ipilimumab is an FDA-approved antibody that targets cytotoxic Tlymphocyte- associated antigen 4 (CTLA-4), which activates T cells and promotes antitumor immunity. In the first clinical trial for ipilimumab in patients with inoperable metastatic melanoma, overall survival increased to ~10 months, compared to 6.4 months for those patients who were not on ipilimumab therapy (65).

Targeting the tumor microenvironment holds great potential for cancer therapy. There are many tumor-promoting factors in the tumor microenvironment, suggesting that inhibition of these tumor-promoting factors or destroying these signaling pathways can prevent the development of cancer. For example, tumors in a stroma xenograft model treated with

the TGF-β inhibitor exhibited a reduction in blood vessels. More research is needed to develop more efficient approaches to combat cancer (58, 59, and 65).

CONCLUSION

Tumors are aberrant cells bearing abnormal characteristics reported in a relatively important number of otherwise healthy persons (66). It is now widely accepted that tumors contain cancer stem cells (CSC) bearing self-renewal potential and resistant to conventional cancer therapy with greater invasiveness and metastatic behavior (67). Identification of these cells and their niche is critical for identifying molecular targets in order to inhibit their growth and to destroy their niche (18). In recent years the study of tumor microenvironment, its cellular and molecular components, and how they can affect neoplastic progression, have become an emerging topic in cancer research. This is an exciting time for the TME field, as illustrated by the examples discussed here, which have revealed new biological concepts and identified novel therapeutic strategies to target the TME. Nonetheless, with these advances come new challenges, the most obvious being how to identify and target susceptible nodes in the increasingly complex and interconnected TME (68). This review highlights the evidence for the crucial role of the tumor microenvironment in tumor progression and metastasis. Targeting the tumor microenvironment combined with current clinical approaches holds great potential for developing new efficient therapies. Cancer medicine must move toward a new era of personalized diagnostics and therapeutics that aggressively embraces integrative approaches (69).

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