Review Article: The Influence of Tumor Microenvironment on Tumor Progression; and Anticancer Therapies

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Abstract: All tumors are surrounded by complex environmental components including blood and lymph vessels; cellular components like fibroblasts, endothelial cells, immune cells; and non-cellular stromal cytokines, extracellular vesicles, and extracellular matrix. All of these along with the tumor cells constitute the tumor microenvironment (TME). Also the physical and chemical factors within this tumor microenvironment including extracellular pH, hypoxia, elevated interstitial fluid pressure, and fibrosis closely associate with the tumor progression at local site, its metastasis to remote areas of the body, immunosuppression, and drug resistance exhibited by the tumor. These cellular and extracellular components of TME primarily contribute to the process of carcinogenesis. This review focuses on multiple factors that alter the microenvironment to make it favorable for tumor growth at primary site and its metastasis to secondary sites. Also some of the natural products that may help to treat the tumor conditions via alteration of this microenvironment are mentioned which may provide new venues for development of newer drugs halting the progression of the tumors.

Keywords: Tumor microenvironment, inflammation, hypoxia, metastasis, apoptosis, angiogenesis, oncogene, immunotherapy, catecholamine, necrosis, IL-1, IL-6.

INTRODUCTION

The communication between the tumor cells and the surrounding cells - the microenvironment, helps drive the process of tumor progression and invasion. The tumor microenvironment consists of tumor, immune, stromal, and inflammatory cells which produce soluble cytokines, growth factors; adhesion molecules that promote tumor progression and metastasis; and non cellular component-the extracellular matrix [ECM] [1] Research studies conducted over the past decade have significantly increased our understanding of tumor microenvironment [2-8].

There is an extensive body of experimental data indicating that remodeling of the ECM promotes cancer invasion and metastasis [9,10].

Successive changes occurring at the tumor site during tumor progression resemble chronic inflammation, oxidative stress and immune dysregulation.

This dysregulation is largely devised by the tumor and it appears to promote tumor survival, growth & invasion. Aside from inflammation, hypoxia in the tumor microenvironment (TME) also contributes to tumor growth and spread.

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All solid tumors' microenvironment have the characteristic feature of hypoxia which strongly effects the progression of the tumors and their resistance to therapeutic agents resulting in poor clinical outcome of the therapies. zones of different oxygen concentrations- well oxygenated, poorly oxygenated and inadequately oxygenated (necrotic)- are found in solid tumors [11,12].

Alterations in nutrients, energy metabolism, blood rheology (flow) further contribute to this metabolic invasion. The outcome of metastasis depends on multiple interactions ("cross-talk") between the metastatic subpopulation in the primary tumor and the host organ microenvironment.

Factors Contributing to Tumor Immune Evasion in the Tumor Microenvironment

Tumor cells can influence T-cell trafficking by up regulating adhesion molecules that prevent T cells from infiltrating the tumor [13,14]. In addition, tumors can evade T-cell recognition through alteration of their MHC Class I/ tumor antigenic peptide complexes and antigen presentation machinery [15,16].

Tumor cells utilize a number of altered metabolic pathways to contribute to an unfavorable environment for T-cell expansion. Another mechanism used by tumors to dysregulate T-cell function or induce T-cell apoptosis is the production and secretion of immunosuppressive factors into the microenvironment.

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Finally, tumors can prolong their survival by over expressing various antiapoptotic proteins.

Myeloid Derived Suppressor Cells (MDSCs) are functionally defined as immunosuppressive, immature myeloid cells. Cancer patients who exhibit elevated peripheral MDSCs, show positive correlation with advanced disease and therapeutic inefficacy. Of note, phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil have been found to effectively decrease MDSCs' immunosuppressive capability [17].

After circumventing cell-intrinsic mechanisms of apoptosis, tumor cells are subjected to elimination pressures by the immune system. Tumor cell-specific antigens play a role during this process, which if recognized by cytotoxic immune cells, lead to their destruction [18,19].

Fibroblasts and macrophages within the TME also contribute to suppression of tumor growth [20]; however, these cells may later become re-educated by the tumor to acquire pro-tumorigenic functions [21].

For instance, tumor-associated macrophages (TAMs) support diverse phenotypes within the primary tumor, including angiogenesis, growth, and invasion by secreting a plethora of pro-tumorigenic proteases, cytokines and growth factors (e.g. epidermal growth factor (EGF), which participates in a paracrine signaling loop via tumor-secreted colony stimulating factor (CSF). Tumor cells modify the microenvironment to produce bioactive products such as growth factors, chemokines, matrix-degrading enzymes that enhance the proliferation, survival, invasion, and metastasis of tumor cells.

Platelets aggregate around tumor cells to form a protective layer that makes it difficult for the immune system to effectively operate in the TME. Platelets can also mediate host immune and inflammatory responses. A large number of experimental and clinical data support a pro-metastatic role of platelets in cancer [22-25].

Within the blood compartment, tumor cells can form aggregates with platelets and thus avoid natural killer cell mediated cytotoxicity. Therefore, tumor cell adhesion to platelets and their activation is a crucial step for tumor cell survival within the blood circulation [26].

As tumors grow, immune-suppressor cells, including MDSCs and T cells are mobilized into circulation in response to activated cytokine axes induced by tumorigenesis (e.g. TGF-β, CXCL2 and CXCR5). MDSCs and T cells infiltrate the growing tumor to disrupt immune surveillance via multiple mechanisms, including, but not limited to, disruption of antigen presentation by dendritic cells (DCs), inhibition of T and B cell proliferation and activation, or inhibition of natural killer (NK) cytotoxicity. Cancer-associated fibroblasts (CAFs), which become activated by tumor-derived factors (e.g. TGF-β, FGF, PDGF, etc), secrete extracellular matrix (ECM) proteins and basement membrane components, regulate differentiation, modulate immune responses, and contribute to dysregulated homeostasis [27].

CAFs are also a key source of VEGF, which supports angiogenesis during tumor growth. In addition to cellular contributions, several extracellular properties contribute to tumor progression, including low oxygen tension, high interstitial fluid pressure, low TME pH, and changes in specific components of the ECM [28,29].

Tumor angiogenesis is involved with multiple molecular pathways and provides potential interventional strategies. The VEGF axis is recognized as the primary factor responsible for tumor angiogenesis resistance. VEGF/VEGFR activates oncogenic signaling via mitogen-activated protein kinase (ERK/MAPK) pathway, the phosphatidyl-inositol-3-kinase (PI3K-AKT) pathway, and the phospholipase-C-g (PLC-g) pathway leading to cell proliferation, survival, migration, and vascular permeability [30].

Chronic VEGF/VEGFR inhibition has been found to lead to the emergence of compensatory signaling pathways that sustain angiogenesis. Several of these VEGF-independent signaling pathways rely on key proteins, including the FGF/FGFR, angiopoietin-2 (Ang2), and the MET oncogene [31].

Complementary therapies focused on these alternative pathways have been developed to abrogate acquired resistance. Pan-FGFR inhibitors are used to inhibit the FGF/FGFR axis [32].

The MET/HGF pathway is inhibited by HGF antagonists and by the anti-MET targeted agent cabozantinib [33,34].

TME and the Anti-Tumor Immune Response

Immature T cells, initially born and matured in primary lymphoid organs of the bone marrow and

thymus, respectively, under strictly controlled homeostatic conditions recirculate, carried by a network of blood and lymphatic vessels, to a diverse group of dispersed secondary lymphoid organs (SLO), including hundreds of lymph nodes (LNs) [35].

The immune system is composed of 2 types of immunity. Innate immunity is nonspecific and fast acting, working within minutes to days of an injury or insult. By contrast, adaptive immunity is specific and occurs over time. T and B cells play critical roles here because they develop memory. Upon second exposure to a pathogen, these cells can eliminate a threat much more efficiently because they had learned to recognize and respond to it during a previous, first encounter.

The goal of immunotherapy for cancer, in terms of checkpoint inhibition, is to educate and then liberate the natural underlying cancer immune responses in the adaptive immune system. The seven steps of the cancer immunity cycle include: 1) release of cancer cell antigens, (2) cancer antigen presentation, (3) priming and activation, (4) trafficking of T cells to tumors, (5) infiltration of T cells into tumors, (6) recognition of cancer cells by T cells, and (7) killing of cancer cells. Numerous factors can help to drive or suppress anticancer immunity at each step of the cancer-immunity cycle. These include suppressive factors in the tumor microenvironment (TME), including the cell-associated factor programmed cell death protein-ligand 1 (PD-L1) and its interaction with one of its receptors, programmed cell death protein-1 (PD-1). Other immunosuppressive factors include soluble mediators that impair cancer antigen-presentation capabilities, thereby indirectly causing suboptimal T-cell priming and activation (steps 2 and 3), or inhibit expression of adhesion molecules on endothelial cells to impede T-cell infiltration (step 5). In the case of PD-L1, expression by tumor cells and tumor-infiltrating immune cells impairs cytolytic T-cell activity (step 7). In addition to PD-1, PD-L1 also binds to B7.1 expressed on activated antigen-presenting cells (APCs), which inhibit T-cell responses.

The tumor microenvironment can not only prevent the expansion of tumor antigen-specific helper and cytotoxic T cells but also promote the production of pro-inflammatory cytokines and other factors, leading to the accumulation of suppressive cell populations that inhibit rather than promote immunity [36].

Local production of IL-1 & 6 by tumor-associated macrophages promotes angiogenesis, tumor growth, & metastasis. Tumor microenvironments regulate distinct signal cascades that are critical for determining macrophage polarization and facilitating the expression of key molecules that control interactions with cancer stem cells.

During an immune response to cancer, a tumor produces antigens that are delivered to antigen-presenting cells, such as dendritic cells, which can then activate tumor-specific T cells. This crosstalk between dendritic and T cells typically occurs within the lymph nodes. Activated T cells traffic to the site of the originating tumor, recognize that tumor-specific antigen on the surface of cancer cells, produce cytokines that help to drive further T-cell expansion, and, ultimately, lyse or kill cancer cells in the tumor microenvironment.

This normal immune process can be circumvented when PD-L1, expressed by cancer cells in the tumor microenvironment, binds PD-1 on T cells, rendering them inert. Essentially, the immune system is rendered nonfunctional regarding this cancer. Immunotherapy (via checkpoint inhibition) works by turning it back on, by 'taking the foot off the brake.'

T cells receive and respond to both activating and inhibitory signals. Activating signals stimulate the immune system and accelerate its ability, for example, to fend off viruses or bacteria, whereas inhibitory signals hinder the immune system and can dampen or inhibit T-cell responses. In general, without these inhibitory mechanisms, rampant autoimmune disease would emerge. Checkpoint inhibitors such as those against CTLA-4 and PD-1 or PDL-1, however, are an advantageous example of circumventing these inhibitory signaling mechanisms.

Anti-CD47 antibody may be utilized in several combination strategies to more effectively target tumor cells. First, anti-CD47 antibody may be combined with a second antibody against a tumor-specific antigen either separately or in a bi-specific format to recruit multiple cytotoxic mechanisms: macrophage-mediated phagocytosis, NK cell mediated-ADCC, and/or CDC. Second, anti-CD47 antibody may be combined with agents that augment macrophage effecter cell number and function, including M-CSF or GM-CSF, to increase effecter cells at tumor sites to enable phagocytic elimination. Third, chemotherapy and/or radiation may be combined with anti-CD47 antibody to induce pro-phagocytic signals (calreticulin) on tumor cells to augment anti-CD47 antibody potency. Fourth, given the ability of anti-CD47 antibody to inhibit tumor metastasis through phagocytosis by vascular-lining macrophages or direct inhibition of chemotaxis, this therapy can be

administered systemically and/or infused locally at the time of surgical excision of tumor. Anti-CD-40 antibody works in an analogous way, to enhance the anti-tumor immune response.

Prognostic value of tumor infiltrating lymphocyte subsets in breast cancer depends on hormone receptor status. Interaction between immune-regulatory proteins and tumor infiltrating lymphocytes (TILs) within the TME is complex, and their associations may have significant clinical implications. In survival analyses, increased CD4+ TIL infiltration was associated with better prognosis of the patients. In subgroup analyses, high CD4+ TIL infiltration was revealed as an independent good prognostic factor in hormone receptor-negative subgroup while high FOXP3+/CD8+ T cell ratio was found to be an independent adverse prognostic factor in hormone receptor-positive subgroup, especially in luminal A subtype [37].

FOXP3 is a marker of regulatory T-cells (Tregs) which promote immune tolerance and suppress anti-cancer immune responses, analogous to checkpoint proteins. In cancer patients, immunosuppression through Tregs is a crucial component of tumor immune evasion and contributes to disease progression. Tumor-infiltrating Tregs in particular suppress local effecter T cell responses and are associated with poor prognosis in tumors such as human pancreatic cancer or hepatocellular carcinoma. The chemokine CCL22 is known to recruit Tregs into the tumor tissue and many types of human tumors are known to express high levels of CCL22.Suppression of CCL22 by IL-1 receptor blockade inhibits Tregs migration [38].

The tumor metabolic stress shapes an immunosuppressive tumor microenvironment. An overview of metabolic stress in the TME that mediates immune suppression includes the fact that cancer cells exhibit a substantial demand of nutrients, including glucose, amino acids, and fatty acids, and this contributes to a lack of hydroxyl radicals and maintains high production of H+ ions. These metabolic stresses promote tumor cell growth, increase the expression of immune checkpoint proteins and immunosuppressive cytokine secretion, enhance the inhibitory function of regulatory T cells, and inhibit the anti-tumor effect of tumor-infiltrating cytotoxic T cells, thereby leading to an immunosuppressive TME.

A new approach to cancer therapy uses antibodies that have been specially made to recognize specific cancers. When coupled with natural toxins, drugs, or radioactive substances, the antibodies seek out their target cancer cells and deliver their lethal load. Alternatively, toxins can be linked to a lymphokine and routed to cells equipped with receptors for the lymphokine [39].

Natural Products that Support Cancer Therapy by Modifying the TME

Resveratrol- main sources include grapes (*Vitis vinifera* L.), a variety of berries, peanuts, medicinal plants such as Japanese knotweed and red wine- modulates the natural killer group 2D (NKG2D) and its ligands by increasing expression in transformed target cells and in NK cells. Enhanced expression of NKG2D receptor and cytotoxins in NK cells together with up regulation of NKG2D ligands on target cell surfaces leads to enhanced killing efficacy. NK cells use two different mechanisms to kill the targets: 1) using cytotoxic granule exocytosis and 2) by induction of death receptor-mediated apoptosis. Increased IFN-γ production by resveratrol enhances TRAIL expression, which can facilitate apoptosis induction. Inhibitory signaling is often too weak to prevent NK cell killing due to down- regulated expression of MHC I proteins in malignantly transformed or virus-infected cells [40].

Botanical Extract Compound PHY906 is a herb formula-consisting of Chinese Skullcap *(Sctuellaria baicalensis),* Peonia *(Paeonia lactiflora)*, Chinese Licorice *(Glycyrrhiza uralensis)* and Ziziphis *(Fructus ziziphi)*- used in traditional Chinese medicine for over 1800 years for treating a variety of gastrointestinal distress such as diarrhea, cramps, nausea, vomiting etc. [41]. Yale Medical Center conducted a research on PHY906 as an adjunct to chemotherapy in a Phase I/II double-blind, randomized study on Patients with advanced colorectal cancer

PHY906 has been shown to increase the chemotherapeutic efficacy while decreasing the chemotherapy-related toxicities and side effects of a variety of anticancer agents in various cancers [42].

Such studies have revealed that PHY906 enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment through multiple mechanisms targeting the inflammatory state of the microenvironment of tumor tissue via two of its major ingredients, primarily Scutellariabaicalensis and secondly Paeonia lactiflora. PHY906 also enhanced infiltration of macrophages (M-1 type) into tumors [43].

A cocktail of Turmeric- curcumin, Green tea epicatechin gallate (EGCG) and resveratrol, increased levels of tumor-infiltrating NK cells and CD8+ cytolytic

T cells in C57BL/6 mice bearing HPV+ mouse lung cancer (TC-1 cells). The combination formula repolarized M2-like TAMs (Arg-1highIL-10highIL-12low) to M1-like TAMs (iNOShighIL-10lowIL-12high) in the tumors [44].

Role of Stress and Sympathetic Nervous System

High vascularization and locally secreted factors make the bone marrow (BM) microenvironment particularly hospitable for tumor cells and bones are the preferred metastatic site for disseminated cancer cells of different origins.

Stress and catecholamine neurotransmitters released in response to activation of the sympathetic nervous system modulate various BM cells and may thereby influence cancer progression. Epinephrine (EPI) and nor-epinephrine (NOR)are released in the BM microenvironment from sympathetic nervous system (SNS) fibers entering the bone with blood vessels. EPI and NOR influence interaction of tumor cells with chemokine-expressing BM niche cells, e.g. CXCL12 abundant reticular (CAR) cells, osteoblasts and osteoclasts. In response to adrenergic signaling niche cells release (1) CXCL16 chemokine that interacts with CXCR6 expressed on the surface of several tumor cells types, (2) CXCL12 that chemoattracts CXCR4 expressing cancer cells and (3) RANKL protein that binds RANK-expressing malignant cells. In addition, adrenergic signaling in osteoblasts and also directly in tumor cells themselves can promote release of angiogenic factors thus promoting bone marrow colonization by tumor cells through increased blood vessel density.

Some energy-rich metabolites (L-lactate, ketones and fatty acids) derived from the tumor stroma can be transferred to the adjacent cancer cells and used for energy production via mitochondrial oxidative phosphorylation**.** studies have reported that lactate generated by hypoxic tumor cells is a prominent substrate that fuels the oxidative metabolism of oxygenated tumor cells [45].

These observations imply that glycolytic and oxidative tumor cells mutually regulate their access to energy metabolites. Tumor stroma metabolites such as lactate and ketones may thus promote tumor growth by acting as high-energy metabolites. Metformin, an anti-diabetic agent, inhibits both lipolysis in adipocytes and oxidative phosphorylation, preventing cancer cells from using the energy-rich metabolites derived from the tumor stroma [46].

Acidity of the Tumor Microenvironment

The glycolytic nature of malignant tumors contributes to high levels of extracellular acidity in the tumor microenvironment. Tumor acidity tends to correlate with cancer aggressiveness; in part, this reflects the ability of hypoxia inducing factor 1 (HIF-1) to promote invasiveness and angiogenesis. Oral administration of pH buffers can reduce the development of spontaneous and experimental metastases in mice [47].

Microenvironmental acidity plays an important role in the response of malignant tumors to a wide variety of drugs and contributes to chemotherapeutic failure in cancer treatment. Lactate released as a waste product of glycolytic energy production in the hypoxic tumor microenvironment has been demonstrated to constitute a prominent substrate that fuels the oxidative metabolism of tumor cells in oxygenated regions, and has been shown to be involved in lactate uptake by cancer cells that preferentially utilize lactate for oxidative metabolism [48]. Hydrogen ions flow along concentration gradients into adjacent normal tissue causing normal cell death, extracellular matrix degradation, and also stimulates angiogenesis [48].

Lactate Metabolism in Human Tumors, Alkalinizing the TME

Lactate is metabolized by human lung tumors *in vivo*. Lactate use by tumor cells correlates with high FDG-PET signal and occurs in diverse onco-genotypes. Mono-carboxy transporter 1 (MCT1) enables lactate consumption by some lung cancer xenografts. Lactate's contribution to the TCA (Krebs) cycle *in vivo* can exceed that of glucose [49].

Oral administration of potassium and/or sodium bicarbonate can raise the extracellular pH of tumors, an effect associated with inhibition of metastasis and improved responsiveness to certain cytotoxic agents; clinical application of this strategy appears feasible. Bicarbonate has the highest buffering capacity of any substance and is a specific for Lactic acidosis. Research with mice showed that oral intake of bicarbonate increased the pH of the TME, significantly reducing the spread of metastatic breast cancer [50].

Tumor pH buffering reduced optimal conditions for enzymes involved in tumor invasion such as cathepsins and matrix metalloproteins. InMDA-MB-231 tumor-bearing mice treated with bicarbonate showed significantly lower numbers of circulating tumor cells (CTCs) than untreated mice ($P < 0.01$).

In a mouse model of endogenously arising aggressive B-cell lymphoma, systemic alkalization resulted in concomitant IFN-γ up regulation in NK cells that were sufficient to significantly delay tumor growth without any other immunotherapy. This effect was strictly dependent on NK cells [51].

Acidic pH within the tumor microenvironment has significant immunosuppressive effects, which include suppressed T-cell responses, and an abrogation of IFNγ and TNFα secretion. Mice given oral sodium bicarbonate didn't show a direct impact on reducing the size of melanoma tumors, but there was an increase in T cells within the tumor. Treatment with bicarbonate and CTLA-4 or PD-1 inhibitors reduced melanoma and pancreatic tumor growth in these mouse models when compared to checkpoint inhibitor treatment alone.

CONCLUSION

The tumor microenvironment has been established as a critical contributor to cancer progression because of the supporting roles of its components to the tumors. The presented review provides a comprehensive material on different ways in which the TME becomes favorable for growing tumors as well as throws light on some of the natural treatment agents targeting these specific mechanisms. Further studies on these agents may provide a detailed insight in their mode of actions expanding the boundaries for development of newer anticancer therapeutic agents.

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