Review Article

Tumor Microenvironment and its Role in Metastasis

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Abstract

Tumor microenvironment (TME) refers to the cellular environment where tumor cells reside. It is composed of stromal cell types, tumor vasculature, and extracellular matrix that surround tumor cells. The TME plays a key role in the initiation, progression, and metastasis of tumors. This review highlights the role of TME in tumor progression and metastasis. A thorough knowledge of the role of the TME in tumor initiation and progression provides us with novel approaches to targeting TME for effective anticancer treatment. More studies on the tumor cell-intrinsic pathway and extrinsic pathways in the TME, combined with current clinical approaches, hold a great potential for developing efficient anti-cancer therapy.

Keywords: Cancer, Metastasis, Tumor microenvironment.

Introduction

A thorough knowledge of the tumor microenvironment (TME) and its characterization enables researchers, biological scientists, clinicians, and biomedical engineers to identify new prognostic, predictive biomarkers, to design novel therapeutic strategies, and approaches and to develop innovative drug delivery systems.[1,2]

TME plays a key role in the initiation, progression, and metastasis of tumors.[3] TME refers to the cellular environment where tumor cells reside.[4] It comprises stromal cell types, tumor vasculature, and extracellular matrix (ECM) that surround tumor cells.[5,6] "The stromal cells of the TME include cancer associated fibroblasts (CAFs),[7-10] T lymphocytes, B lymphocytes,[11-14] Natural killer (NK) and NK T cells (NKT) cells,[15-20] tumor associated macrophages (TAMs),[21-23] myeloid derived suppressor cells (MDSC), tumor associated neutrophils,[24-27] terminally differentiated myeloid dendritic cells,[24] vascular endothelial cells,[5] mesenchymal stem cells (MSCs),[25] and rarely adipocytes[26] and pericytes."[27] "The ECM of the TME is highly complex and is composed of collagen, elastin, fibronectin (FN), glycoproteins, and proteoglycans,"[6,28-30] as shown in Table 1.

Cells of the Tme

CAFs

CAFs form a major component of the TME and they "modify" the "soil" within which tumor cells survive. The fibroblasts that reside in the stroma of human cancers are referred to as CAFs. They secrete increased collagen, ECM proteins, and pro-tumor factors. CAFs are derived from activated resident fibroblasts, epithelial – mesenchymal transition (EMT) of resident epithelial cells, endothelial to mesenchymal transition of resident endothelial cells, and differentiation of bone marrow mesenchymal cells. CAFs regulate T lymphocytes and provide an immunosuppressive environment. CAFs also regulate angiogenesis in tumors by secreting pro-angiogenic factors such as fibroblast growth factor 2 (FGF2) and VEGFA. CAFs enable tumor cells to overcome immune surveillance by recruiting M2 macrophages and MDSC. CAF derived ECM proteins include CAF – derived laminin and CAF – secreted versican. CAFs synthesize, secrete, assemble, and modify ECM composition and organization. CAFs produce 2 remodeling enzymes, namely, lysyl oxidase (LOX) family and matrix metalloproteinases (MMPs). The LOX family oxidases catalyze the crosslinking of collagen and elastin by oxidation. This, in turn, results in increased firmness of the tumor stroma. Increased levels of LOX family oxidases

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Table 1: Components of the tumor microenvironment

Cells	Tumor ECM
Cancer-associated fibroblasts	Collagen
T lymphocytes	Fibronectin
B lymphocytes	Elastin
NK and NKT cells	Glycoproteins
Tumor-associated macrophages	Proteoglycans
Tumor-associated neutrophils	
Terminally differentiated myeloid dendritic cells	
Tumor-associated endothelial cells	
Mesenchymal stem cells	
Adipocytes	
Pericytes	

are often associated with cancer progression. MMPs are zinc containing endopeptidases. They facilitate the tumor cells to cross the ECM. MMP9 is overexpressed in various cancers and they aid in metastasis and tumor progression.[7-10]

T Lymphocytes and B Lymphocytes

Tumor infiltrating B-cells play a dual role in TME. They exert both protumorigenic as well as anti-tumorigenic effects, based on the composition of TME, the B-cells phenotypes and the antibodies they secrete. B-cells are present in large numbers in tumor margins or occasionally they occur as tumor associated aggregates. They play an active role in the presenting tumor-derived antigens to $CD8^+$T cells and $CD4^+$T cells. They present tumor associated antigens, captured by B-cell receptors to TAMs and dendritic cells. B-cells release cytokines such as interferon γ (IFN γ) and interleukin 2 (IL2) that induce cytotoxic immune responses. In this manner, the tumor infiltrating B-cells play an antitumor role.[11-14]

NK and NKT Cells

NK cells, a component of the innate immunity, have the ability to kill-altered cells like tumor cells, opsonized cells, and genotoxically changed cells without affecting the normal cells of the human body.[15] NK cells lack surface TCR and associated CD3 molecules. They express neural cell adhesion molecules. They show antitumor activity.[16] MHC downregulated altered cells which escape cytotoxic T lymphocyte killing, such as tumor cells, activate NK cells. Thus, NK cells play a key role in immune surveillance. Cytokines such as IL-2, IL-12, IL-15, IL-21, and IFN - α1B activate NK cells and promote NK cell maturation.[15]

NKT constitutes a type of CD1d restricted T-cells. They usually alternate between different functional subsets depending on cell-cell interaction or interaction with signaling molecules. They are of three types namely TH1 – like cells, TH2 – like cells, and Treg- like cells. TH1 – like cells provoke antitumor response. TH2- like cells and Treg- like cells induce immune escape and tumor progression. NKT cells secrete a large amount of cytokines. Thus, NKT cells play a dual role in cancer. TH1-like NKT cells induce direct tumor cell death on interaction with stress proteins and CD1 molecules. However, when the tumor progresses, TH1-like NKT cells become anergic and may change to TH2-/Treg – like NKT cells which promote tumor progression and immune escape.[17-20]

TAMS

TAMs are essential controllers of therapeutic response in TME. They originate from circulating monocytes. They have two subtypes, M1 and M2 and they can be polarized into either types by appropriate stimuli. Th1 cytokines IF-γ and microbial products activate M1 macrophages, while Th2 cytokines IL-4, IL-10, and IL-13 activate M2 macrophages. M1 macrophages induce antitumor effect, whereas M2 macrophages induce protumor effects. TAMs are plastic and reversible. They promote resistance to some chemotherapeutic agents such as Gemcitabine, 5-fluoroacil, and anti-VEGF treatment. They also produce immune suppressive cytokines such as IL-1β, IL-6, IL-10, and TGF-β.[5,21-23]

Tumor-associated Neutrophils

The neutrophils which are mobilized from bone marrow to the tumor site are known as tumor associated neutrophils. This mobilization occurs in three phases, namely, "i) expansion and maturation of premature neutrophils in the bone marrow, ii) intravasation to circulation through endothelial cell attachment, and iii) chemotactic movement of neutrophils to tumor sites." Neutrophil shows both pro-tumor and antitumor response. Neutrophils exist as 2 phenotypes, namely, N1 (anti-tumor neutrophils) and N2 (pro-tumor neutrophils). "N1 neutrophils show increased expression of TNF α, ICAN- 1, and FAS. N2 neutrophils show increased expression of CCL2, CCL5, neutrophil elastase, cathepsin G, and arginase." N2 neutrophils secrete reactive oxygen species and cytokines/chemokines such as VEGF, IL-18, oncostatin M, HGF, TGF1β, CCL4, CCL2, CCL3, CXCL8, IL17, IL6, BV8, and G-colony stimulating factor (CSF). N1 neutrophils, after contact with cancer cells secrete H_2o_2, which lead to tumor cell death, through Ca^{2+} influx through TRPM2Ca^{2+} channel. N2 neutrophils possess a tumor suppressor function when they come into contact with a tumor cell, through FaS ligand/FaS interaction.[31-33]

Terminally Differentiated Myeloid Dendritic Cells

Dendritic cells are weak, immature, antigen presenting cells with the ability to capture antigen, express costimulatory molecules, and secrete cytokines. Terminally differentiated myeloid dendritic cells form a subset of dendritic cells which include CD $11b^+$DCs (DC1) and CD 103^+DCs (DC2) cells. Monocytes of the TME differentiate into macrophages and inflammatory DCs. Dendritic cells present tumor antigens to CD8 T-cells and induce an antitumor response. They are associated with transcription factors Baft 3, Irf 8, Zbtb 46, and Irf 4.[24]

Tumor-associated Endothelial Cells (TEC)

TEC lines the tumor blood vessels and they vary from normal endothelial cells in proliferation, migration, and response to growth factors. Tumor blood vessel exhibits structural abnormalities and chaotic blood flow. TEC shows aberrations in their adhesive properties. They show reduced E-selectin expression, and decreased expression of intercellular adhesion molecule (ICAM- 1), ICAM-2, and vascular cell adhesion molecule 1. As a result, the tumor specific cytotoxic T-cells recruitment into the tumor is disrupted. TEC permits selective transmigration of immunosuppressive myeloid cells from the blood into the tumor. They express inhibitory molecules such as programmed cell death ligand and PDL2. TEC suppresses T-cell function and impair anti-tumor immune response.[34-36]

MSC

MSCs constitute a group of multipotent stem cells that can differentiate into the tri – lineages – osteoclasts, chondrocytes, and adipocytes. They show positivity for surface markers, "CD 73, CD 105, and CD 90." They originate from the bone marrow, adipose tissue, and dental pulp. MSCs play a dual role in tumors. They promote tumor growth and metastasis by inducing EMT in the primary tumor cells. However, they are thought to have an inhibitory effect on tumor growth in tumors such as breast cancer, Kaposi 's sarcoma, hepatoma, and melanoma. They show a pro-apoptotic effect on tumors. They also exhibit cytotoxic effect on high concentrations. Polarization of MSCs toward protumor or antitumor function depends on the factors secreted by the tumor.[37-39]

Adipocytes

Adipocytes in tumors exhibit hypertrophy that may lead to "hypoxia, reduced angiogenesis, infiltration of macrophages and immune cells, excessive production of reactive oxygen species, low-grade inflammation, mitochondrial dysfunction, and remodeling of ECM." Dysfunctional adipocytes induce cancer progression through dysregulation of inflammatory – immune-angiogenic response system. As a result, hypoxia – inducible factor 1 - α (HIF - 1α) is activated, which upregulates secretion of "TNF - γ, IL – 6, IL-1, monocyte chemoattractant protein, and VEGF which are pro-angiogenic." Adipocytes secrete hormones such as leptin, adiponectin, and visfatin which are involved in cancer progression. Tumor resident adipocytes secrete factors which activate signaling pathways that lead to "cancer cell survival, proliferation, invasion, EMT, angiogenesis, and extracellular remodeling that promote cancer initiation and progression."[39]

Pericytes

Pericytes are vital multifunctional cells in the TME. They envelope the surface of endothelial cells. They play a key role in remodeling basement membrane during angiogenesis and tumorigenesis.[27] They are slender, elongated cells with projections that extend longitudinally and circumferentially around the vessel wall. They express α - smooth muscle actin, desmin, CD 140, platelet derived growth factor receptor, and nerve/glial antigen – 2 proteoglycan. Pericytes favor tumor angiogenesis, tumor progression, metastasis, and resistance to therapy.[40]

Tumor ECM

The ECM of the tumor is characterized by a complex 3D architecture, comprising "collagen, FN, elastin, glycoproteins, and proteoglycans." ECM provides support to the tissue, stores growth factors, and controls tissue stiffness. The integrins present in the cell membrane of cancer cells, mediate cell- ECM interactions. Oxidative stress, disorganized tumor cell growth, and inflammation lead to desmoplasia in the ECM. Hypoxic environment controls ECM remodeling, deposition, and degradation in the TME. HIF1 and HIF2 lead to remodeling of ECM by overexpressing collagens, FNs, and laminins.

Collagen is a key determinant of the physical and biochemical properties of TME and it modulates tumor cell signaling, polarity, and migration. HIFs aid in active regulation of the collagen modifying enzyme (LOX). This cross-links collagen fibers through lysine aldehyde/hydroxylysine aldehyde and forms collagen fiber. FN is another essential component of ECM and it regulates "cell differentiation, adhesion, growth, and migration." FN forms a fibrillar matrix and this matrix binds to integrin, fibrin, collagen, fibulin, and syndecan to form a complex network in the ECM. FN upregulation plays a key role in tumor progression, metastasis, and drug resistance in many cancers. Hyaluronan/hyaluronic acid is a gel-forming ECM proteoglycan. It is produced by CAFs and it regulates autocrine and paracrine signaling between CAFs and malignant cells. It inhibits apoptosis and promotes cell proliferation and EMT in cancer cells and, thus, aids in metastasis. Increased hyaluronan synthesis correlates with aggressive behavior of tumor. The mechanical and biological changes in the ECM are transmitted to cells through integrins present in the cell membrane and this can result in an invasive phenotype.[6,28,29,40]

TME and Metastasis

TME plays a key role in initiation of tumors, their progression, metastasis, recurrence, and drug resistance. Initiation of metastasis includes processes that prepare the malignant tumor cells to invade and circulate into tumor blood vessels in the TME.[4] "It includes 3 processes, namely, angiogenesis, EMT, and invasion/intravasation."

In tumors, CAFs, MSCs, TAMs, lymphocytes, TAEs, and pericytes play a key role in tumor progression and regression. "CAFs promote tumorigenesis, angiogenesis, and metastasis by secreting cytokines and growth factors." They promote TME remodeling through secretion of MMPs. They suppress cytotoxic T lymphocyte activity and promote cancer promotion. CAFs also facilitate drug resistance. TAEs are vital for tumor growth and metastasis. ECM functions as a scaffold for the

tumor cells and it plays an active role in cancer progression. It acts as the key regulator of tumor invasion. NK cells regulate the secretion of FN1, a vital ECM element. Tumor often secretes cytokines, integrins, proteases, and microRNAs that act as signals in ECM remodeling. "Cytokines such as TNF, IL, growth factors, and chemokines regulate cancer progression." Integrins, which are integral membrane proteins aid in cell-cell interactions and cell – ECM interactions. In TME, metastasis-promoting integrins are overexpressed, whereas metastasis-suppressing integrins are repressed. Integrins also affect nuclear alterations in tumor cells. MMPs promote cancer invasion and metastasis. MicroRNAs are endogenous, small non-coding RNAs which negatively regulate target mRNAs. They aid in tumor progression.[4,30,41]

Effect of Stromal Cells on Metastasis

Angiogenesis is the initial process in metastasis and helps cancer cells to migrate to distant sites, in aggressive tumors. Stromal cells affect TME, by secreting both pro-angiogenic and anti-angiogenic factors. VEGF is a pro-angiogenic factor which promotes migration and proliferation of endothelial cells and enhances tumor blood vessels permeability. TGF-β, PDGF, and bFGF regulate VEGF. Thrombospondin is an antiangiogenic factor. It binds to CD 36 on endothelial cells and makes them insensitive to VEGF and bFGF.[4]

CAFs in TME secrete ECM and create a hypoxic microenvironment inside the tumor. As a result, TAMs are recruited to the site and activated TAMs produce HIF-1 α and VEGF. VEGF, in turn, recruits and activates endothelial cells. CAFs also secrete cytokines like CXCL2 which promotes angiogenesis. The other pro-angiogenic factors secreted, which include TNF α and CXCL12.[4]

"Metastasis is a dynamic, multistep process which involves local invasion, ECM remodeling, EMT, intravasation, survival of the tumor cells in the circulation, arrest at a distant organ site, extravasation, micrometastasis formation, metastatic colonization, and macroscopic metastasis."[41,42]

Invasion is the process wherein tumor cells migrate from the primary site to another by breaking the ECM or basement membrane. MMPs secreted by cells in the TME, aid in the degradation of the ECM, and basement membrane. MMP7 secreted by epithelial cancer cells, cleaves the ECM and E-cadherin, a cell surface adhesion molecule, and disrupt the basement membrane and cell-cell junctions. CAFs and TAMs secrete MMPs which trigger proteolysis of ECM, thus leading to cancer cell invasion. Intrinsic fibroblast caveolin-1 activates Rho GTPase and remodels ECM.[4]

ECM remodeling and cancer cell invasion can be facilitated by specialized structures namely invadopodia and podosomes. Invadopodia are actin-rich membrane protrusions which degrade ECM. They are formed by invasive cancer cells. Podosomes are molecular structures with ventral membrane protrusions and invaginations and they are secreted by macrophages. Podosomes are regulated by CSF-1.[43]

EMT refers to the transition of tumor cells from epithelial status to mesenchymal status. It offers migrating and invasive abilities to tumor cells. "Cells such as CAFs, MSCs, and TAMs play a key role in EMT, through the secretion of growth factors such as TGF-β, PDGF, EGF, VEGF, HGF, and MMP1." Of these, TGF-β plays a key role in EMT and "it induces EMT through two pathways, namely, smads dependent and smads independent pathways." EGF, VEGF, and HGF induce EMT through activation of RAS/RAF/MEK/ERK/MAPK pathway. MMPs play a key role in EMT by degrading cell-matrix adhesions and cell-cell junctions in TME. Stromal cells secrete microRNAs such as miR21 and miR200 family members which induce EMT. MSCs and CAFs secrete TGF-β which promotes EMT and invasion.[4,44]

"Intravasation includes the process in which tumor cells migrate into blood vessels or lymph vessels through trans-endothelial migration." It is of two types, (i) paracellular intravasation and (ii) transcellular intravasation. During paracellular intravasation, tumor cells migrate through the vessel walls by opening junctions between endothelial cells. This occurs as a result of retraction of endothelial cells. In transcellular intravasation, tumor cells migrate through the blood vessels directly through the body of endothelial cells. It occurs as a result of degradation of exoskeleton of endothelial cells and their contraction. MSCs and CAFs secrete urokinase – type plasminogen activator. These proteins bind to PAR and breakdown plasminogen into plasmin, which leads to intravasation. VEGF, bFGF, PDGF, and microRNAs also promote intravasation by promoting angiogenesis.[4,45,46] CCL2 and CCR2 secreted by cells in the TME facilitate tumor invasion. Platelets secrete TGFβ1, activate the TGFβ/Smad pathway, and induce intravasation.[43,46]

Once cancer cells enter micro circulation, most of them get destroyed by anoikis, a damage due to hemodynamic shear forces and by NK cells. Tumor cells can survive, if they recruit platelets to form a protective coat on them and protect them from cytolysis. Activated platelets secrete chemokines, growth factors, and protease, which cause formation of heteroaggregates, containing tumor cells.[43]

The tumor cells in circulation arrest at a distant organ site. When the new site is conditioned for new metastatic tumor growth, factors secreted by the primary tumor, such as Angpt14, EREG, COX-2, MMP1, and MMP2 bring about extravasation by displacing vascular endothelial cell-cell junction.[41]

Once the tumor cells arrive at a secondary site, growth factors secreted by the primary tumor modify the phenotype, and function of the distant microenvironment.[43,47] This results in the establishment of pre-metastatic niche and metastatic niche. Pre-metastatic niche formation is a comprehensive, co-effort mechanism, whereby the ECM of the distant microenvironment is changed. This is achieved by recruitment

Table 2: Effects of stromal cells and their secreted factors on metastasis

Cells of TME	Secreted factors	Effects on tumor
CAFs	VEGF	Angiogenesis, EMT, Intravasation
	CXCL2	Angiogenesis
	MMPs	EMT
	UPA	Invasion/intravasation
	CXCL12	Tumor progression
MSC	TGF-β	EMT
	VEGF	Angiogenesis, EMT, intravasation
	UPA	Invasion/intravasation
TAMs	HIF - 1	Angiogenesis
	TGF-β	EMT
	VEGF	Angiogenesis, EMT, intravasation
	MMP	EMT, invasion/intravasation
	EGF	Intravasation
B lymphocytes	IFN ɣ	Tumor progression, metastasis, immune suppression
	IL 10	Proliferation and metastasis of tumor cells
T lymphocytes	IL 17	Angiogenesis, anti-tumor immunity
Tumor associated endothelial cells	PDL1	Suppression of T-cell function
	PDL2	Impairment of anti-tumor immune response
Pericytes	PDGFR β	Angiogenesis
	NG2 proteoglycan	Tumor growth, metastasis, drug resistance

PDGFR: Platelet derived growth factor receptor, NG2: Nerve/glial antigen – 2, UPA: Urokinase – type plasminogen activator

of CAFs and by factors like "MMPs, RhOA, ROCK, and non-muscle myosin – III and paladin." Pre-metastatic niche supports cancer cell engraftment. This is followed by formation of a metastatic niche. "It is a complex process involving loss of cell-cell adhesion, EMT, development of a motile, and invasive phenotype and ability to survive in circulation." Metastatic niche differs for different secondary organ sites in the body.[48-50]

Pro-tumor growth factors such as VEGF-A, TGF-β, TNF-α, and serum amyloid A further facilitate engraftment and growth of the tumor cells in the distant organ site,[4] as shown in Table 2.

Conclusion

This review highlights the key roles of TME in tumor progression and metastasis. The tumor environment, along with the cancer cells, plays a dynamic role in tumor progression. A thorough knowledge of TME in tumor initiation and progression can be harnessed to develop novel approaches to targeting TME for effective anticancer treatment. More studies on the tumor cell-intrinsic pathway and extrinsic pathways in the TME, combined with current clinical approaches, and hold a great potential for developing efficient anti-cancer therapy.

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