Tumor Microenvironment in Cancer Metastasis

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Metastasis, the process by which cancer cells escape primary tumor site and colonize distant organs, is responsible for most cancer-related deaths. The tumor microenvironment (TME), comprises different cell types, including immune cells and cancer-associated fibroblasts, as well as structural elements, such as collagen and hyaluronan that constitute the extracellular matrix (ECM).

tumor microenvironment immune system metastasis drug delivery cancer therapy

1. Introduction

Metastasis is responsible for more than 90% of cancer mortality; however, the underlying mechanisms driving this multistep process, ranging from local invasion at the primary site to the outgrowth of metastatic cells at the secondary sites, remain elusive. The communication between the neoplastic cells and the adjacent stromal cells begins at the earliest stages of tumor formation and continues during primary growth, local invasion, intravasation and establishment at the secondary site. While it was initially established that genetic aberrations are predominantly responsible for tumor initiation and progression [1], it has become clear during the last two decades that the tumor microenvironment (TME) plays an equally important role in modulating the aggressiveness, motility, dissemination, and colonization of cancer cells to distal organs [2]. The TME comprises the extracellular matrix (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. Cancer cells secrete growth factors and cytokines (including IL-6, IL-1β, TGF-β1, TGF-β2, 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).

2. Roles of Cellular TME Components in Regulating the Metastatic Cascade

2.1. Role of Immune Cells in Modulating Cancer Metastasis

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 [3]. During every step of this lethal process, cancer cells are being exposed to the immune system which attacks them to restrain their growth [4]. These anti-tumor effects are primarily mediated by $CD8^+$ T cells as well as natural killer (NK) cells, which have been shown to restrict metastatic outgrowth of tumor cells, whereas their depletion

enhances metastasis without affecting primary tumor growth [5][6][7]. However, during tumor evolution, cancer cells develop strategies not only to avoid immune surveillance but also to induce systemic responses by exploiting types of immune cells, such as myeloid cells, in order to enhance their metastatic efficiency [8].

The main type of myeloid cells implicated in regulating metastasis are macrophages, which are derived by hematopoietic stem cells (HSC) in the bone marrow and considered “professional” antigen presenting cells (APCs) [9]. They present foreign antigens to helper T cells and can prime naïve T cells. Macrophages are recruited to the tumor site via chemokines produced from cancer and stromal cells and are, thus, referred to as tumor-associated macrophages (TAMs). 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)-γ and IL-12. 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 [10][11].

TAMs enable metastasis at various stages of the process, including activation of epithelial-to-mesenchymal transition (EMT), local invasion, and intravasation into the blood stream, transfer of cancer cells through the circulation, extravasation, and seeding at the secondary site, and finally promotion of survival and outgrowth of cancer cells at distant organs [12][13]. They achieve this by secreting numerous chemokines, inflammatory molecules, and growth factors that promote metastatic progression.

At the primary tumor site, TAMs help create a suitable microenvironment that allows tumor invasion [14]. The term “tumor microenvironment of metastasis” (TMEM) is proposed to describe the close arrangement of cancer cells, perivascular TAMs, and endothelial cells often located at sites of intravasation. Increased TMEM density in breast carcinoma patient samples positively correlates with increased risk of distant organ metastases [15]. During EMT, growth factors and cytokines, including TGF-β, Wnt, and EGF, can lead to the activation of an orchestrated transcriptional program during which tumor cells lose epithelial characteristics and gain mesenchymal features leading to increased capacity for invasion and metastasis [16][17]. Inflammation-induced EMT has also been reported and TAMs appear to play an important role in this transition. In hepatocellular carcinoma (HCC), TAMs are recruited by cancer cells by expressing glypican and secrete TGF-β, PDGF, VEGF, chemokine (C-C motif) ligand 2 (CCL2), and M-CSF [18][19]. In the tumor microenvironment, TAMs secrete many cytokines such as TGF-β and IL-6 that can induce EMT [20]. In pancreatic cancer, M2-polarized TAMs expressing Toll-like receptor 4 (TLR4) promoted EMT via TLR4/IL-10 signaling. Specifically, TAMs upregulated mesenchymal markers vimentin and snail, induced MMP-2 and MMP-9 proteolytic activity and diminished E-cadherin levels, leading to increased fibroblastic morphology, proliferation, and migration of pancreatic cancer cells [21]. TAMs exhibiting a $CD68^{+}HLA^{-}DR^{+}$ surface marker phenotype can induce migration of HCC cells via the NF-*κ*B/FAK pathway [22]. TAMs can further facilitate the invasiveness of cancer cells induced by phosphatase of regenerating liver (PRL-3), a marker of colorectal cancer (CRC) liver metastasis. CRC cells also produce PRL-3 and tumor necrosis factor-α (TNF-α) that increase the expression of intermediate-conductance Ca^{2+}-activated potassium (KCNN4) channels in TAMs [23]; KCNN4 induce the secretion of IL-6 and IL-8 by TAMs and improve CRC cell invasiveness [24]. In addition, TAMs can release CCL18 chemokine that can stimulate angiogenesis and promote tumor progression in breast cancer [25]. In

addition to their role in regulating migration and invasion of primary tumor cells, TAMs also mediate crucial functions on cancer cells disseminated at secondary tissues [26].

The term “metastasis-associated macrophages” (MAMs) is proposed to describe the role of macrophages that have infiltrated at the metastatic site. MAMs are essential for the extravasation of circulating tumor cells (CTCs) and their successful outgrowth at the secondary site, partly through VEGF expression [27]. The expression of CCL2 and the infiltration of the tumor site by macrophages have been correlated with metastatic disease in breast cancer [28][29]. MAMs that originate from inflammatory monocytes (IMs), are recruited to secondary sites along with monocytes expressing the CCR2 receptor. The stroma, as well as the tumor itself, are responsible for attracting these cells at the metastatic site by expressing CCL2 [30]. CCR2 activation following binding to CCL2 in MAMs, induces the secretion of the chemokine ligand CCL3 by macrophages at the metastatic site; this enables the retention of macrophages at the lung and increases the number of lung metastatic foci, whereas inhibition of CCR1, the receptor of CCL3, may have therapeutic implications in breast cancer lung metastasis [31]. Moreover, vascular cell adhesion molecule-1 (VCAM-1) expressed in breast cancer cells has been associated with lung metastasis relapse [32]. Following infiltration of breast cancer cells to the leukocyte-rich microenvironment of the lung, VCAM-1 provides a survival advantage by tethering MAMs to cancer cells via counter-receptor α4 integrins [32].

2.2. Role of Mesenchymal Stem Cells in Regulating Metastasis

Mesenchymal stem (or stromal) cells (MSCs) are multipotent stem cells that reside in many adult tissues, such as the bone marrow, adipose tissue, liver, lung, periosteum, muscle connective tissue, and spleen. They are important for generating and repairing skeletal tissues, such as cartilage and bone [33]. MSCs reside in most tumors and significantly influence the development and function of the TME. These cancer-associated MSC (CA-MSC) are reprogrammed by the tumor to exert pro-tumorigenic functions, such as enhancing EMT, promoting angiogenesis and metastasis.

Importantly, MSCs facilitate metastases by secreting exosomes which interact with cancer cells to affect their proliferation and migration [34][35]. They are the only type of cells that can mass produce exosomes [36]. Exosomes derived from MSCs are microvesicles (60–200 nm size) that have a phospholipid bilayer carrying proteins, lipids, miRNAs and mRNA [37]. They act in a paracrine fashion and can be detected in various body fluids [38]. In a breast cancer model, treatment with MSC-exosomes led to an enhanced migratory ability, through increased β-catenin levels and activation of WNT pathway target genes, Axin2 and Dkk1 [39]. Gastric cancer tissue-related mesenchymal stem cells (GC-MSCs), excrete exosomes carrying miRNAs that following delivery into gastric cancer cells can promote gastric cancer metastasis [40]. Particularly, the expression of miR-221 was significantly increased and correlated with enhanced local invasion, advanced tumor-node-metastasis stage, and lymphatic metastasis [41]. Overall, the presence of MSC-derived exosomes induced an EMT program and promoted migration and invasion of HGC-27 gastric cancer cells [42]. Bone marrow-derived mesenchymal stem cells (BM-MSCs), can also promote the migration of multiple myeloma cells by producing exosomes which selectively carry cytokines, such as chemotactic proteins MCP-1, MCP-2, MCP-3, 40 SDF-1, 41,42, and IGF-1 [43].

Contradicting to these reports, MSCs were also found to suppress metastatic tumor growth through their excreted exosomes carrying different strands of miRNAs. MSCs that interact with disseminated breast cancer cells in the bone marrow during the early stages of dissemination, promote cancer cell dormancy and enable an extended period of cycling quiescence in which cancer cells are maintained in G_0/G_1 phase of the cell cycle [44][45]. MSCs that produce exosomes with increased miR-23b and decreased MARCKS expression suppress cell cycle and promote dormancy of metastatic breast cancer cells [46][47].

2.3. Cancer-Associated Fibroblasts in Promoting Metastasis

CAFs constitute one of the most abundant stromal components in solid tumors. CAFs are distinguished from different cell subtypes based on the presence of several stromal markers, including integrin β1 (CD29), fibroblast activation protein (FAP), and α-smooth muscle actin (α-SMA) [48][49]. CAFs can be derived from different cell types of the TME: local fibroblasts that undergo mesenchymal–mesenchymal transition (MMT), epithelial cells via epithelial-to-mesenchymal transition (EMT), endothelial cells following endothelial-to-mesenchymal transition (endMT), bone marrow originated from hematopoietic stem cells or mesenchymal stem cells and adipocytes [50]. Cancer cells can activate fibroblasts in a three-step process: recruitment, transformation to CAFs, and maintenance in the TME. Following their activation, CAFs release signaling molecules to favor the survival of cancer cells and promote the recruitment and transformation of other cell types within the TME [51]. CAFs facilitate remodelling of the ECM by releasing collagen and fibronectin, producing MMPs, and increasing VEGF levels. This leads to the re-organization of the matrix, creating tracks which neoplastic cells exploit to directionally migrate, accompanied by CAFs [52][53][54][55][56][57].

The presence of a specific subset of CAFs in the microenvironment, CAF-S1, was recently shown to suppress the immune system by attracting and promoting the survival, differentiation, and activation of $CD4^+CD25^+$ T lymphocytes [49]. 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 [58].

2.4. Endothelial Cells Attract Cancer Cells to the Metastatic Site

The lymphatic vessels that support the tumor at the secondary site are lined with loosely-connected lymphatic endothelial cells (LECs) that may also promote metastasis [59][60]. LECs recruit tumor cells by producing chemoattractants, such as CCL21 and SDF-1, which bind to CCR7 and CXCR4 receptors expressed in cancer cells, respectively [61]. Tumors developing at secondary organs produce factors that condition LECs to facilitate with cancer cell recruitment, extravasation, and outgrowth [62]. One example is the secretion of IL-6 by tumor cells that leads to STAT3 activation in LECs and subsequently high VEGF expression [62]. The expression of VEGF induced by tumor cells has been associated with the activation of HIF-1 in LECs, suggesting that tumor-secreted factors may support and direct lymphatic metastasis.

2.5. Components in the Blood Microenvironment That Facilitate Metastasis

During their dissemination throughout the body, circulating tumor cells (CTCs) encounter other cell types and factors in the peripheral blood that facilitate not only their survival but also their metastatic ability. These include various components, such as platelets, immune cells, cytokines, and circulating tumor microemboli (CTMs), which interact with CTCs and promote their survival [63]. Metastatic tumor cells can induce platelet adhesion and aggregation through the production of platelet activators such as ADP, thrombin, thromboxane, and von Willebrand factor [64]. Platelets enable the survival of cancer cells during their transit within the blood circulation and their colonization at the secondary site [65]. Platelets are a major source of lysophosphatidic acid (LPA), a natural lysophospholipid, which can bind to six different G-protein coupled receptors (GPCRs—LPA1-6 receptors) expressed on eukaryotic cells and activate multiple intracellular signaling pathways involved in cell survival, proliferation, differentiation, motility, cytoskeleton rearrangement and cytokine secretion [66]. Tumor cells induce platelet aggregation and production of LPA. Autotaxin (ATX), a lysophospholipase D also produced and released in platelet α-granules, is responsible for the basal concentration of LPA in blood. LPA interacts with different GPCRs found on cancer cells and promotes metastasis. The presence of certain cytokines in serum, including IL-17A, has also been correlated with increased number of CTCs and metastatic burden [67][68].

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