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Review

Tumor cell-mediated neovascularization and lymphangiogenesis contrive tumor progression and cancer metastasis

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ABSTRACT

Robust neovascularization and lymphangiogenesis have been found in a variety of aggressive and metastatic tumors. Endothelial sprouting angiogenesis is generally considered to be the major mechanism by which new vasculature forms in tumors. However, increasing evidence shows that tumor vasculature is not solely composed of endothelial cells (ECs). Some tumor cells acquire processes similar to embryonic vasculogenesis and produce new vasculature through vasculogenic mimicry, trans-differentiation of tumor cells into tumor ECs, and tumor cell–EC vascular co-option. In addition, tumor cells secrete various vasculogenic factors that induce sprouting angiogenesis and lymphangiogenesis. Vasculogenic tumor cells actively participate in the formation of vascular cancer stem cell niche and a premetastatic niche. Therefore, tumor cell-mediated neovascularization and lymphangiogenesis are closely associated with tumor progression, cancer metastasis, and poor prognosis. Vasculogenic tumor cells have emerged as key players in tumor neovascularization and lymphangiogenesis and play pivotal roles in tumor progression and cancer metastasis. However, the mechanisms underlying tumor cell-mediated vascularity as they relate to tumor progression and cancer metastasis remain unclear. Increasing data have shown that various intrinsic and extrinsic factors activate oncogenes and vasculogenic genes, enhance vasculogenic signaling pathways, and trigger tumor neovascularization and lymphangiogenesis. Collectively, tumor cells are the instigators of neovascularization. Therefore, targeting vasculogenic tumor cells, genes, and signaling pathways will open new avenues for anti-tumor vasculogenic and metastatic drug discovery. Dual targeting of endothelial sprouting angiogenesis and tumor cell-mediated neovascularization and lymphangiogenesis may overcome current clinical problems with anti-angiogenic therapy, resulting in significantly improved anti-angiogenesis and anti-cancer therapies.

Contents

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1. Introduction

Cancer metastasis accounts for approximately 90% of all cancer-related deaths. Effective approaches to inhibit cancer metastasis have not yet been developed. Robust neovascularization and lymphangiogenesis are found in a variety of aggressive malignant tumors [1,2] and contribute to tumor progression and cancer metastasis [3–7]. The initial stage of cancer metastasis involves invasion of tumor cells through the walls of small blood vessels or lymph vessels with subsequent spread to distant sites. Cancer cells then settle into a niche that promotes proliferation, vasculogenesis, and metastasis. Finally, cells find a suitable home for developing into a metastatic tumor [6]. Metastatic tumors have strong lymphangiogenic activities, which are closely related to tumor growth, cancer metastasis, and poor survival of cancer patients [8–10]. Thus, tumor angiogenesis (or neovascularization in a broad view) and lymphangiogenesis play pivotal roles in tumor advancement and cancer metastasis [1–5,8–10].

Angiogenesis is widely recognized as a hallmark of cancer [7]. Folkman first developed a theory regarding tumor angiogenesis in 1971, in which he proposed that a tumor produces its own new vasculature from existing blood vessels [11]. A majority of people believe that tumor blood vessels develop by endothelial sprouting angiogenesis. Inhibition of angiogenesis has become a new avenue for anti-cancer therapy. In particular, anti-angiogenic drugs that target vascular endothelial growth factor (VEGF) and downstream signaling have been widely applied in clinics to treat various cancers. Anti-angiogenic therapy has shown promise as a treatment for several cancers, such as colon cancer and non-small cell lung cancer [1–5,7,11]. However, the anti-tumor effects of current angiostatic drugs are short-lived in most patients. Further, the overall survival rates for most cancer patients are not significantly prolonged [12–17]. Current anti-tumor angiogenic therapies have recently been challenged [18–20]. Thus, new directions beyond VEGF-induced endothelial sprouting angiogenesis have been examined to overcome the problems with current anti-angiogenesis therapies [18–20].

Increasing evidence suggests that some tumor blood vessels do not consist of vascular endothelial cells (EC). A variety of tumor cells actively participate in tumor neovascularization. Vasculogenic tumor cells can directly line up to form functional blood vessels through EC-independent vasculogenic mimicry (VM) [21,22]. Tumor cell-dominant VM is closely associated with tumor progression, cancer metastasis, and poor prognosis in cancer patients [23,24]. VM is one of six important mechanisms mediating tumor neovascularization [1]. Trans-differentiation of tumor cells into tumor ECs has emerged as another important mechanism of tumor neovascularization [25,26]. Notably, tumor ECs have characteristics that are distinct from normal ECs with respect to genetics, morphology, and angiogenic capabilities [27,28]. Furthermore, tumor cells may cooperate with ECs to form mosaic tumor blood vessels through vascular co-option [29,30]. Moreover, tumor cells may stimulate robust lymphangiogenesis, which fosters tumor growth and metastasis [8–10]. Collectively, vasculogenic tumor cells are important players in tumor neovascularization and lymphangiogenesis and promote tumor advancement and cancer metastasis (Fig. 1).

Recent progress in tumor cell-mediated neovascularization and lymphangiogenesis research has broadened the landscape of tumor angiogenesis and provided new insights into the mechanisms of tumor progression and cancer metastasis. The non-canonical mechanisms of tumor cell-mediated neovascularization and lymphangiogenesis are intriguing. However, these mechanisms are controversial, and our understanding of tumor vascularity remains poor. Remarkably, the molecular mechanisms underlying tumor cell-mediated neovascularization and lymphangiogenesis remain largely unidentified. In the current review, we will mainly focus on the contributions of tumor cell-mediated neovascularization and lymphangiogenesis to tumor progression and cancer metastasis. In addition, we will introduce recent advances in the understanding of mechanisms that mediate tumor cell-induced neovascularization and lymphangiogenesis, which are relevant to tumor progression and dissemination. Finally, we will discuss dual targeting of vasculogenic tumor cell-mediated neovascularization and lymphangiogenesis with endothelial sprouting angiogenesis as a therapeutic strategy to block tumor progression and metastasis.

2. Tumor cell-mediated neovascularization contributes to tumor progression and cancer metastasis

Malignant tumors display the atavism phenomenon, because they express various embryonic genes that are normally silent after birth and during adult life [31]. Tumor cells produce several angiogenic factors, including VEGF, which induce robust endothelial sprouting angiogenesis. In addition, vasculogenic tumor cells actively participate in neovascularization through VM, trans-differentiation to tumor ECs, and vascular co-option [1,21–25,27–30].

2.1. Tumor cell-dominant vasculogenic mimicry promotes tumor progression and cancer metastasis

In 1999, Hendrix and colleagues found that metastatic melanoma cells directly form blood vessel-like structures through a process called VM, which does not require vascular ECs [21]. Vessels that are lined with tumor cells are functional and can supply oxygen and nutrition to the tumor. Histochemical staining shows that tumor cell-derived blood vessels formed through VM are positive for the periodic acid Schiff (PAS) reaction. The inner layer of the vessel is composed of major extracellular matrix (ECM) components, including laminins, collagen IV, heparan sulfate, and integrin-$\alpha v\beta 3$, which are likely produced and deposited by tumor cells [21]. Uveal melanoma is an aggressive and highly metastatic malignant tumor that shows strong PAS-positivity. Uveal melanomas have tumor cell-lined capillaries and loops, are highly malignant, and carry a poor prognosis. In contrast, cutaneous melanomas with PAS-negative blood vessels show reduced malignant potential and low morbidity rates [21]. Tumor cell-dominant VM has received increased attention recently in the cancer research field. Thus far, VM has been reported in 14 types of malignant tumors, including melanoma [21,22,32–34], ovarian cancer [35,36], breast cancer [37–40], prostate cancer [24,41,42], osteosarcoma [41,43], bladder cancer [44], colorectal cancer [45,46], gastric cancer [47–49], hepatic cancer [50,51], lung cancer [23,52–54], oral/laryngeal squamous cell carcinoma [23,55–57], glioma [25,26,58], medulloblastoma [59], and clear cell renal cell carcinoma [60].

Increasing evidence shows that tumor cell-dominant VM plays an important role in tumor progression and metastasis. For example, metastatic melanoma has an abundance of tumor cell-lined vasculature. The