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The Function of VEGF in Systemic Disease and Cancer Metastasis

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Abstract

Metastasis is the leading cause of cancer-associated mortality and the underlying mechanisms of cancer metastasis remain elusive. Both blood and lymphatic vasculatures are essential structures for mediating distal metastasis. The vasculature plays multiple functions, including accelerating tumor growth, sustaining the tumor microenvironment, supplying growth and invasive signals, promoting metastasis, and causing cancer-associated systemic disease. VEGF is one of the key angiogenic factors in tumors and participates in the initial stage of tumor development, progression and metastasis. Consequently, VEGF and its receptor-mediated signaling pathways have become one of the most important therapeutic targets for treating various cancers [1-15]. Today, anti-VEGF-based antiangiogenic drugs (AADs) are widely used in the clinic for treating different types of cancer in human patients. Despite nearly 20-year clinical experience with AADs, the impact of these drugs on cancer metastasis and systemic disease remains largely unknown. In this review article, we focus our discussion on tumor VEGF in cancer metastasis and systemic disease and mechanisms underlying AADs in clinical benefits.

Introduction

Cancer metastasis is the largest cause of cancer-related mortality, and the processes that cause cancer metastasis are unknownThe blood and lymphatic vasculatures are both necessary for distal metastasis to occur. The vasculature serves a variety of roles, including speeding tumour growth, maintaining the tumour microenvironment, delivering growth and invasive signals, supporting metastasis, and producing cancer-related systemic illness. VEGF is one of the most important angiogenic factors in tumours, and it plays a role in tumour growth, progression, and metastasis.

As a result, VEGF and its receptor-mediated signalling pathways have emerged as one of the most important therapeutic targets for cancer treatment. Anti-VEGF-based antiangiogenic medicines are now commonly utilised in the clinic to treat a variety of cancers in humans. Despite over two decades of clinical experience with AADs, little is known about their influence on cancer metastasis and systemic illness.

Subjective heading

Vascular endothelial growth factor (VEGF) represents a family of structurally and functionally related protein molecules, which include VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor (PlGF) The biologically active forms of these factors are constituted as homodimers or heterodimers that bind structurally and functionally related tyrosine kinase (TK) receptors expressed on the cell surface, including VEGFR1, VEGFR2, and VEGFR3 Upon receptor activation by their respective ligands, the targeted cells elicit cascade signaling events, embroiling phosphotidylinositol-3 kinase (PI3K), mitogen-activated protein kinase (MAPK), cytoplasmic tyrosine kinase Src, and phospholipase C gamma (PLCγ) pathways.

Discussion

While VEGFA-binding VEGFR1 and VEGFR2 are mainly expressed in blood vessel endothelial cells (ECs), VEGFR3 is mainly expressed in lymphatic endothelial cells (LECs), defining its binding ligands VEGFC and VEGFD as lymphangiogenic factors Consequently, VEGFA (often named VEGF) promotes angiogenesis, vascular permeability, vascular remodeling, and vessel survival. VEGFC and VEGFD potently stimulate lymphangiogenesis, albeit they also stimulate hematogenous angiogenesis through VEGFR2. VEGFB and PlGF belong to VEGFR1 specific binding ligands and accumulating experimental evidence shows that these two factors do not seem to stimulate angiogenesis, but are rather involved in vascular remodeling. The biological inert features of the VEGFB and PlGF also support the fact that VEGFR1 serves as a decoy receptor, opposing the VEGFR2 function. Thus, the balance of expression levels and activation of thesereceptors collectively control vascular homeostasis, growth, regression, survival, and remodeling

A bulk of experimental evidence from animal and human tumors demonstrates that VEGF is highly expressed in growing tumor tissues relative to their corresponding healthy tissues. It appears that both genetic alterations and microenvironmental changes contrib ute to high VEGF expression. In particular, tumor hypoxia is a potent driving force for VEGF expression. Another interesting feature of VEGF-induced tumor angiogenesis is that the VEGF-instigated vasculature consists of highly primitive vasculature networks, which are highly leaky, sinusoidal, disorganized, and vascular plexus that lack separation between microvessels. These abnormal features of tumor vasculatures by VEGF are commonly shared in various solid tumors Because of these pathological features of tumor vessels, VEGF promotes tumor growth, invasion and metastasis.

The first evidence of targeting VEGF for therapeutic development was observed in inhibition of glioblastoma growing in mice by a neutralizing antibody that blocks VEGF functions. This landmark work initiated tremendous interests in developing anti-VEGF-based AADs for cancer therapy. Today, clinically available anti-VEGF drugs include large molecular weight biologics and small chemical molecules that mainly target TK of the VEGFRs. However, each of these drugs is unique because of their specific targets. For example, an anti-VEGF neutralizing antibody is a monospecific drug that only neutralizes

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VEGF and an anti-VEGFR2 neutralizing antibody blocks 2–3 ligands that bind to this common receptor. Syphilis is an infection caused by Treponema pallidum. Usually, *T*. pallidum is transmitted through sexual intercourse. In addition, syphilis greatly increases the risk of infection and transmission of acquired immune deficiency syndrome. In recent years, the global incidence of syphilis has increased because of the ability of *T*. pallidum to evade host immune defenses and spread from the initial site of infection to other organs and tissues. Hence, it is also termed a "stealth pathogen. How *T*. pallidum overcomes the immune response and damages tissue is incompletely understood. Explaining the pathogenesis and immune mechanism of action of *T*. pallidum has become a key link to controlling syphilis.

placental growth factor are all members of the Vascular Endothelial Growth Factor family of structurally and functionally related protein moleculesThese factors are biologically active as homodimers or heterodimers that bind physically and functionally similar tyrosine kinase receptors on the cell surface. The targeted cells activate phosphotidylinositol-3 kinase (PI3K), mitogen-activated protein kinase (MAPK), cytoplasmic tyrosine kinase Src, and phospholipase C gamma (PLC) pathways once their receptors are triggered by their respective ligands

VEGF is substantially expressed in growing tumour tissues compared to their comparable healthy tissues, according to a large body of experimental evidence from animal and human cancers High VEGF expression appears to be influenced by both genetic and microenvironmental changes Tumor hypoxia, in particular, is a powerful inducer of VEGF expression Another intriguing aspect of VEGF-induced tumour angiogenesis is the presence of relatively primitive vasculature networks, which are highly leaky, sinusoidal, and disordered, as well as vascular plexus with no microvessel separation. These VEGF-induced abnormalities in tumour vasculatures are seen in a variety of solid malignancies VEGF promotes tumour growth, invasion, and metastasis pathways because of these pathological characteristics of tumour vasculature.

The role of VEGFs in cancer metastasis

Several extensive reviews have detailed the processes by which VEGFs are elevated in TME and their impact on tumour formation. The importance of VEGF signalling in the tumour metastatic cascade will be summarised here. Because of the systemic and local substances released during tumour growth, the metastasis process is phenotypically variableDespite the fact that recent research have begun to explain metastasis from spatiotemporal or omics perspectives, accurately describing the landscape of metastasis remains difficult. The metastatic cascade, which includes local invasion and intravasation, survival in the circulation, arrest at a distant organ and extravasation, and re-colonization, is the most life-threatening feature of cancer VEGFs have been implicated in many stages of carcinogenesis and metastasis, according to extensive research. The function

Local invasion and intravasation

Invading surrounding tissues and crossing the endothelial barrier is the initial step of tumor metastasis. As one of the hallmarks of malignancy, invasion is driven by intrinsic and extrinsic factors in the TME and starts from tumor cells detaching from tumor mass. The shed tumor cells sequentially enter the blood vessels with the assistance of various types of cells. This process is closely associated with the vascular endothelium and is known as intravasation.

I According to the standard explanation, tumour cells release VEGF, which attracts VEGFR-expressing ECs and orchestrates angiogenesisHowever, the widespread expression of VEGFRs on tumour cells suggests that VEGFs may have an autocrine effect on tumour cell activity Indeed, investigations in pancreatic cancer colorectal cancer and ovarian cancer have found that VEGF aids tumour invasion and survival. As a result, autocrine VEGF signalling promotes tumour cell migration and invasion via dedifferentiation and epithelial-mesenchymal transition (EMT) processes.

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At the transendothelial migration stage, VEGFA plays a major role in CTC-EC crosstalk. CTC-derived VEGF robustly increases the extravasation and is confirmed in a zebrafish-based dynamic visualization system]. EC barrier function depends on VE-cadherin. Src kinase, a VEGFR downstream signaling molecule, regulates cadherin function CD146, another endothelial cell adhesion molecule, was reported to mediate VEGF-induced tumor cell extravasation. Interestingly, various types of VEGF-expressing cells may facilitate CTC transendothelial migration. In experimental metastasis models using VEGF-null tumor cells, VEGF blockade withdrawal creates a critical window of high VEGF levels in host organs, which is suitable for visualizing host organ-derived VEGF in promoting extravasation. As a result, host-derived VEGF robustly promotes CTC extravasation via producing an angiogenic vascular phenotype Similar to the intravasation process, vascular-associated cells such as macrophages, produce VEGF for transendothelial migration.

VEGF signaling is involved in premetastatic niche formation. VEGFR1$^+$ bone marrow-derived HPCs can be recruited to premetastatic sites and form clusters before tumor cell arrival, and blocking VEGFR1 signaling abrogates tumor metastasis. In another study, VEGFR1 signaling mediates matrix metalloproteinase 9 (MMP9) expression in premetastatic lung endothelial cells and macrophages for promoting metastasis. However, contradictive reports suggest that, alternative pathways may mediate the priming of distal organ tissues In the bone microenvironment, osteoblast-derived VEGFA is detected in the matrix of the trabeculae of bone metaphyses, to where breast cancer cells preferentially traffic Indirect mechanisms have also been reported.

VEGFA indirectly recruits MDSCs into premetastatic sites via macrophage-derived CXCL1. These data suggest that VEGF signaling is involved in directing premetastatic niche formation and preparing for CTC entry.

By the arrival of the tumor cells, various cell compartments are recruited for the outgrowth of disseminated tumor cells (DTCs) and many pro-metastatic signals ultimately activate stemness, survival, mechanical, regeneration, and inflammatory pathways. VEGF is one of the key signals for successful colonization and overt. Using a chick embryo model in which anti-human VEGF antibody does not affect chick embryo angiogenesis, metastatic colonization is demonstrated as tumor-derived VEGF-. The critical role of VEGF has also been demonstrated in a vascularized organoid in vitro model designed for investigating metastatic colonization. Apparently, the role of VEGF during colonization is similar to that of primary tumors, with the potential to induce a suppressive immune microenvironment and possibly act directly on DTCs, in addition to strongly inducing angiogenesis for tumor growth. Interestingly, VEGF in distal organs may have extra roles that are different from those in the primary tumor. For example, other than educating the ECs in distal organs , induced VEGF expression in breast cancer cells promotes metastatic colonization and increases desmoplasia, which facilitates colonization. Host cell-derived VEGF also contributes to DTC colonization. Another report shows that, $S100A4^{+}$ stromal fibroblasts express VEGF for creating the angiogenic microenvironment for metastatic, demonstrating a crucial role for local fibroblasts in providing the soil for metastatic colonization.

Similar to primary tumor growth, the growth of metastatic nodules is also dependent on angiogenesis. In the absence of neovascularization, distal metastases remain microscopic tiny sizes, which may consist of a few hundred cells. It is likely that dormant metastases lack their ability to switch to an angiogenic phenotype, which is essential for metastatic growth. Interestingly, malignant cells in dormant metastases may undergo active proliferation, which is balanced by cellular apoptosis]. Continuous proliferation of tumor cells in dormant metastases increases the possibility of genetic alterations that switch on angiogenesis. In this context, VEGF levels are elevated in KRAS and p53-mutated cancer cells and serve as a key mediator for angiogenesis in metastases. Along with expansion of metastatic masses, VEGF levels are further elevated owing to tumor hypoxia, inflammation, acidosis, and infiltration of stromal cells. Thus, systemic delivery of AADs that target VEGF has profound impact on the suppression of metastatic tumor growth.

Lymphatic metastasis is another important mechanism for the dissemination of human cancer. Similar to blood vessel metastasis, lymphatic metastasis can be divided into several steps, including detachment and locomotion into the matrix, intravasation into lymphatics, survival in the lymphatics, settling in lymph nodes (LNs), and colonization After penetrating the basement membrane, tumor cells were carried partly by hydrostatic pressure towards lymphatics. Tumor-associated lymphatic vessels play an important role in mediating lymphatic dissemination of tumor cells to tumor-draining lymph nodes. An early, necessary step in the lymphatic metastasis cascade is the intravasation of lymphatic vessels. In the invasion/intravasation step, VEGFC and VEGFD-induced lymphangiogenesis is intensively investigated. VEGFR3 neutralizing antibody significantly inhibits tumor lymphatic metastasis in animal models.

Conclusion

CTCs can be arrested in the capillary vasculature and extravasate into the distal organs in a manner similar to the extravasation of white blood cells. Firstly, a firm cell-cell contact between tumor cells and ECs is established by adhesion molecules including selectins, integrins, cadherins, and CD44. Secondly, chemokines such as chemokine (C-X-C motif) ligand 12 (CXCL12) attract tumor cells to migrate from the lumen into the stroma of distal organs. Finally, tumor cells undergo transendothelial migration with the support of various EC-modulating signaling

At the CTC arrest stage, there is no evidence that VEGF directly mediates the adhesion of CTCs and endothelial cells. However, VEGF significantly promotes the expression of adhesion molecules. Platelets exhibit pro-CTC-arrest effects for CTC adhesion and extravasation via various adhesion molecules CTC-associated platelets may participate in VEGF-induced CTC arrest by binding these adhesion molecules.

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Conflict of Interest

The authors declare that they are no conflict of interest.

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