Angiogenesis in Cancer and Its Therapeutic Targeting

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Vascular endothelial growth factors (VEGFs) are the key regulators of vasculogenesis in normal and oncological development. VEGF-A is the most studied angiogenic factor secreted by malignant tumor cells under hypoxic and inflammatory stress, which made VEGF-A a rational target for anticancer therapy. However, inhibition of VEGF-A by monoclonal antibody drugs led to the upregulation of VEGF-D. VEGF-D was primarily described as a lymphangiogenic factor; however, VEGF-D's blood angiogenic potential comparable to VEGF-A has already been demonstrated in glioblastoma and colorectal carcinoma. These findings suggested a role for VEGF-D in facilitating malignant tumor growth by bypassing the anti-VEGF-A antiangiogenic therapy. Owing to its high mitogenic ability, higher affinity for VEGFR-2, and higher expression in cancer, VEGF-D might even be a stronger angiogenic driver and, hence, a better therapeutic target than VEGF-A.

VEGF-D angiogenesis lymphangiogenesis growth factors

1. Introduction

In order to meet the increased nutrient and oxygen demand, growing malignant tumors require blood supply, and hence, promote angiogenesis from existing vessels by inducing sprouting [1]. The malignant tumor vasculature has a significantly different structure and physiology as compared to normal blood vessels [2]. Vascular endothelial growth factors (VEGFs) are the primary growth factors regulating angiogenesis. Upon binding their corresponding vascular endothelial growth factor receptors (VEGFRs), VEGFs promote the proliferation and migration of endothelial cells, tube formation, increase vascular permeability and vascular endothelial cell survival, altogether angiogenesis [3]. Under pathologic conditions such as malignant tumor development, poor vasculature, and hypoxia trigger the expression of VEGFs, which activate ECs both in an autocrine and paracrine fashion, thereby increasing EC proliferation and migration [4]. Secreted VEGFs also increase vascular permeability and facilitate the transfer of plasma proteins into the extracellular matrix, where these proteins provide provisional support to the incoming ECs and facilitate vasculogenesis [3][5].

VEGFs belong to the Platelet Derived Growth Factor (PDGF) family, an important mitogenic family that modulates various biochemical pathways involved in cell growth, proliferation, and survival, as well as maintaining the structural integrity of the cell [6]. VEGFs are particularly important for blood vessel formation during embryogenesis. In mammals, members of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and Placental Growth Factor (PIGF). There are three types of VEGF receptors to which the members of the VEGF family can bind with varying affinity and specificity, thereby eliciting different responses. VEGFR-1 and VEGFR-2 are expressed on

vascular endothelial cells (VECs) and, in some instances, on non-endothelial cells [7]. VEGFR-3 is expressed particularly on lymphatic endothelial cells (LECs) [3][8][9].

2. Angiogenesis in Cancer and Its Therapeutic Targeting

A tumor cell's ability to induce angiogenesis is one of the hallmarks of cancer, as angiogenesis is essential for tumor cells to survive [10]. Furthermore, the autocrine production of growth factors and cytokines by the active ECs promotes tumor progression [11]. Tumor angiogenesis (the angiogenic switch) is initiated in response to hypoxic or inflammatory stimuli in the tumor microenvironment. During the angiogenic switch, ECs are activated and start to produce angiogenic growth factors such as Fibroblast Growth Factors (FGFs), TGF-β, PDGF, and VEGFs (A and D) [12][13]. The binding of these growth factors to their EC receptors leads to the production of matrix-degrading enzymes, enabling blood vessel growth. VEGF-A mediated activation of VEGFR-2 leads to degradation of the basement membrane followed by the transformation of ECs to motile tip cells at the sprouting end of the vessel [13][14] endothelial cell migration [15], and EC proliferation [16][17][18]. Angiogenesis is mediated by the coordination of dynamic tip cells with filopodia and stalk cells. Tip cells sense the pro or antiangiogenic factors in the tumor microenvironment and migrate, while the stalk cells have less filopodia and a faster proliferation rate to facilitate tube formation [14]. The new ECs establish tight junctions, and hence, a luminal vessel is produced [19][20]. The newly formed vessels are then covered by tumor-recruited pericytes, which provide support to the vessels from outside (maturation step) [21]. Unlike normal blood vessels, blood vessels in tumors are more permeable and tortuous, which is attributed to the altered endothelial cells (ECs) referred to as Tumor Endothelial Cells (TECs) [22][23]. Furthermore, besides the autocrine production of proangiogenic factors by tumor cells, tumor cells can prime immune cells to produce more angiogenic factors, which results in a loss of balance between the pro and antiangiogenic factors, rendering the tumor vasculature unruly and poorly developed [24]. Tumour blood vessels thereby have loose junctions, an incomplete basement membrane distribution, and reduced pericyte support. This deformed vascular physiology leads to poor blood supply and, therefore, hypoxia and reduced drug delivery [12][25].

Tumor vasculature and angiogenesis are important prerequisites of tumor cell proliferation, survival, and progression. Therefore, it is a feasible approach to inhibit tumor angiogenesis to target cancer proliferation. In the early 1990s, a murine anti-human VEGF-A antibody was developed that could reduce angiogenesis in vivo. A few years later, the antibody was humanized and was termed Bevacizumab (Avastin), which had the ability to bind and neutralize all VEGF-A isoforms [26]. Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) as a first-line antiangiogenic therapy for colorectal cancer (CRC) in 2004 and is a common drug of choice for various cancers today [27]. Ever since the discovery of Avastin, tumor angiogenesis and factors that might be involved in the regulation of the process have been extensively researched. There have been several candidates, but only a few were approved for antiangiogenic therapy to treat cancer, age-related macular degeneration (AMD), and diabetic retinopathy. Approved VEGF-A specific monoclonal antibodies for the treatment of cancer include Bevacizumab (Avastin for non-small cell lung cancer (NSCLC), glioblastoma, metastatic renal cell-, and cervical cancer) and ramucirumab (Cyramza for gastric, NSCLC and metastatic colorectal cancer). Further anti-VEGF-A antibodies are approved for macular edema (Ranibizumab (Lucentis) and Aflibercept (Eylea)). In addition, the

targeted therapy, antibodies with a broader target range targeting tyrosine kinase receptor, i.e., sorafenib (Nexavar), regorafenib (Stivarga), and sunitinib (Sutent) are also used to inhibit VEGFR activation and hence angiogenesis [28][29].

2.1. VEGF-D and Blood Capillary Angiogenesis

Like many other types of anticancer treatments, tumor cells developed resistance to antiangiogenic therapies [30][31][32]. Altered gene expression of angiogenesis-related genes in tumor cells was demonstrated in response to antiangiogenic drugs. Particularly, the expression of VEGFs was altered both in tumor cells and the surrounding stroma [28][32][33][34]. Since other members of the VEGF family could activate VEGFR-2 in the absence of VEGF-A, this could be a potential mechanism of antiangiogenic therapy resistance [35]. An interesting finding was that Avastin-mediated VEGF-A inhibition led to an upregulation of VEGF-D expression in gliosarcomas, and although the tumor growth was slower, the tumors when established, had better vascularization [36]. The normalization of this neo vasculature post-VEGF-A inhibition resulted in morphological changes: increased pericyte coverage, less leaking, less dilation and functional changes; decreased interstitial fluid pressure, increased tumor oxygenation, and improved penetration of drugs into these tumors [37]. VEGF-D can, therefore, execute all steps of tumor angiogenesis in the absence of VEGF-A with comparable efficiency [17][38].

Similarly, upregulated VEGF-D expression was reported in inflammatory breast cancer after treatment with celecoxib (non-steroidal anti-inflammatory drug) and VEGFR-2 inhibitor SU5416 [39]. Furthermore, patients with nonresectable hepatocellular carcinoma, already receiving bevacizumab, had a higher VEGF-D expression and promoted disease progression [40]. The ability of VEGF-D as an inducer of blood capillary angiogenesis was first characterized in rabbit retinal tissue [41] and was confirmed in human embryonic kidney cell line: induced VEGF-D expression resulted in the formation of highly vascularized and non-oedemic tumors as compared to tumors of wild type cells in mice [42]. VEGF-D can induce CD-31, as well as LYVE-1 positive vessels, by activating either VEGFR-2 or VEGFR-3, respectively, in the absence of VEGF-A [42]. Upon adenoviral vector delivery to skeletal muscles, mature VEGF-D was an excellent inducer of both lymphangiogenesis and angiogenesis, promoting pericyte recruitment and vascular permeability and a more diffused angiogenesis pattern [43]. A similar dose-dependent angiogenic response was observed in pig hearts [44]. VEGF-D also induced angiogenesis in the brain after blood–brain barrier breakdown by activating both VEGFR-2 and VEGFR-3 [45]. VEGF-D modulates angiogenesis by inducing EC proliferation and migration to branching points and facilitating tube formation [43][46][47]. Based on these findings, VEGF-D expressed by tumor cells could be a way for cancer to circumvent VEGF-A targeting antiangiogenic therapy [48][49][50]. Interestingly, other forms of anticancer therapies, such as docetaxel and vinorelbine, also upregulate VEGF-D expression and induced angiogenesis in vitro in HUVEC and BC cells in relation to melatonin signaling [51]; this further indicates that VEGF-D has a unique yet unidentified expression and signaling pattern which should be explored to facilitate multi-targeted antiangiogenic therapy.

2.2. VEGF-D Mediated Angiogenic Signaling in Cancer

Since VEGF-D can activate VEGFR-2 mediated signaling, it mainly activates signaling pathways involved in the proliferation, migration, survival, and physiology of EC cells [29], essentially maintaining the vascular system in development and disease [52]. Although researchers are in agreement that upregulated VEGF-D in response to antiangiogenic drugs might be one of the key factors enabling antiangiogenic drug resistance in cancers [28], little is known about the signaling pathways and expression regulators involved.

One of the main factors promoting VEGF-D expression in response to antiangiogenic therapy would be therapy-related hypoxia [53]. Achen et al. reported that VEGF-D was secreted exclusively by tumor cells in two independent model systems, acting in a paracrine fashion to activate VEGFR-2 positive blood vessels in tumors [54]. Furthermore, VEGF-D secreted by the tumor cells was localized in metastatic melanoma blood vessels endothelial cells near the immune-positive tumor cells but not in the distant blood vessels, which further supports that VEGF-D promotes angiogenesis in a paracrine fashion [55][56][57]. However, due to the localized production of VEGF-D by tumors and its role in promoting tumor cell progression, migration, and metastasis, it might also have an autocrine function in addition to its paracrine signaling as reported in endometrial carcinoma [58] and invasive cervical carcinoma [59]. Furthermore, VEGF-D could induce proangiogenic phenotype in HUVECs by upregulating genes involved in matrix modulation and cell membrane alteration in an autocrine manner [60]. Interestingly, in Gastric cancer (GC), VEGF-D transcription was facilitated by proteolytic activation of transcriptional factor CDP/Cux p200 by protease cathepsin L (CTSL). This upregulated VEGF-D translated to higher angiogenesis in GC [61]. Recently, in GC, a long noncoding RNA (LncRNA) CRART16 was found to downregulate miR-122-5p, thereby upregulating transcriptional factor FOS and hence upregulated VEGF-D expression and angiogenesis both in vitro and in vivo [62].

Some interesting points for research would include investigating if VEGF-D activates the same downstream signaling cascades as VEGF-A when activating VEGFR-2. Based on the bioinformatics analysis, VEGF-D potentially activates the MAPK signaling pathway, promoting cell proliferation, differentiation, and survival [63]. Secondly, as in glioblastoma, vascular, breast, and lung cancer, the tumor tissue has high expression of VEGFR-3 that unconventionally contributes to maintaining endothelial integrity in tumor blood vascular angiogenesis [64][65][66][67]. It would be interesting to investigate how VEGF-D/VEGFR-3 signaling is stimulating angiogenesis.

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