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- Review -

The Molecular Insight into the Vascular Endothelial Growth Factor in Cancer: Angiogenesis and Metastasis

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This review discusses the pivotal role of vascular endothelial growth factors (VEGF) in angiogenesis and lymphangiogenesis, vital processes influencing vascular permeability, endothelial cell recruitment, and the maintenance of tumor-associated blood and lymphatic vessels. VEGF exerts its effects through tyrosine-kinase receptors, VEGFR-1, VEGFR-2, and VEGFR-3. This VEGF-VEGFR system is central not only to cancer but also to diseases arising from abnormal blood vessel and lymphatic vessel formation. In the context of cancer, VEGF and its receptors are essential for the development of tumor-associated vessels, making them attractive targets for therapeutic intervention. Various approaches, such as anti-VEGF antibodies, receptor antagonists, and VEGF receptor function inhibitors, are being explored to interfere with tumor growth. However, the clinical efficacy of anti-angiogenic agents remains uncertain and necessitates further refinement. The article also highlights the physiological role of VEGFs, emphasizing their involvement in endothelial cell functions, survival, and vascular permeability. The identification of five distinct VEGFs in humans (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PLGF) is discussed, along with the classification of VEGFRs as typical receptor tyrosine kinases with distinct signaling systems. The family includes VEGFR-1 and VEGFR-2, crucial in tumor biology and angiogenesis, and VEGFR-3, specifically involved in lymphangiogenesis. Overall, this review has provided a comprehensive overview of VEGF and VEGFR, detailing their roles in various diseases, including cancer. This is expected to further facilitate the utilization of VEGF and VEGFR as therapeutic targets.

Key words : Angiogenesis, lymphangiogenesis, metastasis, signaling, tumor

Insite into the function and signaling mechanisms of VEGF family

Vascular Endothelial Growth Factor (VEGF) represents a protein integral to various physiological processes, including endothelial cell migration, proliferation, survival, and vascular permeability. VEGFs assume a crucial role in both the establishment and preservation of blood and lymph vessels. Notably, during the genesis of newly formed blood vessels, certain VEGFs stimulate the proliferation of vascular endothelial cells, thereby facilitating the creation of novel vascular structures. In 1983, Senger et al. initially designated Vascular Endothelial Growth Factor (VEGF) as Vascular Permeability Factor (VFP) [58]. Subsequently, in 1989, Ferrara et al. isolated VEGF and provided conclusive evidence of its involvement in the angiogenic process, particularly in the formation of nascent blood vessels [33]. As of the present, the identification of five distinct VEGFs in humans stands documented: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and Placenta Growth Factor (PLGF).

VEGF-A stands as the inaugural member of its family to be identified and represents the most extensively studied variant. The human VEGF-A gene is situated on chromosome 6p12 and encompasses 8 exons. Notably, VEGF-A exhibits diversity through alternative splicing, resulting in eight distinct isoforms denoted as VEGF-A111, VEGF-A121, VEGF-A145, VEGF-A165, VEGF-A165b, VEGF-A189, VEGF-A206, and VEGF-AX, where the numerical value denotes the count of amino acid residues. While exons 1-5 and 8 are common to all isoforms, exons 6 and 7 contribute to the variability

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observed among them [54]. The VEGF homology domain (VHD), a conserved feature among all family members, is encoded by exons 3 and 4 [17]. Notably, exon 6 encodes the heparin-binding domain, and exons 7 encode an NRP1/ heparin-binding domain, resulting in the inability of VEGF-A111 and VEGF-A121 to bind heparin [54]. The heparin-binding domain of VEGF-A plays a pivotal role in augmenting downstream VEGF-mediated signaling and pulmonary proliferative effects [69]. During embryonic and pseudoglandular stages, VEGF-A expression is observed in both epithelial and mesenchymal compartments, with a subsequent shift towards increased restriction to the epithelium during the canalicular stage. This robust expression during embryogenesis underscores its critical involvement in proper blood vessel formation. Beyond embryonic stages, VEGF-A's significance persists into adulthood, where it assumes a crucial role in mediating physiological angiogenesis. Particularly evident during the female reproductive cycle in the uterus, ovary, and breast, as well as in processes such as wound healing, bone repair, and skeletal muscle response to exercise [38]. VEGF-A consistently functions as a potent angiogenic factor. While it maintains robust expression in adults, it does not induce widespread angiogenesis in resting tissue. The intricate interplay between pro-angiogenic and anti-angiogenic factors, coupled with cell-specific expression and diverse regulatory mechanisms, intricately shapes the role of VEGF. The generation of distinct VEGF isoforms through alternative splicing, characterized by tissue-specific patterns, contributes to the nuanced vascular development observed in different contexts. Additionally, extracellular modifications, including proteolytic processing, further modulate the bioavailability of VEGF. The actions of VEGF, mediated by receptors such as VEGFR1, VEGFR2, Nrp-1, and Nrp-2, are subject to complex interactions, indicating a finely tuned regulation of angiogenesis in diverse tissue environments [38]. The crystal structure of VEGF-A was elucidated at a resolution of 2.5 Å by Muller, Yves A., et al (Fig. 1A) [45].

VEGF-B serves exclusively as a ligand for Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1) and is situated on chromosome 11q13. This particular variant of VEGF shares approximately 43% amino acid sequence identity with VEGF and gives rise to two distinct isoforms, designated VEGF-B167 and VEGF-B186, comprising 167 and 186 residues, respectively. The genomic structure of VEGF-B encompasses 7 exons, with alternative splicing yielding the isoforms. Notably, the VEGF homology domain (VHD) of VEGF-B is encoded by exons 3 and 4 [17]. In the context of adult

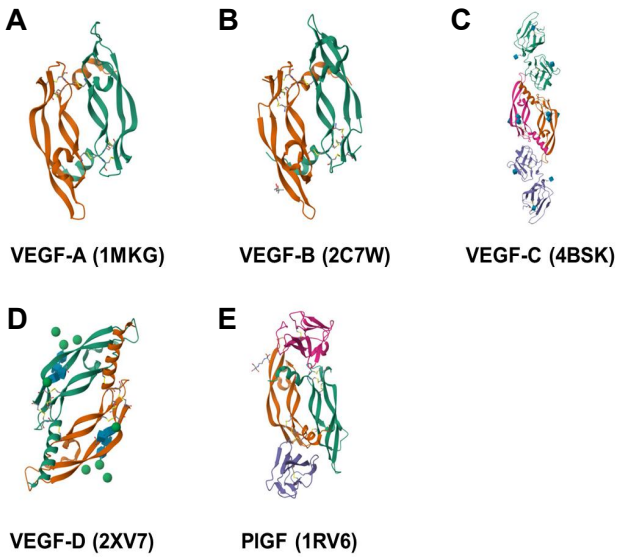

Fig. 1. VEGF structural data available in PDB. (A-E) Some of the major VEGF family structures uploaded to the Protein data bank (PDB) so far are shown in this diagram. The VEGF-A, VEGF-B and VEGF-D structures are shown in their homodimer form. The VEGF-C and PlGF structures are shown in their homodimer forms and as a complex with VEGFR-1 domain 1. The combination of numbers and letters after the protein name indicates the PDB ID.

mice, VEGF-B exhibits its highest expression levels within the heart, skeletal muscle, and diaphragm, while lower expression levels are discernible in various other tissues. The initiation of VEGF-B gene expression commences early in fetal development in mice, with embryonic expression notably observed in the heart, central nervous system (CNS), and brown adipose tissue situated within the interscapular and neck regions [46]. Comparative to VEGF-A, VEGF-B appears to hold lesser significance, as evidenced by the absence of major abnormalities in VEGF-B-deficient mice [2, 36]. The crystal structure of VEGF-B was determined by Iyer, Shalini et al. at a resolution of 2.48 Å (Fig. 1B) [20].

VEGF-C, a protein located on chromosome 4q34.1-q34.3, serves as a ligand for both Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) and VEGFR-3, actively participating in the formation of vascular and lymphatic systems, respectively. During embryonic development, the expression of VEGF-C mRNA has been identified in mesenchymal cells of post-implantation mouse embryos. Particularly noteworthy is its presence in regions where lymphatic vessels sprout from embryonic veins, such as the perimetanephric, axillary, and jugular regions [6]. High expression levels of VEGF-C have also been detected in the developing mesentery, which is

characterized by its abundance of lymphatic vessels [27]. Additionally, embryonic expression of VEGF-C has been observed in the heart, central nervous system (CNS), and kidney of mice [27]. These observations collectively imply a regulatory role for VEGF-C in the angiogenic processes of the lymphatic vasculature during embryonic development [28]. In normal human tissues, robust expression of VEGF-C is evident in colon and mammary epithelium, skeletal and cardiac muscle, thyroid, ovary, and prostate. Weaker expression is also discernible in hepatocytes near the terminal hepatic venules of the liver, vascular smooth muscle, and placenta. However, no consistent expression has been detected in the spleen or thymus [21]. The genomic architecture of VEGF-C comprises a total of seven exons, with the VEGF homology domain (VHD) encoded by exons 3 and 4 [17]. The mature form of VEGF-C necessitates processing that cleaves the propeptide at both the N- and C-termini. To date, the elucidation of the structure of the complex involving VEGF-C and its receptors has been achieved. Notably, the structures of the complexes with VEGFR-2 (PDB ID: 2X1W) and VEGFR-3 (PDB ID: 4BSK) have been determined, providing crucial insights into the molecular interactions underlying the signaling cascade mediated by VEGF-C in the context of vascular and lymphatic systems (Fig. 1C) [31, 32].

Filip Farnebo et al. conducted an examination of VEGF-D mRNA expression patterns in developing and adult mice, revealing predominant expression in lung tissue, notably upregulated prior to birth. The study reports that during embryonic stages, the expression of VEGF-D mRNA is low or absent in tissues beyond the lung. However, a notable increase in expression is observed in the embryonic lung preceding birth, suggesting a specific involvement of VEGF-D in the vascularization of lung tissue during late fetal development [13]. In adult human tissues, VEGF-D mRNA exhibits the highest abundance in the heart, lung, skeletal muscle, colon, and small intestine [1]. Functionally, VEGF-D binds to both VEGFR-2 and VEGFR-3, akin to VEGF-C. VEGF-D and VEGF-C share a significant degree of structural and sequence similarity, particularly evident in the VHD where the domains of the two proteins share 60% sequence identity [30]. Similar to VEGF-C, VEGF-D undergoes a series of processing steps involving truncation at both ends to attain full-length activation of the receptor. The genomic locus of VEGF-D is situated on chromosome Xp22.31 and comprises seven exons, with exons 3 and 4 encoding the VHD domains [17]. A comprehensive understanding of the molecular characteristics of VEGF-D is further enhanced by the crystal structure determination conducted by Leppänen, Veli-Matti et al., achieving a resolution of 2.9 Å (Fig. 1D) [30].

PlGF is the first growth factor to be identified as a VEGFR-1 specific ligand. Within the human VEGF family, VEGF-A is most closely related to PLGF [37]. As its nomenclature suggests, PlGF is prominently expressed in the placenta during embryonic development. Interestingly, the expression of PlGF is generally low or absent in most healthy adult tissues. However, its activity becomes notably upregulated in pathological conditions such as diabetes, atherosclerosis, arthritis, and cancer, rendering it an appealing target for therapeutic interventions [5]. PlGF primarily interacts with VEGFR-1, though it can also bind to VEGFR-2 in conjunction with VEGF-A when forming a heterodimer. The biological effects of PlGF encompass the promotion of endothelial cell growth, facilitation of placental vasculogenesis and development, as well as induction of uterine vasodilation [59]. The genomic locus of PlGF is situated on chromosome 14q24-q31 and consists of seven exons [17]. Notably, exons 3 and 4 encode the VEGF homology domain (VHD). Alternative splicing of PlGF gives rise to four distinct isoforms: PlGF-1, PlGF-2, PlGF-3, and PlGF-4. A structural perspective on the interaction between PlGF and VEGFR-1 is provided by the determination of the complex's crystal structure, achieved at a resolution of 2.45 Å (Fig. 1E) [7].

Structural and functional studies of vascular endothelial growth factor receptor family

VEGF receptors are classified as typical receptor tyrosine kinases (RTKs). Similar to other RTKs, VEGFRs are composed of an extracellular domain, a transmembrane segment, a juxtamembrane segment, and a protein kinase domain. The extracellular domain is constituted by seven immunoglobulin (Ig) domains. VEGFRs engage with their ligands to form homodimers or heterodimers, initiating the phosphorylation of tyrosine within the protein kinase domain. This phosphorylation event triggers downstream signaling cascades. Each receptor elicits a distinct signaling system, all of which contribute to the activation of proteases necessary for degrading the extracellular matrix－an essential step in angiogenesis [56]. The VEGFR family primarily includes VEGFR-1 and VEGFR-2, both of which play crucial roles in tumor biology and angiogenesis. Additionally, VEGFR-3 is a member of this family and is specifically involved in lymphangiogenesis, emphasizing its significance in regulating the formation of lymphatic vessels [23].

VEGFR-1 is a receptor with a molecular weight ranging from 180 to 185 kDa, capable of binding VEGF-A, VEGF-B, and PlGF as ligands. Notably, domain 2 serves as the primary binding site for these ligands. In contrast to VEGFR-2, VEGFR-1 exhibits lower efficiency in phosphorylation. This difference in phosphorylation efficiency is attributed to the presence of an asparagine residue in VEGFR-1. Previous studies have highlighted a distinctive region in VEGFR-1 with asparagine residues instead of aspartate when compared to other receptors. Mutation of this region in VEGFR-1, substituting Asn with Asp, resulted in increased autophosphorylation compared to the wild type. Conversely, in VEGFR-2, mutation of the corresponding region from Asp to Asn inhibited autophosphorylation compared to the wild type. This suggests that Asn may act as an inhibitor of autophosphorylation, contributing to the relatively low phosphorylation efficiency of VEGFR-1 [42]. Initial proposals by Park et al. suggested that VEGFR-1 may not primarily function as a receptor transmitting mitogenic signals but rather as a 'decoy' receptor. This decoy role involves negatively regulating the activity of VEGF on the vascular endothelium by preventing VEGF binding to VEGFR-2 [52]. Complex configurations where PlGF and VEGF-B are bound to domain 2 and VEGF-A is bound to domains 1-6 have been identified by structural investigations of VEGFR-1 (Fig. 2A) [7, 19, 40].

VEGFR-2 is a protein with a molecular weight ranging from 200 to 230 kDa, serving as a receptor for various ligands, including VEGF-A, VEGF-C, and VEGF-D. The primary binding sites for these ligands reside in domains 2 and 3 of VEGFR-2, while domain 4 is crucial for dimerization. Despite the extracellular domain of VEGFR-2 exhibiting a lower affinity for VEGF compared to VEGFR-1, it demonstrates higher phosphorylation of tyrosine residues [16, 42, 43]. The binding of VEGF to VEGFR-2 stimulates endothelial cell proliferation, enhances vascular permeability, and induces chemotaxis in endothelial cells. VEGFR-2 stands as one of the earliest markers of embryonic endothelial cells, playing vital roles in yolk sac blood island formation and angiogenesis during mouse embryonic development. In adults, it is a key player in angiogenesis and is implicated in various pathological processes, including diabetic retinopathy, rheumatoid arthritis, psoriasis, inflammatory diseases, as well as tumor growth and metastasis. VEGFR-2 has the capacity to form either homodimers or heterodimers with VEGFR-1. X-ray diffraction studies have revealed the three-dimensional structure of domain 7 of VEGFR-2 and the kinase domain of VEGFR-2. Additionally, the structures of the binding interactions between the ECD of VEGFR-2 and VEGF-A, as well as between domains 2-3 of VEGFR-2 and VEGF-C, have been elucidated (Fig. 2B) [3, 31, 41, 66].

VEGFR-3 is a protein with a molecular weight ranging from 195 to 200 kDa. It functions as a receptor tyrosine kinase, binding specifically to VEGF-C and VEGF-D. The primary binding sites for these ligands are located in domains 1-3 of VEGFR-3. VEGFR-3 plays a crucial role in cancer-induced angiogenesis and lymphangiogenesis. It is expressed in both blood vascular endothelial cells and lymphatic vessels. The signaling initiated by VEGFR-3 and its ligands is essential for embryonic angiogenesis and lymphangiogenesis, contributing significantly to blood vessel and lymphatic vessel development during embryogenesis [11, 12]. In later embryonic stages and in adults, VEGFR-3 expression is generally low or absent in most blood vessels but can be detected in specific structures such as high endothelial venules and fenestrated capillaries[53]. The expression of VEGFR-3 is upregulated in peritumoral or inflammatory areas, and it is often highly expressed in endothelial tip cells [10, 50, 61]. Notably, the structure of VEGFR-3 extracellular domains D4-5 (PDB ID: 4BSJ) and the structure of VEGFR-3 extracellular domains D1-2 in complex with VEGF-C (PDB ID: 4BSK) have been revealed through structural studies (Fig. 2C) [32].

The association of vascular endothelial growth factor (VEGF) in cancer

Breast cancer have been occurring frequently disease in women worldwide arises from metastasis [25]. It represented characteristic malignancy, and aggressive growth of breast cancer cells. Approximately, breast cancer was totaled for 31% of all new cancer cases and 15% of all cancer deaths among females by cancer statistics, 2023 [60]. Moreover, breast cancer is a fatal disease in male due to males cancerous breasts account for less than 1% of all breast cancers [15]. Breast cancer stage was determined by the size of the tumor and the condition of the lymph nodes that are responsible for a level of metastasis. Most researchers indicated that irregular angiogenesis is significantly involved in metastasis including breast cancer 4, 14]. Angiogenesis participates in critical factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and other growth factors [9]. Neuropilin-2 (NRP2) is a single-pass transmembrane receptor protein that is responsible for the migration and development of blood and lymphatic endothelial cells. NRPs are conserved in the vertebrates [67]. NRPs con-

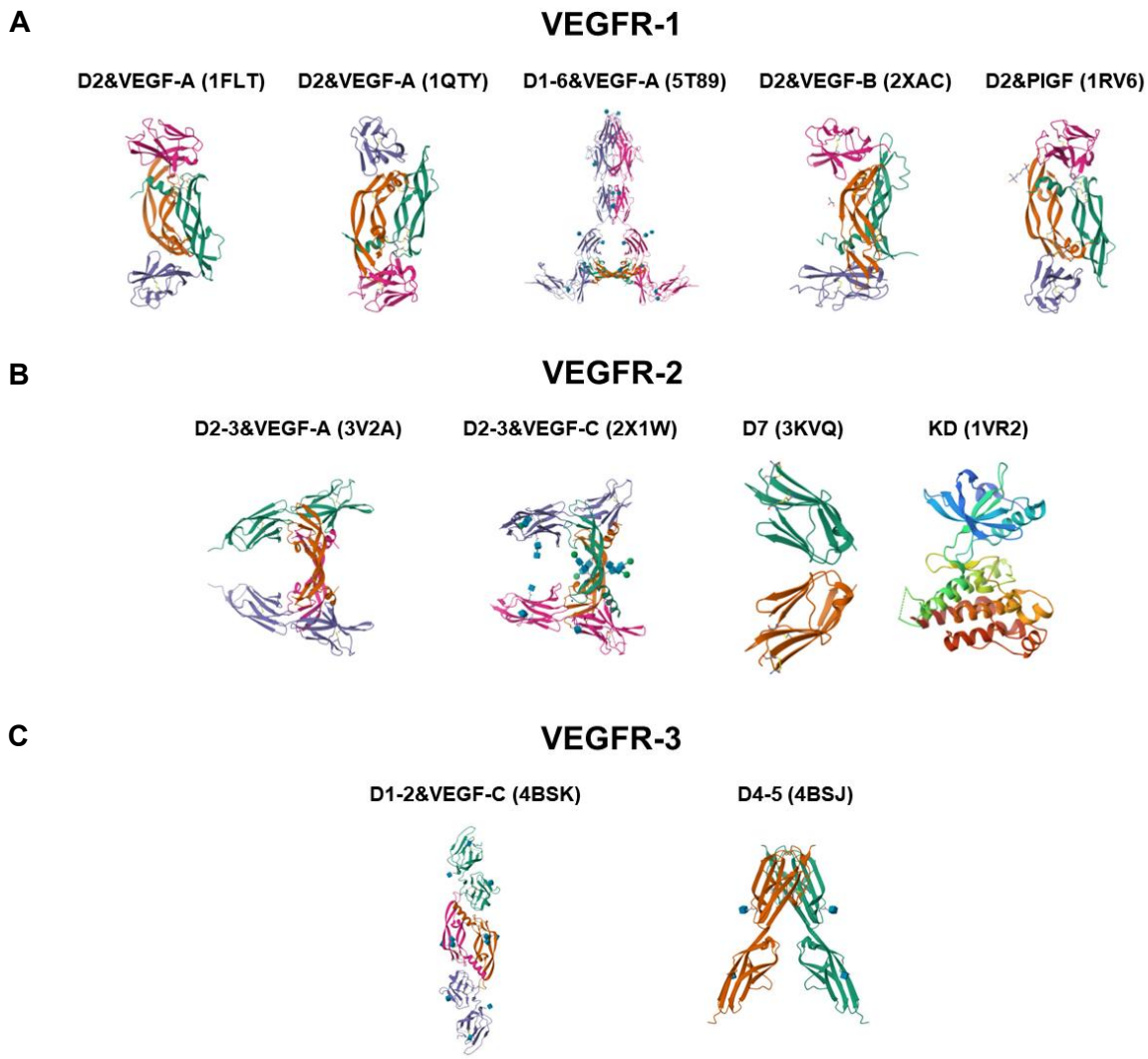

Fig. 2. VEGFR structural data available in PDB. (A-C) This diagram shows some of the major VEGFR family structures uploaded to the PDB so far. Most are shown in a complex consisting of their binding domain and ligand. However, some structures of the domains of VEGFR-2 and VEGFR-3 are shown in single molecule or homodimer form. For convenience, 'domain' is denoted by 'D' and 'kinase domain' is denoted by 'KD'. The combination of numbers and letters following the protein name indicates the PDB ID.

sist of an N-terminal extracellular domain, a transmembrane domain, and a cytoplasmic tail. The extracellular domain of NRPs binds VEGF ligands, resulting in the activation of VEGF downstream signaling [18]. Recent research represented that blocking of binding VEGFs between NRP2 inhibits metastasis of triple-negative breast cancers [65]. Expression of NRPs in cancerous cells is responsible for tumor progression, metastasis, lymphangiogenesis, and poor prognosis [18]. This research described that the generation of specific antibodies aNRP2 mAbs targets NRP2 as a therapeutic strategy in tumor cells [65]. Especially, TNBC is characterized by subpopulations of tumor cells, different differentiation degrees, and other properties on the microenvironment surrounding usual tumor cells. Recent evidence suggests that TNBC cells highly regulate of stemness pathway, which represents increased activity of pluripotency mediators and regulators of the cell cycle compared to non-TNBC cancer, contributing to stemness phenotype [29, 71]. This specific antibody aNRP2 mAb blocks of VEGF-C binding, which treating with aNRP2 mAb diminishes mammosphere formation of hMDA-MB-468 highly expressed NRP2, resulting in aNRP2 mAb inhibits self-renewal for cancer stem cells in TNBC [65]. Considerable evidence that the expression degree of VEGFC and VEGFD is represented by breast cancer patients, which induce either intratumoral or peritumoral lymphangiogenesis. Research about VEGF expression degree

in breast cancer patients suggests that tumor-derived VEGFC and VEGFD induce lymphatic invasion and metastatic spread [72]. Immunohistochemical analysis shows that these factors stained positive cytoplasmic in breast cancer cells. It is resulted in the expression levels of VEGFC and VEGFD being higher in primary breast carcinoma than the control fibroma tissues, in which VEGFC and VEGFD expression associated with peritumoral lymphatic vessel density (LVD) that is related to lymph node metastasis, lymphatic vessel invasion [72]. Also, a recent study shows that the level of VEGF was significantly increased at the serum level and that genetic polymorphism was confirmed in VEGF genes in breast cancer patients in breast cancers [44]. Most authors studied the connection between VEGF and breast cancer confirmed significant relevance [26].

Non-small-cell lung carcinoma (NSCLC) was reported the most prevalent of lung cancer, which accounts for ~80% of all lung cancer cases [57]. Lung cancer significantly increases the death rate in most common cancers, including the colorectum, pancreas, breast, prostate, and liver [8]. NSCLC has consisted of three subtypes, squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma [70]. The common type of NSCLC is adenocarcinoma, it possesses around 40% of lung cancer [49]. Lung cancer patients have been shown advanced and metastatic properties. Lung cancer metastasis is related to the condition of hypoxia, formation of lymphangiogenesis, and angiogenesis [51]. Even in present, the therapeutic of NSCLC remains challenging for most researchers. The canonical treatment strategy of NSCLC is combination chemotherapy. The shortcomings of chemotherapy have been shown excessive side effects and non-specificity [47]. Lymphangiogenesis occurs in lymphatic tubes around cancer by forming lymphatic endothelial cells [24]. VEGF significantly increases lymphatic endothelial cell-mediated lymphangiogenesis [48]. According to recent research, Adipokine angiopoietin-like protein 2 (ANGPTL2) secreted by adipocyte tissue is related to the production of VEGFA. The adipokines involve metastasis in diverse types of cancer and execute the growth factor of vascular endothelium [22]. Several studies suggested that the abnormal expression level of ANGPTL2 was enhanced in lung cancer cells [35, 68]. Moreover, the progression of lung cancer is related to ANGPTL2 levels. This research suggested that ANGPTL2 level is related to positively VEGF-A production. Through a xenograft mouse model analysis, ANGPTL2 overexpression upregulated VEGF expression in lung cancer tissues, which accelerates VEGF-A-dependent LEC lymphangiogenesis [34].

Prostate cancer was reported to second most frequent malignancy in different cancers worldwide. Prostate cancer has discovered a high amount of PD-L1 and is related to poor prognosis. Also, a prostate cancer patient demonstrated a high degree of mortality by existing resistance therapy [55, 64]. A recent study suggested that decreased PD-L1 expression leads to a result increased immune cell infiltration [63]. Also, Bevacizumab noted VEGF therapy diminished PD-L1 expression by blocking VEGF-NRP signaling, which increases infiltrating immune cells. Furthermore, VEGF/NRP signaling related to PD-L1 expression led to aggressive prostate cancer cells. These research authors described that blocking NRP has consequences of antitumor activity [63].

Conclusion

Vascular endothelial growth factors (VEGFs) play an important regulator in vascular development at embryonic and well-known specific endothelial cell mitogens. The VEGFs have an ambivalent capacity that generates physiological and pathological angiogenesis. The most interesting development discovered that VEGF signaling contributes to tumorigenesis, angiogenesis, and characteristic cancer stem cells (Fig. 3). Also, VEGF expression is related to signaling pathways that are associated with oncogenic formation, in which hypoxia-inducible factor (HIF)-mediated transcription induces VEGF expression in tumors. It may be considered important that hypoxia conditions induce signaling-related angiogenesis and lymphangiogenesis in tumors. Furthermore, several studies suggested that inducing epithelial-mesenchymal transition (EMT) might stimulation of VEGF in differentiated carcinoma cells [39, 62]. However, despite enormous research efforts, the therapeutic approaches toward angiogenesis and lymphangiogenesis remain a difficult problem to solve. Thus, these points could understand an association of VEGF signaling in tumorigenesis and angiogenesis. And the comprehension of VEGF signaling-related vascular development may lead to more superior therapeutic strategies.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest

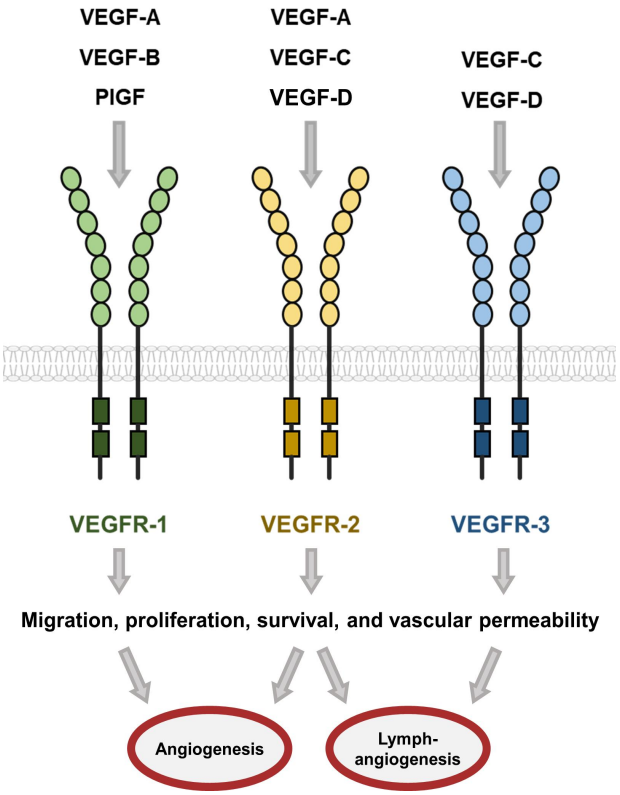

Fig. 3. Schematic representation of VEGFR and VEGF signaling. The depicted diagram illustrates the signaling pathways associated with VEGFs and VEGFRs. Specifically, VEGF-A, VEGF-B, and PlGF are implicated in the activation of VEGFR-1. On the other hand, VEGF-A, VEGF-C, and VEGF-D instigate the activation of VEGFR-2. VEGF-C and VEGF-D are instrumental in the induction of VEGFR-3 activation. Upon activation, these receptors promote various cellular responses, including endothelial cell migration, proliferation, survival, and enhancement of vascular permeability. VEGFR-1 and VEGFR-3 induce angiogenesis and lymphangiogenesis, respectively. Additionally, VEGFR-2 exhibits the capacity to promote both angiogenesis and lymphangiogenesis.

with the contents of this article.

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초록 : 암의 혈관내피 성장인자에 대한 분자적 통찰: 혈관신생과 전이

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이 리뷰 논문에서는 혈관 투과성, 내피세포 모집, 종양관련 혈관 및 림프관의 유지 등에서 핵심적인 과정인 angiogenesis와 lymphangiogenesis에 있어서 vascular endothelial growth factors (VEGF)가 이행하는 중요한 역할에 대해 재조명하고자 한다. VEGF는 tyrosine-kinase receptor인 VEGFR-1, VEGFR-2, VEGFR-3를 통해 그 역할을 이행하며, 이러한 VEGF-VEGFR 시스템은 암에서뿐만 아니라 비정상적인 혈관 및 림프관 형성으로 인해 야기되는 다른 질병들에 있어서도 핵심적인 요소로 각광받고 있다. 암의 측면에서 보았을 때, VEGF와 그 수용체는 종양관련 혈관 및 림프관을 형성하는 과정에서 필수적이라는 점에서 치료적인 타겟으로 이목을 끌고 있다. 때문에 암세포의 성장을 방해하기 위한 항VEGF 항체, 수용체 길항체, 수용체 기능 억제제 등과 같은 여러 가지 시도들이 있었지만, 아직까지 그 임상효과가 불확실하며 더 많은 연구들이 필요한 실정이다. 이 논문에서는 VEGF의 생리적 역할을 VEGF-A, VEGF-B, VEGF-C, VEGF-D, PLGF에 따라 나누어 설명하면서 VEGF/VEGFR 시스템의 중요성을 강조한다. VEGFR-1과 VEGFR-3은 각각 angiogenesis와 lymphangiogenesis에 핵심적인 인자이며, VEGFR-2의 경우 두 가지 모두를 일으킨다. 전반적으로 이 리뷰는 현재까지 밝혀진 암을 포함한 다양한 질병에서의 VEGF와 VEGFR의 역할에 대해 상세히 설명하고자 하였다. 이를 통해 치료 표적으로서 VEGF와 VEGFR의 활용이 더욱 촉진될 것으로 기대된다.