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VASCULAR ENDOTHELIAL GROWTH FACTOR THE LUNG: FRIEND OR FOE

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Summary

The discovery of vascular endothelial growth factor (VEGF) changed the field of angiogenesis. We have learned that VEGF has broader actions than merely a driver of tumor angiogenesis, particularly that VEGF controlled several fundamental functions and properties of endothelial cells and non-endothelial cells. The lung is one of the main organs where VEGF controls several critical physiological functions. These actions rely on tightly regulated temporal and concentration gradients of VEGF and VEGF receptor expression in the lung. Excessive or diminished VEGF have been linked to abnormal lung phenotypes and, in humans, linked to several diseases. The beneficial and detrimental actions of VEGF underscore that therapeutic targeting of VEGF in disease has to carefully consider the lung biology of VEGF.

INTRODUCTION

VEGF-A, also known as vascular permeability factor (VPF) [1], plays a fundamental role in physiological and pathophysiological forms of angiogenesis and regulation of endothelial cell differentiation. In contrast to fibroblast growth factor, which requires cell damage or basement membrane proteolysis for its release and binding to multiple cell targets, VEGF is actively secreted and has high specificity for endothelial cells. The lung contains the highest level of transcripts [2] amongst a wide range of organs that express VEGF. VEGF is necessary for the formation of vascular beds of several organs during embryo development, as demonstrated by the lethality of VEGF knockout mice and abnormal vasculogenesis of the heart and large vessels with loss of only a single copy of the VEGF gene [3]. VEGF contributes to endothelial cell nitric oxide (NO) production in coronary arteries and cultured umbilical vein endothelial cells [4]. The increase in endothelial cell nitric oxide synthase activity relies on activation of Src and MAP kinase [5] and the PI3K/Akt pathway [6]. VEGF has an anti-inflammatory action, decreasing leukocyte adhesion in an NO-dependent manner [7].

VEGF prevents death of endothelial cells, both in vitro and in animal models of oxygen-mediated retinopathy [8]. VEGF-dependent survival of endothelial cells relies on activation of PI3 kinase, Akt and Src [5]. The discovery of the parent VEGF-A molecule led to the subsequent identification of the subforms B through E. In this review, we will focus on VEGF-A (designated hereafter as VEGF).

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VEGF binds to 2 tyrosine-kinase receptors present on endothelial cells, Flt or VEGF receptor 1 (VEGFR-1) and KDR or VEGFR-2. Dominant negative mutant forms of VEGFR-2 can abrogate VEGF-induced signal transduction in vitro and reduce blood vessel proliferation in vivo models of brain tumors [9]. VEGFR-1 binds VEGF with approximately 10-fold higher affinity than KDR [10], undergoes receptor autophophorylation, and stimulates Ca^{++} influx. VEGF binding to VEGFR-2 results in cell ruffling, mitosis, chemotaxis, and actin rearrangement [11]. VEGFR-2 undergoes autophosphorylation more efficiently than receptor 1 upon ligand binding. Inhibition of VEGFR-2 blocks proliferation of cultured umbilical vein endothelial cells, in vivo angiogenesis, and vascular permeability [12]. VEGFR-2 is also stimulated in an autocrine manner by endothelial VEGF, which was recently found to be essential for endothelial survival [13]. VEGFR-1 plays a role in the organization of development of embryonic blood vessels [14] and in enhanced monocyte adhesion to endothelial cells [15]. There is the potential for cross interaction of both VEGF receptors as they are approximately 70% homologous and possibly heterodimerize in vivo. VEGFR-1 might act as a silent receptor for VEGF since it has a poor kinase activity. However, its downstream cell signaling remains poorly delineated [16]. It may also serve as a decoy for VEGF [17], as documented by the excess numbers of endothelial cells in amniotic membrane vessels of embryonic bodies lacking VEGFR-1 in the presence of intact VEGFR-2 [18]. On the other hand, VEGFR-1 enhances VEGF-induced VEGFR-2 signaling during abnormal angiogenesis, since it prevents endothelial cell apoptosis. As there are no conditional knockouts of VEGFR1 and 2, loss-of-function experiments have relied on neutralizing antibodies (such as DC101 against VEGFR-2 and MF1 against VEGFR-1), soluble chimeric molecules with the ligand binding domain of VEGFR-1 (VEGF traps), or chemical inhibition with small molecule inhibitors such as SU5416, which prevents VEGF-induced phosphorylation of VEGF-R2 [12] and, subsequently shown, to also block VEGF-R1 [19].

VEGF IS A FRIEND IN THE LUNG ROLE AS A CRITICAL LUNG ENDOTHELIAL CELL MORPHOGENETIC AND MAINTENANCE FACTOR

Lung morphogenesis requires the continuous physical and molecular interaction between the mesenchymal stroma and epithelial elements [20]. During airway growth, the lung progressively acquires a rich blood supply through the growth of endothelial cells and vascular cells in the pulmonary mesenchyme. This growth is paralleled by the expression of VEGF and its receptors [21], which play central morphogenetic functions throughout fetal lung maturation. Lung VEGF is synthesized by alveolar epithelial cells, epithelial bronchial cells, smooth muscle cells, and alveolar macrophages [22;23]. This topographical compartmentalization allows for the interaction of VEGF with components of the extracellular matrix, therefore generating concentration gradients that regulate physiological functions of VEGF in the lung [24]. Overexpression of lung VEGF during development results in a markedly dysmorphic lung structure [25]. Conversely, neutralization of VEGF throughout fetal development with Fc-VEGFR1 extracellular domain promotes an overtly simplified lung in newborn mice [26].

The critical role of VEGF signaling in lung structure maintenance is supported by the findings that SU5416 impairs lung development in neonatal rats [27], decreased levels of VEGF may contribute to bronchopulmonary dysplasia [28], and mice with deleted hypoxia inducible factor-2 or treated with anti-VEGFR-2 show respiratory distress and lung prematurity. Administration of VEGF to these mice partly rescues lung immaturity and respiratory distress syndrome [29].

VEGF also plays an important role in postnatal lung growth, since blockade of VEGFR-1 and VEGFR-2 with DC101 and MF1, respectively, arrests lung growth and leads to an emphysematous mouse phenotype [30]. Inhibition of VEGF results in regression of tracheal

capillaries and endothelial cell death in adult mouse lungs, while most vessels become resistant to VEGF withdrawal after embryonic development [31].

ROLE IN EMPHYSEMA

VEGFR blockade with SU5416 results in endothelial cell apoptosis and, consistent with the importance of septal endothelial cells in alveolar integrity, SU5416 causes apoptosis-dependent emphysema in rats [32]. In agreement with our findings with VEGFR- blockade by SU5416, transgenic mice in which lung VEGF was deleted by means of Cre-recombination of two Lox-P recognition sites flanking the VEGF gene show emphysema after 4 weeks of intratracheal instillation of adenoassociated virus-CRE [33]. The association between advanced human emphysema and decreased lung or plasma levels of VEGF provided evidence in support of an alveolar structural maintenance role for VEGF in humans [34]. An imbalance of VEGFR1 vs. R2 activation may also allow for apoptotic alveolar enlargement as shown in mice overexpression of placenta growth factor (Plgf) [35].

In addition to its well-known functions as a trophic and growth factor, VEGF may play novel biological roles in the maintenance of lung homeostasis. Lung cellular homeostasis requires the prompt removal of apoptotic corpses to keep the overall number of cells constant. The efficient removal of damaged cells decreases the risk of necrosis, inflammation, or neoplasia and, via binding of apoptotic cells to the phosphatidylserine receptor, a host of immunosuppressive cytokines (TGF-β, PGE2, PGI2, IL10) are released to suppress inflammation and reduce the risk of autoimmune diseases [36]. VEGF may contribute to efferocytosis [37], which in turn leads to further VEGF production, therefore favoring cell repair in face of tissue destruction [38].

ROLE IN PULMONARY HYPERTENSION

Like its participation in acute lung injury (ALI), VEGF may have a dual role in pulmonary hypertension. A recent review addressed the pathology and pathobiology of pulmonary hypertension [39], which provides a useful framework for the present discussion. Endothelial cell injury underlies the development of a severe form of experimental pulmonary hypertension, such as that caused by the alkaloid monocrotaline (MCT). MCT-pulmonary hypertension is associated with decreased VEGF expression [40] and VEFG overexpression protects against MCT-induced pulmonary hypertension [41]. Highlighting the critical prosurvival role of VEGF in lung endothelial cells, a second model of severe pulmonary hypertension was developed based on early endothelial cell apoptosis due to the combination of VEGF receptor blockade with SU5416 and chronic hypoxia [42]. These results are concordant with the observation that VEGF inhibition with haptamers causes neonatal pulmonary hypertension in an ovine model [43]. Chronic hypoxia is a common inducer of experimental pulmonary hypertension; however, hypoxic pulmonary hypertension is relatively mild and reversible upon re-exposure to normal oxygen levels. Despite the evidence of increased expression of VEGF in hypoxic lungs [23], overexpression of VEGF protects rats against hypoxic pulmonary hypertension [44]. However, once intravascular endothelial cells accumulated in the pulmonary circulation of rats with pulmonary hypertension caused by SU5416+chronic hypoxia, administration of VEGF does not afford protection against severe pulmonary hypertension. In fact, it causes a small increase in pulmonary artery pressures [45]. These findings suggest that VEGF may indeed have a dual role in pulmonary hypertension, with early protection followed by a potentially pathogenic induction of pulmonary vascular remodeling.

VEGF IS A LUNG FOE ROLE IN ACUTE LUNG INJURY (ALI)

ALI consists of an acute clinical syndrome caused by alveolar leakage of plasma proteins, alveolar epithelial cell necrosis, scattered infiltration by neutrophils, and characteristic hyaline membranes, which impair oxygen diffusion, leading to hypoxemia. This syndrome can be caused by a variety of fulminant events, including sepsis, extensive trauma, oxygen or drug toxicity, viral infections, blood transfusions, and pancreatitis, among others. Its idiopathic form is known as acute interstitial pneumonia. The pathogenetic hallmark event in ALI is a marked increase in lung capillary endothelial cell permeability and alveolar cell injury. VEGF was originally discovered as a vascular permeability factor that accounted for the increased permeability of cancers seeded in the peritoneal cavity [1]. This permeability enhancing property of VEGF occurs when the growth factor is produced in high levels and targets a suitable vasculature as demonstrated by VEGF overexpression in the rabbit ear [46]. An excellent review on the role of VEGF in ALI correctly placed the VEGF-enhanced permeability in the context of angiopoetins 1 and 2, proteins that either decrease or enhance vascular permeability, respectively [22]. VEGF, when bound to extracellular matrix, can be released by activated extracellular matrix proteases, including plasmin and metalloproteases [24], which are also involved in the pathogenesis of ALI. Moreover, inflammatory cells (neutrophils and macrophages) and parenchymal cells activated by cytokines such as IL-1, IL-6, and TGF-β cause enhanced expression of VEGF. Heightened VEGF expression allied to an increased expression of angiopoietin-2 may account for the link between VEGF and increased capillary permeability in ALI. Recent evidence supports a central role of enhanced angiopoietin-2 in alveolar oxygen injury in the neonatal lung and in ALI [47]. However, it is recognized that VEGF may play an important role in septal cell recovery from ALI since established alveolar injury is associated with decreased expression of VEGF [48]. In summary, VEGF may play a pathogenetic role in ALI when increased, leading to enhanced alveolar and capillary permeability in active sites of injury and, when decreased, precluding proper and immediate cell repair.

ROLE IN ASTHMA

We have recently summarized the aggregate of data that support a potential pathogenetic role of VEGF in airway remodeling and inflammation in asthma [34]. Increased VEGF, VEGFR, and angiopoietin-1 level are observed in lung biopsies of asthmatic patients [49] and VEGF levels correlate with airway vascularity [50]. The proinflammatory actions of VEGF in eosinophils might account for part of their migration in the asthmatic lung. Furthermore, VEGF may promote hypervascularity and edema in the asthmatic bronchial mucosa [51] and enhanced dendritic cell recruitment and maturation, therefore driving TH2 inflammation in experimental models. In murine asthma models [52], part of these VEGF actions seem to be mediated by the VEGF-NO pathway [53]. Glucocorticoids, which are used to treat asthma, suppress VEGF transcription in vitro [54] and reduce VEGF levels in proportion to decreased vascularity [55], further suggesting a role of VEGF in pathophysiology of the disease.

ROLE IN PULMONARY HYPERTENSION

Although the aforementioned experimental data support a beneficial role of VEGF in pulmonary hypertension, there is evidence of increased expression of VEGF in remodeled hypertensive arteries (summarized in [34]). The coordinated expression of VEGF and VEGFR-2 in plexiform lesions in idiopathic pulmonary hypertension [56] further support the concept that these angioproliferative lesions have features in common to neoplastic processes [57] and with angiogenic cancers such as Kaposi's sarcoma [58]. Of note, experimental studies of pulmonary vascular remodeling and pulmonary hypertension caused by cigarette smoke inhalation also demonstrate that VEGF is upregulated early in the pulmonary vascular

pathology and may potentiate pulmonary vascular remodeling in combination with upregulated endothelin [59]. However, there is evidence for a friendly role of VEGF in pulmonary vascular disease as discussed previously.

CONCLUSION

The lung's requirement on VEGF is more complex than that documented with most organs. For the past 13 years, we have learned that VEGF is both a friend and a foe. Too much or too little of VEGF is catastrophic to the lung-an observation that is shared with manipulations of other highly important molecules. However, the final verdict for VEGF still awaits clear therapeutic interventions, which will fulfill the central elements of Koch's postulate on the role of VEGF in lung diseases. At the present time, the evidence supports a beneficial role of VEGF, as its loss may underlie lung immaturity, pulmonary hypertension, emphysema, and the repair stage of ALI. Furthermore, the broader actions of VEGF in the lung warrant that the pathobiological effects of VEGF supplementation or blockade be carefully considered in therapeutic trials.

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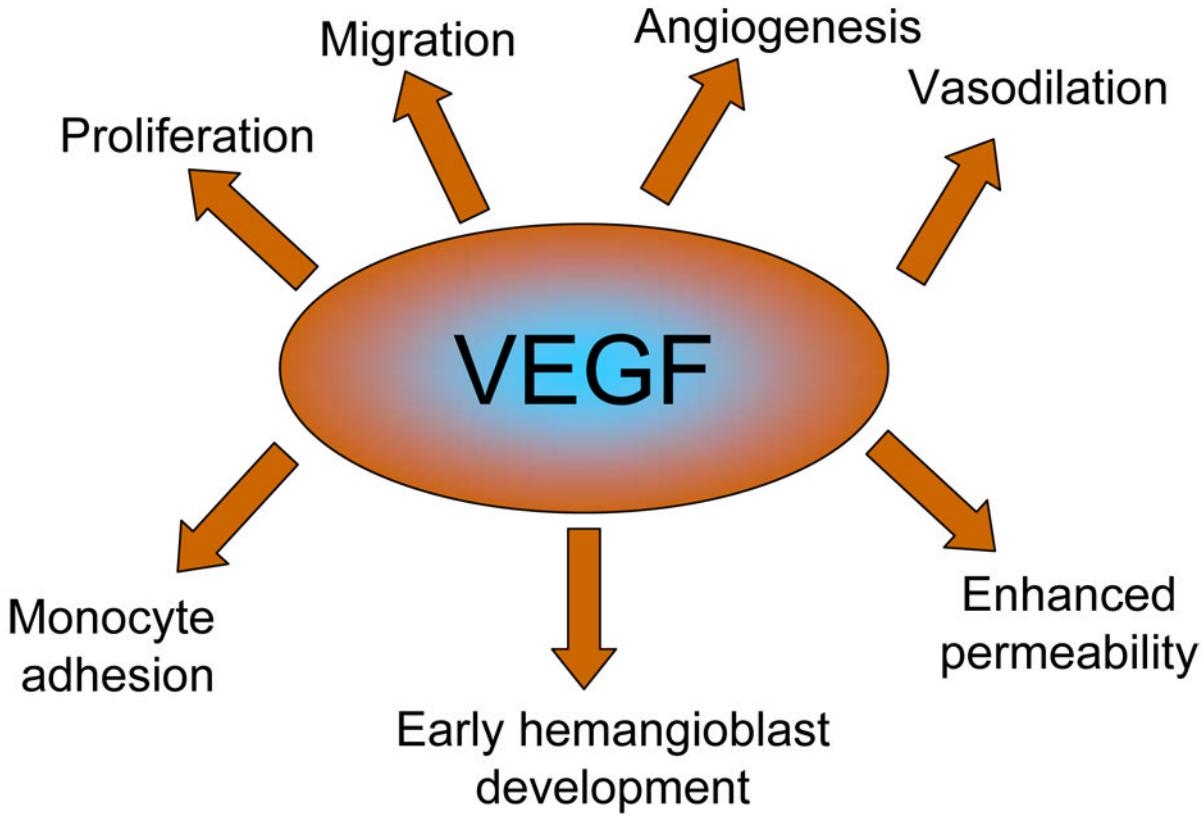

Figure 1.
Biological actions of VEGF.

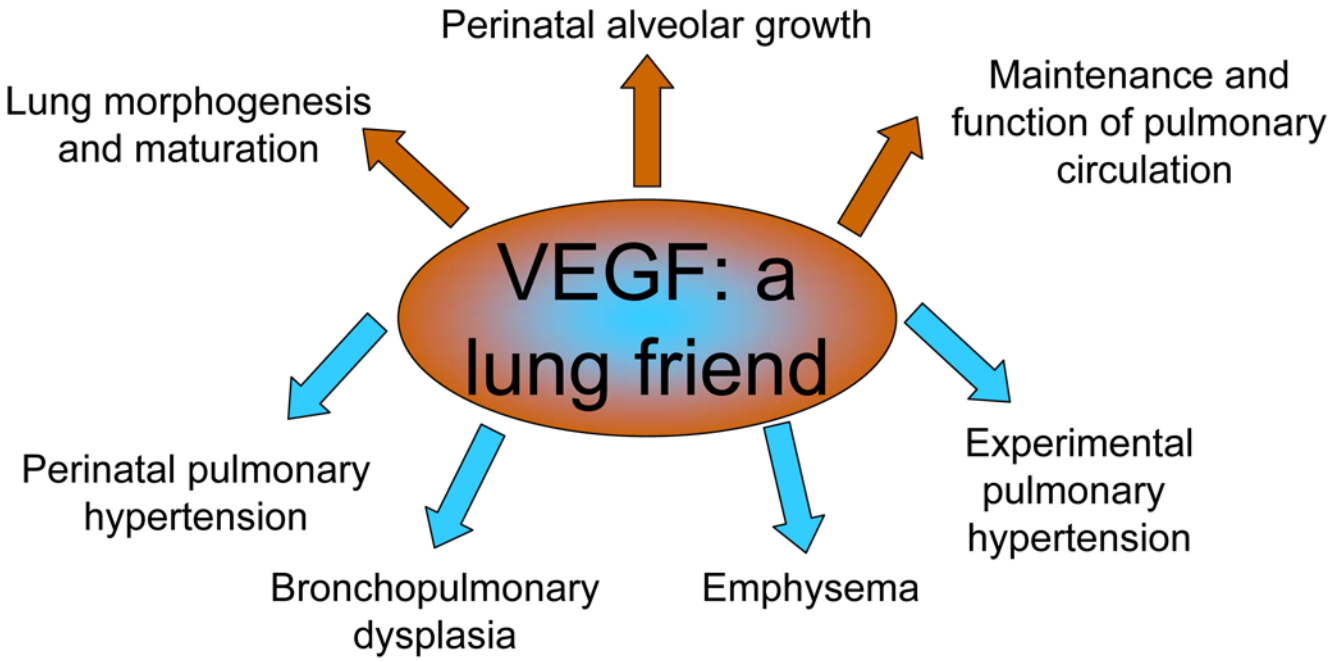

Figure 2.
VEGF is a friend. Shown are the biological functions of VEGF form the basis of its role in the diseases, given the impact of decreased VEGF levels or protective effects of VEGF overexpression.

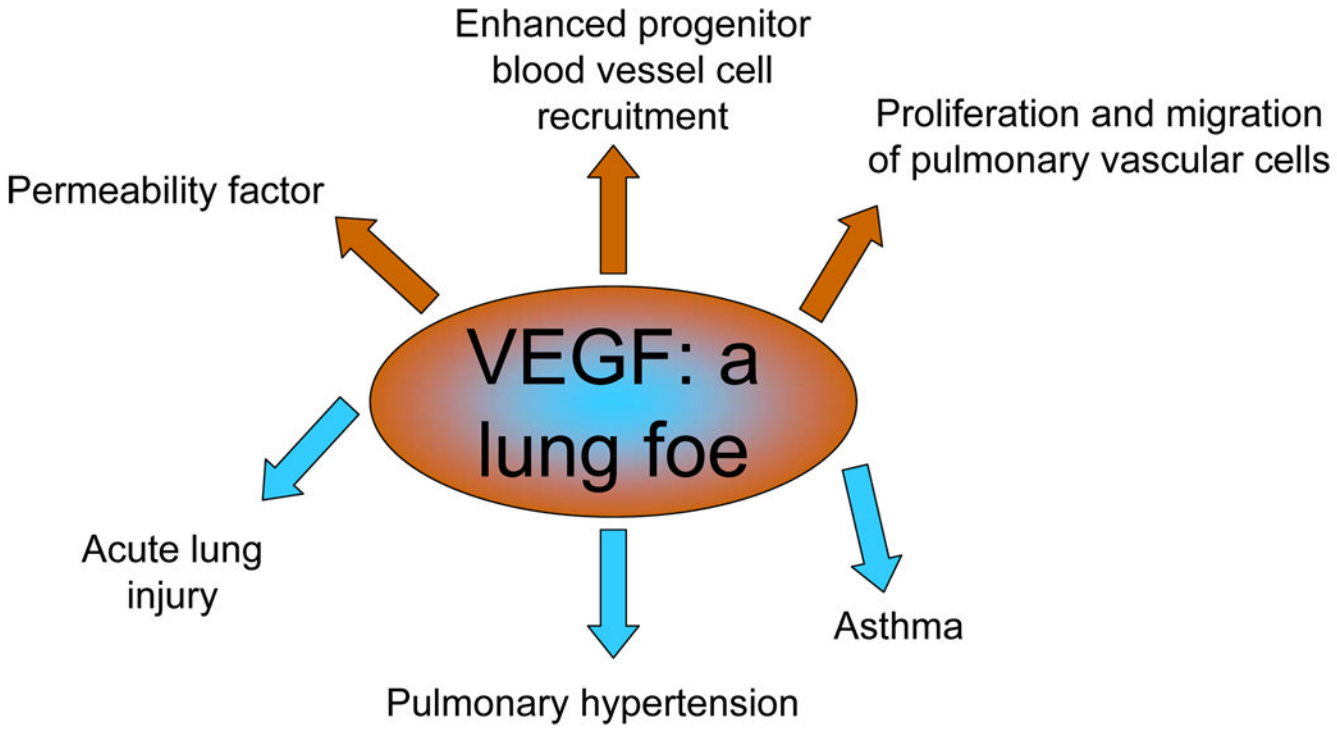

Figure 3.
VEGF is a foe. Shown are the biological properties of VEGF that underlie its detrimental actions in the context of the listed diseases.