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VEGF$_{165}$a and VEGF$_{165}$b: Molecular effects of opposing isoforms in angiogenesis

VEGF$_{165}$a ve VEGF$_{165}$b: Anjiyogenezde zıt izoformların moleküler etkileri

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ABSTRACT

This review aims to comparatively examine the structural differences, receptor interactions, downstream signaling effects, and pathophysiological roles of the two main isoforms of the *VEGF*A gene, VEGF$_{165}$a and VEGF$_{165}$b, which arise from alternative splicing of exon 8. Recent experimental and clinical studies conducted between 2020 and 2025 in both human and animal models were systematically reviewed to evaluate the biological functions, receptor-binding properties, and pro- and anti-angiogenic effects of VEGF$_{165}$b. VEGF$_{165}$a promotes endothelial cell proliferation, migration, and vascular permeability by activating VEGFR-2 through PI3K/Akt and MAPK/ERK pathways. In contrast, VEGF$_{165}$b binds to the same receptors but induces weak signaling and competitively inhibits the effects of VEGF$_{165}$a. While VEGF$_{165}$b is predominantly expressed in healthy tissues, a shift in favor of VEGF$_{165}$a is observed in pathological conditions such as cancer, proliferative diabetic retinopathy, and age-related macular degeneration. Conversely, excessive VEGF$_{165}$b expression is associated with impaired angiogenesis in diseases such as peripheral artery disease, systemic sclerosis, and preeclampsia. Disruption in the VEGF$_{165}$ isoform balance underlies many diseases characterized by either excessive or insufficient angiogenesis. In this context, isoform-specific therapeutic strategies—such as the modulation of alternative exon usage via splice-switching oligonucleotides—may allow the development of more precise and targeted vascular therapies in the future. The VEGF$_{165}$a/VEGF$_{165}$b ratio also holds promise as a biomarker for guiding personalized angiogenesis-modulating treatments.

Keywords: *Angiogenesis, Alternative splicing, Isoforms, Vascular endothelial growth factor A, VEGFR-2, Signal transduction*

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ÖZ

Bu derleme, *VEGFA* geninin alternatif ekzon 8 bölgesinden türeyen iki ana izoformu olan VEGF$_{165}$a ve VEGF$_{165}$b'nin yapısal farklılıklarını, reseptör etkileşimlerini, sinyal yolakları üzerindeki etkilerini ve bu izoformların hastalıklardaki patofizyolojik rollerini karşılaştırmalı olarak incelemeyi amaçlamaktadır. İnsan ve hayvan modellerinde yapılan deneysel ve klinik çalışmalara ait 2020–2025 yılları arasındaki güncel literatür taranmış, VEGF$_{165}$b'nin biyolojik işlevleri, reseptör bağlanma özellikleri, pro- ve anti-anjiyogenik etkileri ile ilgili bulgular sistematik olarak derlenmiştir. VEGF$_{165}$a, VEGFR-2 üzerinden PI3K/Akt ve MAPK/ERK yolaklarını aktive ederek endotel hücre proliferasyonu, göçü ve damar geçirgenliğini artırırken; VEGF$_{165}$b bu reseptörlere bağlanmasına rağmen sinyallemeyi zayıf biçimde tetiklemekte ve VEGF$_{165}$a'nın etkilerini kompetitif olarak baskılamaktadır. VEGF$_{165}$b ekspresyonu sağlıklı dokularda baskın iken, kanser, proliferatif diyabetik retinopati ve yaşa bağlı makula dejenerasyonu gibi hastalıklarda VEGF$_{165}$a lehine bir dengesizlik gözlenmektedir. Öte yandan, periferik arter hastalığı, sistemik skleroz ve preeklampsi gibi durumlarda VEGF$_{165}$b'nin aşırı ekspresyonu yetersiz anjiyogenez ile ilişkilidir. VEGF$_{165}$ izoform dengesindeki bozulmalar, anjiyogenez fazlalığı ya da yetersizliği ile seyreden birçok hastalığın temelinde yer almaktadır. Bu bağlamda, izoformlara özgü tedavi yaklaşımları (örneğin splice-switching oligonükleotidlerle alternatif ekson kullanımının yönlendirilmesi) gelecekte daha hassas ve hedefe yönelik damar tedavileri geliştirilmesine olanak sağlayabilir. VEGF$_{165}$a/VEGF$_{165}$b oranının biyobelirteç olarak kullanımı, kişiye özel anjiyogenez modülasyonuna yönelik önemli bir potansiyel taşımaktadır.

Anahtar Kelimeler: *Anjiyogenez, Alternatif dizi birleştirme, İzoformlar, Vasküler endotelyal büyüme faktörü A, VEGFR-2, Sinyal iletimi*

INTRODUCTION

Vascular endothelial growth factor A (*VEGFA*) is one of the most important molecules that regulate blood vessel formation and maintain vascular integrity (1). Through alternative mRNA splicing, *VEGFA* produces several isoforms, among which $VEGF_{165}$ is the most common and biologically active. $VEGF_{165}$ is a heparin-binding glycoprotein that can exist in both soluble and extracellular matrix-bound forms. This allows it to deliver spatially controlled signals to surrounding cells (2). By binding to its main endothelial receptors— Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1; Flt-1) and Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2; KDR/Flk-1)—$VEGF_{165}$ activates intracellular signaling pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (3). These pathways support endothelial cell survival, proliferation, migration, and the formation of new blood vessels (4).

$VEGF_{165}$ plays a key role in several physiological processes including embryonic vascular development, postnatal angiogenesis, wound healing, and neurovascular protection. However, when $VEGF_{165}$ is overexpressed in an uncontrolled manner, it can lead to pathological angiogenesis *in diseases such as cancer, diabetic retinopathy (DR), and* age-related macular degeneration (AMD). Tumors rely on $VEGF_{165}$-induced angiogenesis to grow and spread, while in the eye, excessive $VEGF_{165}$ increases vascular permeability, causing edema and vision loss (5, 6).

Importantly, $VEGF_{165}$ is not a single molecule—it includes two splice variants with different effects: the pro-angiogenic $VEGF_{165}$a and the anti-angiogenic $VEGF_{165}$b. These variants differ due to an alternative splicing event in exon 8 of the *VEGFA* gene, which changes the last six amino acids of the protein (7). This small change significantly alters how each isoform interacts with receptors and affects signaling. $VEGF_{165}$b was first described in 2002 and was initially classified as a natural inhibitor of angiogenesis. However, recent studies have shown that $VEGF_{165}$b may act as a weak agonist in some situations. Therefore, its effects can vary depending on the biological context (8).

This review compares the structural differences, receptor interactions, and cellular effects of $VEGF_{165}$a and $VEGF_{165}$b. It also discusses how the balance between these isoforms influences diseases with excessive or insufficient angiogenesis, such as cancer, retinal disorders, ischemia, fibrosis, and preeclampsia. The literature was reviewed to evaluate the varying roles of $VEGF_{165}$b, and recent therapeutic approaches targeting isoform-specific expression or function are discussed. Understanding the regulatory balance between $VEGF_{165}$a and $VEGF_{165}$b could help develop more targeted and safer angiogenesis-based therapies.

$VEGF_{165}$ isoforms

The human *VEGFA* gene contains eight exons. Alternative splicing at exon 8 produces two functionally distinct $VEGF_{165}$ isoforms. When the proximal splice site of exon 8 (exon 8a) is used, it generates the pro-angiogenic isoform $VEGF_{165}$a. In contrast, use of the distal splice site (exon 8b) results in $VEGF_{165}$b, which has anti-angiogenic properties. Exons 1 through 5 are common to all isoforms and encode the core domains of *VEGFA*, while exon 8a or 8b determines the unique C-terminal sequence. $VEGF_{165}$a and $VEGF_{165}$b are identical except for their final six amino acids: $VEGF_{165}$a ends in CDKPRR, a strongly basic sequence, while $VEGF_{165}$b ends in SLTRKD, which is less positively charged. Although this difference is small, it has a major impact on receptor binding and signaling (8, 9).

Both $VEGF_{165}$a and $VEGF_{165}$b bind to VEGF receptors 1 and 2 with similar affinity. However, only $VEGF_{165}$a efficiently activates these receptors. It induces VEGFR-2 dimerization and phosphorylation, triggering downstream signaling pathways such as PI3K/Akt and MAPK/ERK, which promote endothelial cell proliferation and migration. $VEGF_{165}$b, on the other hand, binds to VEGFR-2 but does not activate it fully. Instead, it holds the receptor in an inactive state and prevents $VEGF_{165}$a from binding, acting as a competitive inhibitor. In cell studies, $VEGF_{165}$b leads to little or no activation of Akt or ERK, in sharp contrast to the strong signals induced by $VEGF_{165}$a (10). One key reason for this difference is co-receptor interaction. $VEGF_{165}$a contains a heparin-binding domain at its C-terminus that allows it to bind to neuropilin-1 (NRP1) and heparan sulfate proteoglycans. NRP1 enhances VEGFR-2 signaling. The unique CDKPRR tail of $VEGF_{165}$a is essential for this binding. Since $VEGF_{165}$b lacks this sequence, it cannot recruit NRP1 effectively. As a result, $VEGF_{165}$b–VEGFR-2 complexes are formed without sufficient co-receptor support, leading to weak or incomplete signaling. Additionally, the more acidic tail of $VEGF_{165}$b may reduce its ability to bind to the extracellular matrix, limiting receptor clustering and signaling efficiency (11).

$VEGF_{165}$b may also affect VEGFR-1 differently than $VEGF_{165}$a. VEGFR-1 has a higher affinity for VEGF but a lower signaling capacity and is often considered a decoy receptor. Studies suggest that in ischemic tissues, $VEGF_{165}$b can bind to VEGFR-1 and block its pro-angiogenic signaling. For example, in a diabetic mouse model of peripheral artery disease (PAD), ischemia led to increased $VEGF_{165}$b expression, which in turn inhibited VEGFR-1–signal transducer and activator of transcription 3 (STAT3) signaling. Neutralizing $VEGF_{165}$b restored VEGFR-1 phosphorylation and improved angiogenesis, without significantly affecting VEGFR-2. These findings suggest $VEGF_{165}$b may act as a fine-tuner of VEGFR-1 activity in specific physiological conditions (12).

$VEGF_{165}$a is strongly pro-angiogenic. It stimulates all key steps of angiogenesis: endothelial proliferation and migration, matrix remodeling, nitric oxide (NO) production leading to vasodilation, and increased vascular permeability. By loosening endothelial junctions, it also enhances microvascular permeability (13).

In contrast, $VEGF_{165}$b does not promote new blood vessel formation. Instead, it antagonizes $VEGF_{165}$a's effects and can suppress angiogenesis. In several animal models, externally applied $VEGF_{165}$b has reduced pathological angiogenesis. However, $VEGF_{165}$b is not completely inactive. It may deliver low-level survival signals to endothelial cells

without promoting their proliferation or migration. For example, another anti-angiogenic isoform, VEGF121b, was shown to protect endothelial cells from apoptosis under stress despite inhibiting their movement. This suggests that $VEGF_{165}b$ and related isoforms may support vessel stability without triggering angiogenic growth (8).

The balance between $VEGF_{165}a$ and $VEGF_{165}b$ varies depending on tissue state. In healthy adult tissues, $VEGF_{165}b$ and other anti-angiogenic isoforms (collectively called VEGFxxxb) are more highly expressed than pro-angiogenic isoforms. This helps maintain vascular stability. During active angiogenesis—for instance, in the placenta during pregnancy or in wounded tissue—the balance shifts toward $VEGF_{165}a$. Hypoxia increases total *VEGFA* expression through hypoxia-inducible factor-1 alpha (HIF-1α) and favors production of $VEGF_{165}a$. Growth factors and hormones also push splicing toward the pro-angiogenic form. When angiogenesis is no longer needed, $VEGF_{165}b$ levels rise again to restore balance. For example, after wound healing or at the end of the menstrual cycle, $VEGF_{165}b$ may help return the tissue to a quiescent state. This dynamic regulation allows *VEGFA* activity to be finely tuned after transcription (14) (Table 1).

$VEGF_{165}a$ exerts its pro-angiogenic effects by binding to endothelial receptors and activating key intracellular kinase pathways. VEGFR-2 is the principal mediator of these signals. Upon $VEGF_{165}a$-induced dimerization of VEGFR-2 on the cell surface, specific intracellular tyrosine residues undergo autophosphorylation. This initiates several downstream cascades: the Ras–MAPK/ERK pathway (which drives endothelial proliferation), the PI3K–Akt pathway (promoting cell survival and NO production), and focal adhesion kinase pathways (facilitating cell migration and vascular permeability). A key outcome of this signaling is the upregulation of endothelial nitric oxide synthase (eNOS), resulting in local vasodilation and increased microvascular permeability—hallmarks of VEGF activity. Additionally, $VEGF_{165}a$ promotes extracellular matrix remodeling via protease induction and recruits bone marrow-derived endothelial progenitor cells to sites of neovascularization (15).

Although VEGFR-1 also binds $VEGF_{165}a$ with high affinity, its signaling capacity is weaker. In various contexts, VEGFR-1 can function as a decoy receptor, sequestering $VEGF_{165}a$, or as an active signaling receptor—particularly in monocytes, macrophages, and pathological angiogenesis—through pathways such as STAT3. Furthermore, $VEGF_{165}a$'s C-terminal heparin-binding domain facilitates interaction with NRP1, a co-receptor that enhances VEGFR-2 signaling. This interaction promotes high-density VEGF presentation at the endothelial surface, amplifying signal transduction (15, 16).

In contrast, $VEGF_{165}b$ lacks the C-terminal motif required for NRP1 binding and fails to induce significant phosphorylation of VEGFR-2. It acts as a partial agonist or a competitive antagonist by binding VEGFR-2 and inducing receptor dimerization without triggering a full conformational activation. Consequently, $VEGF_{165}b$ produces minimal downstream activation of MAPK or Akt signaling. Notably, recent studies suggest $VEGF_{165}b$ may preferentially bind to VEGFR-1 and suppress its activity. In a mouse model of PAD, $VEGF_{165}b$ acted as an endogenous VEGFR-1 inhibitor. Neutralizing $VEGF_{165}b$ restored VEGFR-1–STAT3 signaling and improved angiogenesis without affecting VEGFR-2 activity. This finding challenges the prior assumption that $VEGF_{165}b$ solely antagonizes VEGFR-2, highlighting its role in fine-tuning the balance between VEGFR-1 and VEGFR-2 signaling (12).

Table 1. Comparison of $VEGF_{165}a$ and $VEGF_{165}b$ Isoforms

Feature	$VEGF_{165}a$ (Pro-angiogenic)	$VEGF_{165}b$ (Anti-angiogenic)
Exon 8 Splice Site	Proximal (exon 8a)	Distal (exon 8b)
C-terminal Sequence	CDKPRR (basic, + charge)	SLTRKD (less basic, more acidic)
Amino Acid Difference	Final 6 amino acids: CDKPRR	Final 6 amino acids: SLTRKD
Receptor Binding	Binds VEGFR-1 and VEGFR-2	Binds VEGFR-1 and VEGFR-2
Receptor Activation	Efficiently activates VEGFR-2	Weak or no activation of VEGFR-2
Downstream Signaling	Strong PI3K/Akt, MAPK/ERK activation	Little/no PI3K/Akt, MAPK/ERK signal
Co-receptor Interaction	Binds neuropilin-1 (NRP1) and HSPGs	Poor NRP1 binding
Matrix Binding	Strong (via basic tail)	Weaker (more acidic tail)
Effect on VEGFR-1	May activate or act as decoy	Can block VEGFR-1 signaling
Angiogenic Activity	Potent stimulator of angiogenesis	Inhibits angiogenesis
Cellular Effects	Promotes proliferation, migration, NO production, permeability	May provide survival signals, does not promote proliferation or migration
Expression in Tissues	Upregulated in active angiogenesis (e.g., placenta, wounds, tumors)	Dominant in healthy adult tissues, upregulated post-healing
Physiological Role	Drives vessel growth and remodeling	Maintains vascular quiescence, opposes excess angiogenesis
Response to Hypoxia/GFs	Upregulated by HIF-1α, growth factors, hormones	Not upregulated by hypoxia; increased as angiogenesis resolves

VEGFR: Vascular Endothelial Growth Factor Receptor,
NRP1: Neuropilin-1,
HSPGs: Heparan Sulfate Proteoglycans,
PI3K: Phosphoinositide 3-Kinase,
Akt: Protein Kinase B,
MAPK: Mitogen-Activated Protein Kinase,
ERK: Extracellular Signal-Regulated Kinase,
HIF-1α: Hypoxia-Inducible Factor 1-alpha,
GF: Growth Factor

Moreover, external factors such as metabolic stress can influence *VEGFA* isoform expression via splicing regulators. For instance, in an atherosclerosis model induced

by a high-fat diet, upregulation of the splicing kinase SR protein kinase 1 (SRPK1) favored $VEGF_{165}a$ production over $VEGF_{165}b$, enhancing pathological angiogenesis (17).

Pathophysiological roles of $VEGF_{165}a$ and $VEGF_{165}b$ in disease

The ratio between $VEGF_{165}a$ and $VEGF_{165}b$ plays a pivotal role in regulating angiogenic activity across various pathological conditions. An imbalance—either through excessive $VEGF_{165}a$ or insufficient $VEGF_{165}b$—can drive disease progression. Below, the contributions of these isoforms are examined in the context of cancer biology (18).

Cancer and tumor angiogenesis

Many tumors exploit the VEGF pathway to promote angiogenesis and support their growth. *VEGFA*, particularly the $VEGF_{165}a$ isoform, is commonly overexpressed in malignancies and correlates with poor clinical outcomes. High levels of $VEGF_{165}a$ in the tumor microenvironment stimulate the development of structurally abnormal and hyperpermeable blood vessels, thereby facilitating tumor expansion and metastasis. In breast cancer, for example, elevated $VEGF_{165}$ expression is associated with more aggressive phenotypes. Additionally, $VEGF_{165}a$ may function in an autocrine manner, supporting tumor cell survival independent of angiogenesis (19).

In contrast, $VEGF_{165}b$ is frequently downregulated in tumors. A shift in *VEGFA* mRNA splicing towards exon 8a leads to suppression of VEGFxxxb isoforms, including $VEGF_{165}b$. Clinical studies have shown significantly reduced $VEGF_{165}b$ expression in melanoma and colon carcinoma tissues compared to adjacent non-cancerous counterparts. This loss removes a key inhibitory control on angiogenesis, enabling unregulated vessel sprouting—an essential component of the "angiogenic switch" during tumor development (20).

However, the presence and regulation of $VEGF_{165}b$ in tumors appear context-dependent. Some reports indicate that $VEGF_{165}b$ may still be expressed in certain cancers and may even be upregulated in response to anti-angiogenic or hormonal therapies. For instance, in subsets of breast cancer, $VEGF_{165}b$ expression increased following treatment, suggesting it might function as a feedback regulator under specific conditions. Yet, the mere presence of $VEGF_{165}b$ does not guarantee effective angiogenesis inhibition; its function depends on the relative abundance of $VEGF_{165}a$ and other angiogenic factors (21).

A study by Catena et al. (2010) clarified this complexity by demonstrating that the efficacy of $VEGF_{165}b$ in suppressing tumor growth depends on baseline $VEGF_{165}a$ levels. In tumors with high $VEGF_{165}a$ expression, $VEGF_{165}b$ competes for VEGFR binding, reducing signaling and inhibiting angiogenesis. In contrast, in tumors with low VEGF expression, $VEGF_{165}b$'s weak signaling may paradoxically provide a minimal angiogenic stimulus. Thus, $VEGF_{165}b$ can either inhibit or, in rare contexts, modestly support angiogenesis, depending on the tumor microenvironment (22).

Therapeutically, increasing $VEGF_{165}b$ levels in tumors has shown promise in preclinical models. Overexpression or delivery of $VEGF_{165}b$ in xenograft models such as prostate cancer, renal cell carcinoma, and Ewing's sarcoma led to reduced angiogenesis and slowed tumor growth. These findings support the concept that shifting the $VEGF_{165}a/VEGF_{165}b$ ratio toward the anti-angiogenic isoform may impair tumor vascularization. However, such interventions are likely to be most effective in tumors with strong $VEGF_{165}a$-driven angiogenesis. In cancers where angiogenesis is VEGF-independent, $VEGF_{165}b$-based therapies may have limited efficacy or even counterproductive effects (14).

Diabetic retinopathy and ocular neovascular disease

Pathological angiogenesis in the eye – as seen in proliferative diabetic retinopathy (PDR) and neovascular AMD – is largely driven by excess *VEGFA*. In the retinal milieu of diabetic patients with retinopathy, there is a pronounced skew toward the pro-angiogenic isoform. Clinical samples show that the ratio of $VEGF_{165}b$ to total *VEGFA* is significantly lower in the ocular fluids of diabetics with retinopathy compared to diabetics without retinopathy. In other words, PDR patients have relatively deficient $VEGF_{165}b$ (or an excess of $VEGF_{165}a$), removing an inhibitory constraint and permitting aberrant blood vessel proliferation in the retina (23).

This insight has spurred interest in supplementing $VEGF_{165}b$ for therapeutic effect in eye diseases. Experimental studies have delivered recombinant $VEGF_{165}b$ into animal models of retinal neovascularization. Remarkably, a single intravitreal injection of $VEGF_{165}b$ significantly reduced pathological preretinal neovascular growth in an ischemic retinopathy model, without adversely affecting the normal retinal vessels. This contrasts with standard anti-VEGF drugs (like bevacizumab or ranibizumab), which indiscriminately neutralize all *VEGFA* isoforms and therefore can somewhat affect the healthy vasculature. $VEGF_{165}b$ appears to specifically counteract the pathological angiogenic drive ($VEGF_{165}a$-mediated) while sparing baseline vasculature – likely because $VEGF_{165}b$ won't fully shut down the minimal VEGF signals needed for maintenance. Additionally, $VEGF_{165}b$ can mitigate vascular leakage. In diabetic rats, intravitreal $VEGF_{165}b$ administration reduced retinal vascular permeability and edema. This is an important finding since macular edema (due to leaky vessels) is a major cause of vision loss in DR. By stabilizing endothelial junctions (perhaps by blocking $VEGF_{165}a$-induced junction disassembly), $VEGF_{165}b$ could help control edema (23).

Current anti-VEGFA therapies for DR and wet AMD consist of antibodies or decoy receptors that sequester all *VEGFA* isoforms – effectively neutralizing both $VEGFA_{165}a$ and $VEGFA_{165}b$. These treatments (e.g., ranibizumab, aflibercept, and off-label bevacizumab) have markedly improved clinical outcomes by inhibiting pathological neovascularization and preserving visual function in a substantial proportion of patients (24, 25).

However, they pose a theoretical concern: by neutralizing $VEGFA_{165}b$ alongside $VEGFA_{165}a$, they may inadvertently eliminate an endogenous protective factor (8).

Indeed, chronic anti-VEGF therapy has been associated with choroidal vessel atrophy and progressive degeneration of the outer retina in AMD, possibly reflecting excessive suppression of physiological VEGF signaling (26). The retina relies on a finely regulated *VEGFA* level for homeostasis – excessive amounts promote macular edema and pathological neovascularization, whereas insufficient levels may compromise the viability of the retinal pigment epithelium and the integrity of the choroidal vasculature (26).

This raises a compelling question: could ocular neovascular diseases be treated by selectively inhibiting $VEGFA_{165}a$ while preserving or enhancing $VEGFA_{165}b$? Theoretically, yes. An isoform-specific inhibitor that selectively neutralizes $VEGFA_{165}a$ but spares $VEGFA_{165}b$ could suppress pathological angiogenesis with fewer adverse effects on physiological retinal function (8). Alternatively, exogenous administration of $VEGFA_{165}b$, or upregulation of its expression via splicing modulation, may provide an intrinsic anti-angiogenic effect. Although such approaches have not yet reached clinical implementation, they represent a next-generation strategy in precision ocular therapy: modulating isoform balance rather than employing indiscriminate *VEGFA* blockade. Notably, $VEGFA_{165}b$ has been tested in non-human primate models without significant toxicity, indicating its potential for therapeutic application or biomimetic use—though challenges such as its short half-life and possible immunogenicity must be considered (27).

Peripheral ischemia (peripheral artery disease)

Ischemic diseases like PAD trigger a compensatory angiogenic response – hypoxic tissues upregulate *VEGFA* to try to grow collateral vessels. However, in chronic ischemia (especially with comorbidities like diabetes), this response often fails. A surprising discovery is that $VEGF_{165}b$ may play a role in this failure (26). In diabetic models of limb ischemia, $VEGF_{165}b$ expression was found to increase in ischemic muscle, even as total *VEGFA* levels rose. The induced $VEGF_{165}b$ acted as a brake on angiogenesis, contributing to the poor recovery of blood flow. When researchers neutralized $VEGF_{165}b$ with an antibody, the ischemic limbs showed significantly improved angiogenesis: blood flow and capillary density increased, essentially "unleashing" vessel growth that had been restrained. This provided direct evidence that $VEGF_{165}b$ was a maladaptive factor in the context of PAD (28).

Mechanistically, as noted earlier, $VEGF_{165}b$ in diabetic ischemia appears to hinder VEGFR-1–mediated angiogenic pathways, which become important when VEGFR-2 signaling is impaired by diabetes. Diabetes is known to cause endothelial dysfunction (e.g., reduced NO production), so VEGFR-2's usual pro-angiogenic signals are blunted. In that setting, alternate routes (like VEGFR-1–STAT3 signaling through inflammatory cells) might help – but $VEGF_{165}b$ prevents VEGFR-1 from contributing. By removing $VEGF_{165}b$, those alternate pathways can engage and partially compensate for the VEGFR-2 impairment, thus restoring angiogenesis.

These findings have spurred interest in isoform-specific pro-angiogenic therapies for ischemia. For instance, one could envision an antibody or small molecule that selectively inhibits $VEGF_{165}b$ without blocking $VEGF_{165}a$. Such a therapy might boost the patient's own angiogenesis in conditions like critical limb ischemia or even ischemic heart disease, especially in individuals where standard pro-angiogenic treatments have failed. In essence, instead of adding more growth factors, this approach would involve removing an endogenous inhibitor ($VEGF_{165}b$) to tilt the balance toward angiogenesis. This strategy contrasts with oncology and ophthalmology, aiming to enhance angiogenesis by inhibiting an anti-angiogenic isoform.

Early experimental support for this concept comes from a recent study in choroidal neovascularization (CNV) model (an eye model of pathological angiogenesis). There, use of an SRPK1 inhibitor – a drug that shifts splicing towards the VEGFxxxb isoforms – was able to abort new vessel growth (29). By increasing $VEGF_{165}b$ relative to $VEGF_{165}a$, the SRPK1 inhibitor suppressed angiogenesis in the CNV model. Translating that to ischemic disease, one might do the opposite (inhibit splicing towards $VEGF_{165}b$ or activate splicing toward $VEGF_{165}a$) to encourage angiogenesis. For example, an activator of SRPK1 or of the splicing factor serine/arginine-rich splicing factor 1 (SRSF1) could theoretically reduce $VEGF_{165}b$ production and favor $VEGF_{165}a$, boosting angiogenic capacity in ischemic tissues. Although these strategies remain theoretical and require further validation, modulating the $VEGF_{165}a/b$ ratio represents a promising approach for future therapeutic development in vascular diseases.

Fibrosis and systemic sclerosis

Systemic sclerosis (SSc) – a fibrotic autoimmune disease – provides another striking example of $VEGF_{165}b$'s impact. SSc patients suffer from severe peripheral ischemia (e.g., in the skin and digits) despite having high circulating VEGF levels. The microvasculature shows rarefaction (loss of vessels) and poor angiogenic repair. A key finding is that $VEGF_{165}b$ is markedly overexpressed in SSc. Skin biopsies from SSc patients have significantly higher $VEGF_{165}b$ mRNA and protein compared to healthy controls (30). In fact, plasma $VEGF_{165}b$ is elevated in SSc and correlates with the degree of capillary loss (30, 31).

This overabundance of the anti-angiogenic isoform offers an explanation for the long-standing puzzle in SSc: why is angiogenesis impaired even though *VEGFA* (normally pro-angiogenic) is elevated? The "angiogenic paradox" in SSc is that total VEGF is high (the body is desperately trying to grow vessels in response to chronic ischemia), but because so much of that VEGF is the $VEGF_{165}b$ isoform, the net effect is anti-angiogenic. Essentially, the pro-angiogenic signal is canceled out by the concurrent presence of $VEGF_{165}b$, leading to futile angiogenesis attempts and persistent tissue ischemia.

This insight positions $VEGF_{165}b$ as both a biomarker and a potential therapeutic target in SSc. High $VEGF_{165}b$ levels could indicate a more severe microvasculopathy (e.g., worse nailfold capillary loss and digital ulcers) (30). Therapeutically, strategies to reduce $VEGF_{165}b$ or block its function might restore angiogenic competence in SSc patients. For example, one could imagine using a neutralizing

antibody against $VEGF_{165}b$ in SSc skin—similar to how it was done in the PAD model—to promote new vessel growth and wound healing. Alternatively, downregulating the splicing factors that favor exon 8b in SSc endothelial cells could shift the balance back to $VEGF_{165}a$. Indeed, studies have noted dysregulation of splicing regulators in SSc (e.g., elevated SRPK1), which might contribute to the high $VEGF_{165}b$ production (32).

It is worth noting that the VEGF pathway in SSc is complex. Other factors (like soluble VEGFR-1 and endostatin) are also elevated and inhibit angiogenesis. Nonetheless, $VEGF_{165}b$ appears to be a significant piece of the puzzle. Manetti et al. (2011) demonstrated that overexpression of $VEGF_{165}b$ in an SSc context led to insufficient angiogenesis, and that patients with SSc had high $VEGF_{165}b$ linked to their capillary loss (30). This underscores that tackling $VEGF_{165}b$ in SSc could be beneficial. Any intervention, however, would need to be careful not to tip the balance too far and cause aberrant angiogenesis or edema.

Pre-eclampsia

Pre-eclampsia is a pregnancy-related hypertensive disorder marked by poor placental vascular development and endothelial dysfunction. While much attention has focused on VEGF inhibitors like sFlt-1 (soluble VEGFR-1) in pre-eclampsia, evidence suggests that *VEGFA* splicing may also be altered (33). The placenta is one of the few normal tissues that predominantly expresses pro-angiogenic VEGFxxxa isoforms, as robust angiogenesis is essential during pregnancy. In healthy pregnancy, $VEGF_{165}b$ levels in maternal plasma gradually rise but remain relatively low in the placenta to allow adequate blood vessel formation. However, in pre-eclampsia, studies have indicated aberrant $VEGF_{165}b$ expression in placental tissue. Some preliminary reports found higher $VEGF_{165}b$ levels in pre-eclamptic placentas or plasma compared to normal pregnancies. For instance, one study noted that women who developed pre-eclampsia failed to upregulate $VEGF_{165}b$ in the first trimester to the same extent as normotensive pregnancies, but later in pregnancy their $VEGF_{165}b$ became inappropriately elevated. The net effect could be insufficient angiogenesis in early placentation, leading to poor placental perfusion and the subsequent cascade of pre-eclampsia symptoms.

The data on $VEGF_{165}b$ in pre-eclampsia are still emerging and, at times, conflicting. Some studies show lower early $VEGF_{165}b$ levels, while others report higher levels later in pregnancy. Nonetheless, the central concept is that a shift toward the anti-angiogenic isoform within the uteroplacental unit could contribute to the shallow trophoblast invasion and limited spiral artery remodeling that characterize pre-eclampsia (34).

If validated, $VEGF_{165}b$ could serve both as a biomarker—such as first-trimester plasma $VEGF_{165}b$ levels predicting pre-eclampsia risk—and as a therapeutic target. For example, strategies aimed at reducing $VEGF_{165}b$ or enhancing $VEGF_{165}a$ expression in the placenta might improve angiogenesis and pregnancy outcomes. Further research is required to determine the safety, feasibility, and potential efficacy of targeting $VEGFA_{165}b$ in the context of pregnancy without compromising fetal development (32).

Summary of isoform imbalance in disease

Across diverse pathological contexts—including cancer, ocular disease, PAD, SSc, and pre-eclampsia—a common theme emerges: the $VEGF_{165}a/VEGF_{165}b$ ratio is critical (8). Pathological angiogenesis (as observed in tumors and PDR) is typically associated with a skew toward $VEGF_{165}a$, reflecting excessive pro-angiogenic signaling with insufficient inhibitory control (26). In contrast, conditions characterized by impaired angiogenesis—such as chronic ischemia and SSc—are often marked by elevated $VEGF_{165}b$ levels, indicating excessive suppression of vascular growth stimuli (8, 30).

This dichotomy suggests that therapeutic restoration of isoform balance could serve as a unifying strategy: inhibiting $VEGF_{165}a$ in diseases of excessive angiogenesis, or conversely, inhibiting $VEGF_{165}b$ (or enhancing $VEGF_{165}a$) in diseases of insufficient angiogenesis. Indeed, ongoing studies and clinical trials are investigating both directions. Conventional agents like bevacizumab exemplify the former approach, although they non-selectively target all *VEGFA* isoforms. In contrast, newer strategies—such as splicing modulators or isoform-specific antibodies—represent more precise and promising alternatives.

Discussion and Therapeutic Perspectives

The dual-isoform nature of $VEGF_{165}$ has prompted a reevaluation of traditional views on VEGF in angiogenesis. Several controversies and areas of active research have emerged in recent years:

1. Conflicting data on $VEGF_{165}b$ in tumors

Early studies highlighted $VEGF_{165}b$ as a tumor-suppressive, anti-angiogenic factor—demonstrating, for example, that adding $VEGF_{165}b$ could slow the growth of certain tumor xenografts (8). However, later findings complicated this picture. Some studies reported that $VEGF_{165}b$ did not inhibit tumor growth, and in some models, it even appeared to promote it (35). This paradox was addressed by Catena et al., who proposed that the effect of $VEGF_{165}b$ depends on the prevailing levels of pro-angiogenic $VEGF_{165}a$ (22).

In VEGF-rich tumors, $VEGF_{165}b$ competes with $VEGF_{165}a$ and reduces net angiogenic signaling, thereby limiting tumor growth. In contrast, in VEGF-poor tumors, $VEGF_{165}b$ may deliver baseline VEGFR stimulation that would otherwise be absent, potentially enhancing angiogenesis and growth. This nuanced view reconciles conflicting data and underscores the therapeutic principle that $VEGF_{165}b$-based treatments may only be beneficial in high-*VEGFA* contexts. Stratifying patients according to tumor VEGF expression profiles may support more tailored therapeutic approaches in line with emerging principles of personalized oncology.

2. Debate over the existence and levels of VEGF$_{165}$b

Following its initial identification, VEGFA$_{165}$b encountered skepticism concerning its biological significance. Detection of VEGFAxxxb isoforms presented notable technical challenges, as various research groups employing ELISA or PCR methodologies reported inconsistent findings. For example, while one study suggested that VEGFAxxxb mRNA constituted over 50% of total VEGFA transcripts in healthy tissues, other investigations failed to detect it at comparable levels in similar samples (7, 8).

Such discrepancies were subsequently attributed to differences in assay sensitivity and specificity. The advent of isoform-specific antibodies and optimized PCR primer designs has since enabled more accurate detection, establishing that VEGFA$_{165}$b is indeed broadly expressed and biologically active (3). Nonetheless, its expression levels vary depending on tissue type and pathological context. For instance, data obtained using validated detection systems confirm that VEGFA$_{165}$b is detectable in normal renal tissue but markedly reduced or absent in many renal carcinoma specimens (7). These early inconsistencies underscore the critical importance of employing highly specific and sensitive tools when investigating isoform biology.

3. Therapeutic Implications – Toward Isoform-Specific VEGF Targeting

The clinical success of anti-VEGF agents—such as bevacizumab in oncology or aflibercept in the management of ocular neovascular diseases—has firmly established *VEGFA* as a therapeutically valid molecular target. However, these agents act in a non-selective manner, neutralizing all *VEGFA* isoforms and consequently inhibiting both pathological and physiological angiogenesis. This broad suppression can result in significant adverse effects, including hypertension, proteinuria, delayed wound healing, and, particularly in ophthalmic applications, choriocapillaris atrophy (36, 37).

In light of these limitations, current research has increasingly focused on the development of more refined and selective strategies. Isoform-specific modulation represents a promising approach, wherein selective inhibition of VEGFA$_{165}$a may be beneficial in disorders characterized by excessive angiogenesis (such as cancer and AMD), while selective inhibition of VEGFA$_{165}$b—or conversely, promotion of VEGFA$_{165}$a—may prove advantageous in conditions marked by insufficient angiogenesis, including PAD and SSc (3).

In ophthalmology, therapeutic strategies aimed at promoting exon 8b splicing or exogenous administration of VEGFA$_{165}$b have been proposed to attenuate pathological neovascularization while preserving physiological vascular integrity (4). Conversely, in ischemic disorders such as PAD or myocardial infarction, upregulation of VEGFA$_{165}$a expression through activation of SRPK1 or modulation of splicing factors such as SRSF1 may enhance therapeutic revascularization (5).

Another innovative strategy involves the use of splice-switching oligonucleotides (SSOs), which are synthetic RNA molecules designed to modulate pre-mRNA splicing patterns. SSOs could potentially be tailored to inhibit exon 8b inclusion—thus favoring VEGFA$_{165}$a expression—or, alternatively, to promote exon 8b usage when VEGFA$_{165}$b is desired. Although SSOs are currently under investigation in the context of other diseases, such as Duchenne muscular dystrophy, their application in angiogenesis modulation presents a compelling therapeutic opportunity. Nonetheless, the efficient and tissue-specific delivery of these molecules—particularly to complex sites such as the placenta or ischemic myocardium—remains a major technical hurdle (6).

4. Biomarker potential

VEGF$_{165}$b is being actively investigated as a biomarker for angiogenic status. For example, one study found that low first-trimester plasma VEGF$_{165}$b predicted the later onset of pre-eclampsia. In oncology, a high VEGF$_{165}$b-to-total *VEGFA* ratio may indicate a restrained angiogenic phenotype and better prognosis, whereas a low ratio may suggest an aggressive, angiogenesis-driven tumor. Measuring VEGF isoform ratios could inform treatment selection—e.g., patients with low VEGF$_{165}$b tumors may benefit from anti-VEGF therapy, while those with high VEGF$_{165}$b may not.

CONCLUSION

VEGF$_{165}$ exemplifies how alternative splicing of a single gene can generate functionally distinct protein isoforms that precisely regulate essential biological processes such as angiogenesis. Although VEGF$_{165}$a and VEGF$_{165}$b are derived from the same gene and possess nearly identical amino acid sequences, they exert diametrically opposing effects on vascular biology. VEGF$_{165}$a is a potent stimulator of neovascularization, whereas VEGF$_{165}$b acts as a critical physiological inhibitor. The dynamic balance between these two isoforms is essential for the maintenance of vascular homeostasis and is frequently perturbed in pathological conditions (5, 29).

Recent studies conducted between 2020 and 2025 have significantly advanced our understanding of the mechanisms by which VEGF$_{165}$b mediates its anti-angiogenic effects. These include competitive binding to VEGF receptors, particularly VEGFR-2, and selective modulation of VEGFR-1 signaling pathways (29). Furthermore, accumulating evidence supports its functional relevance in diseases characterized by aberrant angiogenesis, such as diabetic ischemia, systemic fibrotic disorders, and ocular neovascular pathologies.

From a clinical perspective, profiling the VEGF$_{165}$a/VEGF$_{165}$b expression ratio in individual patients holds promise for improving the precision of anti-angiogenic therapies. In disorders marked by excessive angiogenesis—such as cancer and PDR—therapeutic strategies aimed at enhancing or mimicking VEGF$_{165}$b activity may help suppress abnormal vessel proliferation without entirely abrogating physiological VEGF signaling (7, 38). Conversely, in conditions characterized by impaired neovascularization, including chronic non-healing wounds, PAD and SSc, targeted inhibition of VEGF$_{165}$b or upregulation of VEGF$_{165}$a may facilitate reparative angiogenesis (38).

Future therapeutic avenues may include isoform-specific monoclonal antibodies, small-molecule splicing modulators, or gene therapy vectors designed to modulate *VEGFA* pre-mRNA splicing with high specificity. Preclinical success with SSOs, which redirect *VEGFA* splicing toward a desired isoform, underscores the translational potential of this approach (38, 39).

In conclusion, investigation of $VEGF_{165}$ isoforms has not only enriched our understanding of the fine-tuned regulation of angiogenesis but also opened new therapeutic horizons. While $VEGF_{165}$a continues to serve as a primary therapeutic target in oncology and ophthalmology, $VEGF_{165}$b is increasingly recognized as both a diagnostic biomarker and a potential therapeutic agent. By focusing on the relative balance of VEGF isoforms rather than total *VEGFA* levels, future treatments may achieve a more nuanced modulation of angiogenesis—suppressing it where it is detrimental and promoting it where it is required.

Ongoing clinical trials assessing $VEGF_{165}$b expression levels and splicing-directed interventions will be (39) crucial in translating these molecular insights into tangible clinical benefit. Ultimately, the $VEGF_{165}$a/$VEGF_{165}$b axis illustrates a broader biological principle: that subtle changes in splice isoform expression can have profound effects on disease progression, and targeting this regulatory layer may define the next era in vascular and regenerative medicine.

Ethical Approval

This article is a literature-based review and does not involve human participants or animal experiments; therefore, ethical approval was not required.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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Authors' Contributions

FÇA: Conceptualization, literature review, and drafting of the manuscript.

SNP: Literature review, critical revision, and final approval of the manuscript.

All authors read and approved the final version of the manuscript.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Rom J Morphol Embryol. 2018;59(2):455-67.
2. Teran M. Modulation of vascular endothelial growth factor receptor affinity by neuropilin-1 and heparan sulfate proteoglycans 2016.
3. Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. Clinical science. 2005;109(3):227-41.
4. Guo Y-J, Pan W-W, Liu S-B, Shen Z-F, Xu Y, Hu L-L. ERK/MAPK signalling pathway and tumorigenesis. Experimental and therapeutic medicine. 2020;19(3):1997-2007.
5. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. Cell. 2019;176(6):1248-64.
6. Alsaab HO, Al-Hibs AS, Alzhrani R, Alrabighi KK, Alqathama A, Alwithenani A, et al. Nanomaterials for antiangiogenic therapies for cancer: a promising tool for personalized medicine. International journal of molecular sciences. 2021;22(4):1631.
7. Bates DO, Cui T-G, Doughty JM, Winkler M, Sugiono M, Shields JD, et al. $VEGF_{165}$b, an inhibitory splice variant of vascular endothelial growth factor, is down-regulated in renal cell carcinoma. Cancer research. 2002;62(14):4123-31.
8. Woolard J, Wang W-Y, Bevan HS, Qiu Y, Morbidelli L, Pritchard-Jones RO, et al. $VEGF_{165}$b, an inhibitory vascular endothelial growth factor splice variant: mechanism of action, in vivo effect on angiogenesis and endogenous protein expression. Cancer research. 2004;64(21):7822-35.
9. Raja A, Ganta V. Synthetic Antiangiogenic Vascular Endothelial Growth Factor—A Splice Variant Revascularizes Ischemic Muscle in Peripheral Artery Disease. Journal of the American Heart Association. 2024;13(20):e034304.
10. Melo CFOR, Navarro LC, De Oliveira DN, Guerreiro TM, Lima EdO, Delafiori J, et al. A machine learning application based in random forest for integrating mass spectrometry-based metabolomic data: a simple screening method for patients with Zika virus. Frontiers in bioengineering and biotechnology. 2018;6:31.
11. Parker MW, Xu P, Li X, Vander Kooi CW. Structural basis for selective vascular endothelial growth factor-A (VEGFA) binding to neuropilin-1. Journal of Biological Chemistry. 2012;287(14):11082-9.
12. Ganta VC, Choi M, Kutateladze A, Annex BH. $VEGF_{165}$b modulates endothelial VEGFR1–STAT3 signaling pathway and angiogenesis in human and experimental peripheral arterial disease. Circulation research. 2017;120(2):282-95.
13. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. Nature medicine. 2003;9(6):669-76.
14. Peiris-Pagès M. The role of $VEGF_{165}$b in pathophysiology. Cell adhesion & migration. 2012;6(6):561-8.
15. Wang X, Bove AM, Simone G, Ma B. Molecular bases of VEGFR-2-mediated physiological function and pathological role. Frontiers in Cell and Developmental Biology. 2020;8:599281.
16. Peach CJ, Mignone VW, Arruda MA, Alcobia DC, Hill SJ, Kilpatrick LE, et al. Molecular pharmacology of

VEGFA isoforms: binding and signalling at VEGFR2. International journal of molecular sciences. 2018;19(4):1264.
17. Batlle R, Andrés E, Gonzalez L, Llonch E, Igea A, Gutierrez-Prat N, et al. Regulation of tumor angiogenesis and mesenchymal–endothelial transition by p38α through TGF-β and JNK signaling. Nature communications. 2019;10(1):3071.
18. Bates DO, Catalano PJ, Symonds KE, Varey AH, Ramani P, O'Dwyer PJ, et al. Association between VEGF splice isoforms and progression-free survival in metastatic colorectal cancer patients treated with bevacizumab. Clinical Cancer Research. 2012;18(22):6384-91.
19. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nature Reviews Cancer. 2002;2(10):795-803.
20. Varey A, Rennel E, Qiu Y, Bevan H, Perrin R, Raffy S, et al. $VEGF_{165}b$, an antiangiogenic VEGFA isoform, binds and inhibits bevacizumab treatment in experimental colorectal carcinoma: balance of pro-and antiangiogenic VEGFA isoforms has implications for therapy. British journal of cancer. 2008;98(8):1366-79.
21. Karsten MM, Beck MH, Rademacher A, Knabl J, Blohmer J-U, Jückstock J, et al. $VEGFA_{165}b$ levels are reduced in breast cancer patients at primary diagnosis but increase after completion of cancer treatment. Scientific reports. 2020;10(1):3635.
22. Catena R, Larzabal L, Larrayoz M, Molina E, Hermida J, Agorreta J, et al. VEGF 121 b and VEGF $_{165}$ b are weakly angiogenic isoforms of VEGFA. Molecular cancer. 2010;9:1-14.
23. Jiang F, Chong L, Du S, Duan Y, Wang Y, Wang J, et al. Decreased ratio of $VEGF_{165}b$/VEGF in aqueous humor predicts progression of diabetic retinopathy. Ophthalmic Research. 2020;63(6):517-23.
24. Zhao Y, Singh RP. The role of anti-vascular endothelial growth factor (anti-VEGF) in the management of proliferative diabetic retinopathy. Drugs in context. 2018;7:212532.
25. Amadio M, Govoni S, Pascale A. Targeting VEGF in eye neovascularization: What's new?: A comprehensive review on current therapies and oligonucleotide-based interventions under development. Pharmacological research. 2016;103:253-69.
26. Campochiaro PA. Ocular neovascularization. Journal of molecular medicine. 2013;91:311-21.
27. Kilic Ü, Kilic E, Järve A, Guo Z, Spudich A, Bieber K, et al. Human vascular endothelial growth factor protects axotomized retinal ganglion cells in vivo by activating ERK-1/2 and Akt pathways. Journal of Neuroscience. 2006;26(48):12439-46.
28. Manetti M, Guiducci S, Romano E, Ceccarelli C, Bellando-Randone S, Conforti ML, et al. Overexpression of $VEGF_{165}b$, an inhibitory splice variant of vascular endothelial growth factor, leads to insufficient angiogenesis in patients with systemic sclerosis. Circulation research. 2011;109(3):e14-e26.
29. Nowak DG, Woolard J, Amin EM, Konopatskaya O, Saleem MA, Churchill AJ, et al. Expression of pro-and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors. Journal of cell science. 2008;121(20):3487-95.
30. Manetti M, Guiducci S, Ibba-Manneschi L, Matucci-Cerinic M. Impaired angiogenesis in systemic sclerosis: the emerging role of the antiangiogenic $VEGF_{165}b$ splice variant. Trends in cardiovascular medicine. 2011;21(7):204-10.
31. Guiducci S, Distler O, Distler J, Matucci-Cerinic M. Mechanisms of vascular damage in SSc—implications for vascular treatment strategies. Rheumatology. 2008;47(suppl_5):v18-v20.
32. Nowak DG, Amin EM, Rennel ES, Hoareau-Aveilla C, Gammons M, Damodoran G, et al. Regulation of vascular endothelial growth factor (VEGF) splicing from pro-angiogenic to anti-angiogenic isoforms: a novel therapeutic strategy for angiogenesis. Journal of Biological Chemistry. 2010;285(8):5532-40.
33. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. New England journal of medicine. 2004;350(7):672-83.
34. Bills VL, Hamdollah-Zadeh M, Soothill PW, Harper SJ, Bates DO. The role of VEGFA $_{165}$ b in trophoblast survival. BMC Pregnancy and Childbirth. 2014;14:1-8.
35. Rennel ES, Harper SJ, Bates DO. Therapeutic potential of manipulating VEGF splice isoforms in oncology. Future Oncology. 2009;5(5):703-12.
36. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nature reviews Drug discovery. 2016;15(6):385-403.
37. Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D'Amore PA. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. Proceedings of the National Academy of Sciences. 2009;106(44):18751-6.
38. Harper SJ, Bates DO. VEGFA splicing: the key to anti-angiogenic therapeutics? Nature Reviews Cancer. 2008;8(11):880-7.
39. Havens MA, Hastings ML. Splice-switching antisense oligonucleotides as therapeutic drugs. Nucleic acids research. 2016;44(14):6549-63.