



# VEGF-B: A multifaceted modulator with emerging therapeutic applications

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## ABSTRACT

Long overshadowed by VEGF-A, vascular endothelial growth factor B (VEGF-B) has emerged as a critical regulator of vascular, metabolic, and immune cross-talk. Unlike the potent angiogenic factor VEGF-A, VEGF-B does not induce vascular leakage but modulates tissue-specific functions, including fatty acid transport, neuronal survival, and immunometabolism, through its receptors VEGFR1 and NRP1. Its roles are often paradoxical, suppressing angiogenesis in some cancers while promoting metastasis and immune evasion in others, highlighting its profoundly context-dependent nature of action. Recent discoveries, such as the identification of FGFR1 as a key receptor and the essential role of VEGF-B in T cell survival, have revitalized interest in its therapeutic potential. However, clinical translation remains challenging, as exemplified by the recent failure of the anti-VEGF-B antibody CSL346 in diabetic kidney disease, underscoring our incomplete understanding of VEGF-B biology. This review integrates cutting-edge insights into the diverse functions of VEGF-B, proposes a mechanistic framework for its complex signaling networks, and outlines a roadmap for developing precision therapies for metabolic, cardiovascular, neurodegenerative, and oncological diseases. We address the critical translational challenges to maximize the therapeutic benefits while preserving the crucial homeostatic functions of VEGF-B.

## 1. Introduction

VEGF-B has long been regarded as a minor member of the VEGF family, characterized by limited angiogenic activity and a relatively restricted biological role. However, accumulating evidence has reshaped this view, positioning VEGF-B as a complex, context-dependent regulator of vascular, metabolic, neuronal, and immune homeostasis. In contrast to VEGF-A, which robustly induces angiogenesis and vascular permeability, VEGF-B exerts more subtle, tissue-specific effects such as regulating lipid transport and mediating cellular stress responses without causing vascular leakage [1]. This emerging functional profile underscores VEGF-B's importance as both a molecular mediator of

systemic homeostasis and a promising therapeutic target in conditions such as metabolic disorders, neurodegeneration, cardiovascular diseases, and cancer.

In this context, the development of VEGF-B-targeted therapeutics - most notably the monoclonal VEGF-B antibody CSL346 - and the discovery of previously unrecognized receptors such as FGFR1 and integrins have renewed interest in the translational potential of VEGF-B [2–5]. In parallel, advances in biomarker discovery, particularly those related to VEGF-B isoforms and their tissue-specific actions, promise to enable more refined patient stratification in metabolic and oncological drug pipelines [6]. Beyond its canonical association with VEGFR1 and NRP1, recent studies have revealed VEGF-B's ability to fine-tune

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intracellular pathways linked to mitochondrial dynamics, oxidative stress resistance, and immune cell polarization, further expanding its biological footprint. Moreover, VEGF-B is not a redundant angiogenic ligand but a critical homeostatic modulator integrating vascular, metabolic, and neuronal signals.

Yet despite these advances, our understanding of VEGF-B biology remains fragmented. Isoform-specific functions, cell type-selective signaling through canonical and non-canonical receptors, and the temporal dynamics of VEGF-B activity across different disease stages are still poorly resolved. Moreover, the lack of disease models that faithfully recapitulate human VEGF-B biology and the scarcity of longitudinal studies linking VEGF-B levels to disease trajectories have hampered efforts to translate preclinical findings into the clinic. These gaps have contributed to setbacks in early clinical attempts such as a failure of CSL346 [3], therefore underscoring the need for a deeper mechanistic understanding to inform rational therapeutic design. Together, these converging findings are reshaping how VEGF-B is perceived from a minor factor within the VEGF family to a distinct regulatory axis with broad effects on vascular integrity, metabolic balance, neuroprotection, and tumor biology. Clarifying its molecular mechanisms, isoform-dependent actions, and disease associations will be critical for overcoming current barriers and for exploring its potential as a therapeutic target.

## 2. VEGF family

### 2.1. VEGF family members

The VEGF family comprises five core members - VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PlGF) - that orchestrate blood and lymphatic vessel development, maintenance, and remodeling (Fig. 1A). All VEGF family members share a conserved cystine-knot motif that promotes correct folding of the monomer and provides the structural framework for forming interchain disulfide bonds required for dimerization and receptor binding, while their functional diversity arises from alternative splicing and proteolytic processing [7–10]. Acting through VEGFR1–3 and co-receptors such as NRPs, these ligands regulate overlapping yet distinct physiological and pathological processes.

VEGF-A is the dominant angiogenic driver and exists as multiple isoforms - VEGF-A121, 145, 165, 189, and 206 - that differ in extracellular matrix (ECM) and co-receptor binding [11–13]. In humans, VEGF-A165 (VEGF-A164 in mice) represents the predominant isoform, combining high VEGFR2 affinity with a heparin-binding domain (HBD) that facilitates partial retention within the ECM and at cell surfaces, while detectable levels can also be found in the circulation [14–16]. In contrast, VEGF-A121, lacking the HBD, shows weaker VEGFR2 activation and reduced mitogenic activity, while the longer ECM-bound

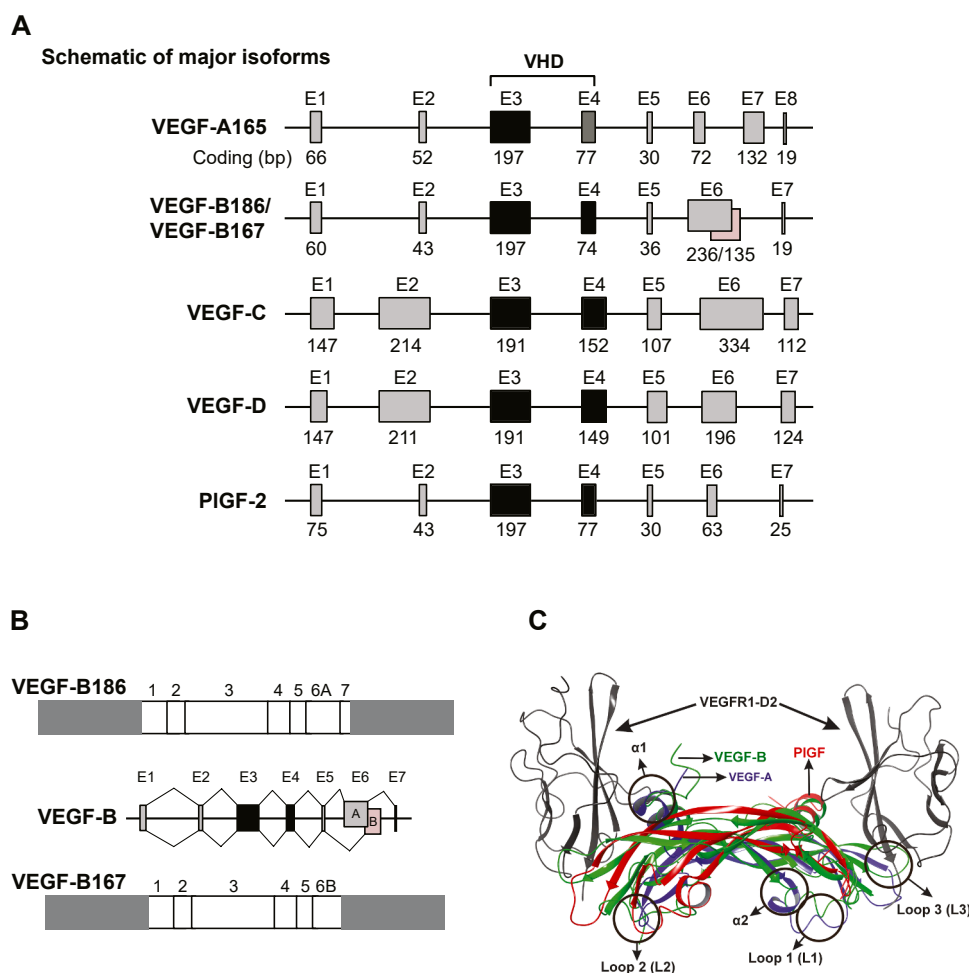


**Fig. 1.** Gene organization, isoforms, and structural comparison of VEGF family members. A. Exon–intron organization of the canonical or major biologically active splice isoforms of human VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF genes. Exons are indicated as numbered boxes with base pairs (bp) indicated below each box. All VEGF genes are depicted in the orientation of the forward strand. B. Alternative splicing of exon 6 produces two distinct VEGF-B isoforms: VEGF-B186 (including exon 6A) and VEGF-B167 (including exon 6B). C. Structural superposition of VEGF family members in complex with VEGFR1-D2. The crystal structures of VEGF-A (1FLT-blue), VEGF-B (2XAC-green), and PlGF (1RV6-red) are shown in complex with the second domain of VEGF receptor 1 (VEGFR1-D2, gray). The key secondary structural elements -  $\alpha$ -helices ( $\alpha$ 1,  $\alpha$ 2) and loops (L1–L3) - involved in receptor binding are indicated.

isoforms VEGF-A189 and VEGF-A206 generate local gradients that drive site-specific angiogenesis [14,17,18].

VEGF-C and VEGF-D primarily mediate lymphangiogenesis via VEGFR3 [19,20]. Both are secreted as inactive precursors requiring proteolytic activation, after which mature VEGF-C also engages VEGFR2, and mature VEGF-D can activate VEGFR2 homodimers and, in some contexts, through VEGFR2/VEGFR3 heterodimers [21–24]. Such proteolytic processing tightly controls their receptor specificity, enabling context-dependent regulation of lymphatic and, in some cases, blood vessel growth.

PlGF binds exclusively to VEGFR1 and is a key mediator of pathological angiogenesis in inflammation and ischemia [25]. Four isoforms differ in ECM binding and tissue distribution. PlGF-1 modulates VEGF-A activity via heterodimerization and receptor competition, while ECM-binding PlGF-2 and PlGF-4 localize signaling to restricted tissue niches [26,27]. PlGF-3 includes a longer C-terminal region generated by alternative splicing largely shared with PlGF-4 which distinguishes these isoforms from PlGF-1 and PlGF-2 [27]. Together, these ligands form an integrated signaling network that shapes blood and lymphatic vascular biology.

## 2.2. VEGF-B

VEGF-B is encoded by a seven-exon gene with an exon–intron structure similar to VEGF-A [28,29]. Alternative splicing of exons 6 and 7 generates two predominant isoforms, VEGF-B167 and VEGF-B186 (Fig. 1B), which share an N-terminal domain (exons 1–5) containing eight conserved cysteines for disulfide bonding and dimerization [28]. This domain represents the VEGF homology domain (VHD), a specialized subset of the PDGF homology domain [16,30]. From an evolutionary standpoint, however, the composition of this network has diversified across vertebrates: VEGF-B is absent in birds and certain reptiles [16], suggesting that other VEGF members, such as VEGF-A and PlGF, may have adopted overlapping or compensatory functions in these lineages.

VEGF-B167 (188 amino acids) includes exon 6B and exon 7 at the C-terminus, producing a highly basic HBD that anchors it to the ECM and cell surfaces via heparan sulfate proteoglycans (HSPG) [28,31]. VEGF-B186 (207 amino acids) instead contains exon 6A, which introduces a frameshift, generating a hydrophobic, O-glycosylated C-terminal domain lacking HBD motifs, which allows great diffusibility [29,32]. While both isoforms lack N-linked glycosylation, VEGF-B186 carries serine/threonine-rich sequences typical of O-glycosylation, a modification that may affect its bioavailability, as seen in viral VEGF-E [33,34]. A third variant, VEGF-B155, results from exclusion of exon 5, producing a protein 12 amino acids shorter than VEGF-B167. This isoform has been detected predominantly in glioblastoma cells, suggesting a tumor-specific expression pattern [35].

VEGF-B mRNA (~1.4 kb) is most abundant in metabolically active tissues including heart, skeletal muscle, brain, and kidney with VEGF-B167 representing over 80 % of transcripts [31]. In both mouse and human tissues, VEGF-B167 and VEGF-B186 are expressed at comparable transcript levels, although VEGF-B167 generally predominates in the heart, skeletal muscle, and brain [29,31]. VEGF-B186 expression varies across tissues and tends to increase under pathological or stress conditions, including tumors and ischemic myocardium [36,37]. This distribution supports context-dependent regulation and functional divergence between the two isoforms. At the protein level, VEGF-B forms disulfide-linked homodimers (44–54 kDa) and can heterodimerize with VEGF-A *in vitro*, though *in vivo* relevance remains unclear [29]. Such heterodimers may alter ligand diffusion and receptor engagement, producing distinct signaling outputs. Functionally, VEGF-B167 binds VEGFR1 with high affinity (Kd 1–3 nM) but induces limited receptor phosphorylation due to an inhibitory juxtamembrane sequence in VEGFR1 [38,39]. This property explains its modest angiogenic activity and supports its primary roles in metabolic regulation and

tissue protection under stress [36,40].

Together, VEGF-B exhibits distinctive isoform-specific structure and biochemical properties that set it apart from other VEGF ligands and provide the molecular basis for its unique receptor interactions and tissue-specific roles.

## 2.3. Receptor binding: VEGFR1 and neuropilin

VEGF-B interacts mainly with two receptors, VEGFR1 (Flt1 in mice) and neuropilin 1 (NRP1) [38,41]. VEGFR1 is a receptor tyrosine kinase composed of seven extracellular immunoglobulin (IgG)-like domains and an intracellular kinase domain [42]. The first three extracellular domains (D1–D3) are sufficient for VEGF-B binding, with sites overlapping those for VEGF-A and PlGF [43]. Comparative binding studies show that VEGFR1 D1–D2 constructs exhibit higher affinity for VEGF-B than for PlGF, whereas D1–D3 constructs displays comparable affinities for both ligands [44]. Structural analyses indicate that although VEGF-A and VEGF-B share key determinants for VEGFR1 binding (Fig. 1C), their interfaces differ significantly. In VEGF-A, the Cys60–Cys68 loop contains Asp63, Glu64, and Glu67, which are essential for VEGFR1 interaction (Fig. 2A) [30,43]. By contrast, VEGF-B carries Asp63, Asp64, and Glu67 in the corresponding loop (Fig. 2B), resulting in subtle structural differences that contribute to VEGFR1 specificity. However, the distinct positioning of Pro86 in VEGF-B loop L3 disrupts VEGFR2 binding [43].

NRP1 serves as a co-receptor for VEGF-A, VEGF-B, VEGF-C, VEGF-D, PlGF, and PDGF-D [45–47], as well as semaphorins in axonal guidance [48,49]. Expressed in neurons, vascular endothelial cells (EC), and perivascular mesenchyme, NRP1 binds both VEGF-B isoforms via their C-terminal regions. VEGF-B167 binds via the HBD encoded by exon 6B, homologous to the NRP1-binding motif of VEGF-A165 [41]. In contrast, VEGF-B186 lacks heparin-binding affinity and requires proteolytic cleavage to expose an NRP1-binding site located within the first 12 amino acids of the cleaved fragment, defining distinct isoform-specific properties [41].

Variations in the C-terminal sequences of VEGF-A (Asp187–Arg191), VEGF-B (VEGF-B167: Arg184–Arg188; VEGF-B186: Arg144–Arg148) (Fig. 2C), and VEGF-C (Ser223–Arg227) determine binding to the b1 domains of NRP1 and NRP2 [50]. NRP1 exhibits higher affinity than NRP2, with VEGF-B167 showing the strongest dual binding, whereas VEGF-A mainly engages NRP1. A VEGF-B167-derived peptide (MGC0123: Arg160–Arg188) binds the NRP1 b1 domain (Fig. 2D) with high affinity and blocks VEGF-A-induced VEGFR2 activation, thereby inhibiting downstream signaling [51]. This region also overlaps with an FGFR1-binding motif [2].

These findings define VEGF-B as a ligand with a complex, context-dependent receptor-binding profile that integrates VEGFR1, NRP1, and FGFR1 interactions underlying its diverse functions. Despite sharing VEGFR1 as a primary receptor with PlGF, VEGF-B elicits distinct outcomes because of its isoform-dependent heparin-binding capacity and differential engagement of co-receptors such as NRP1 and FGFR1. These context-specific receptor combinations may explain why VEGF-B often modulates vascular stability or metabolism rather than driving angiogenesis such as VEGF-A.

## 2.4. Gene expression profile of VEGF-B

During development, VEGF-B exhibits substantial expression in cardiac myocytes with lower levels in skeletal muscle, bone, pancreas, and adrenal tissues. Additionally, it is present in the smooth muscle cell layer of larger vessels [28,32]. Because the promoter lacks hypoxia-inducible factor (HIF) sites [52], VEGF-B expression is generally oxygen-independent, with retina as a reported exception [53]. However, VEGF-B expression appears to remain stable without stimulation by growth factors, cytokines, or other signals. Further study is needed to understand the mechanisms controlling VEGF-B expression under hypoxia.

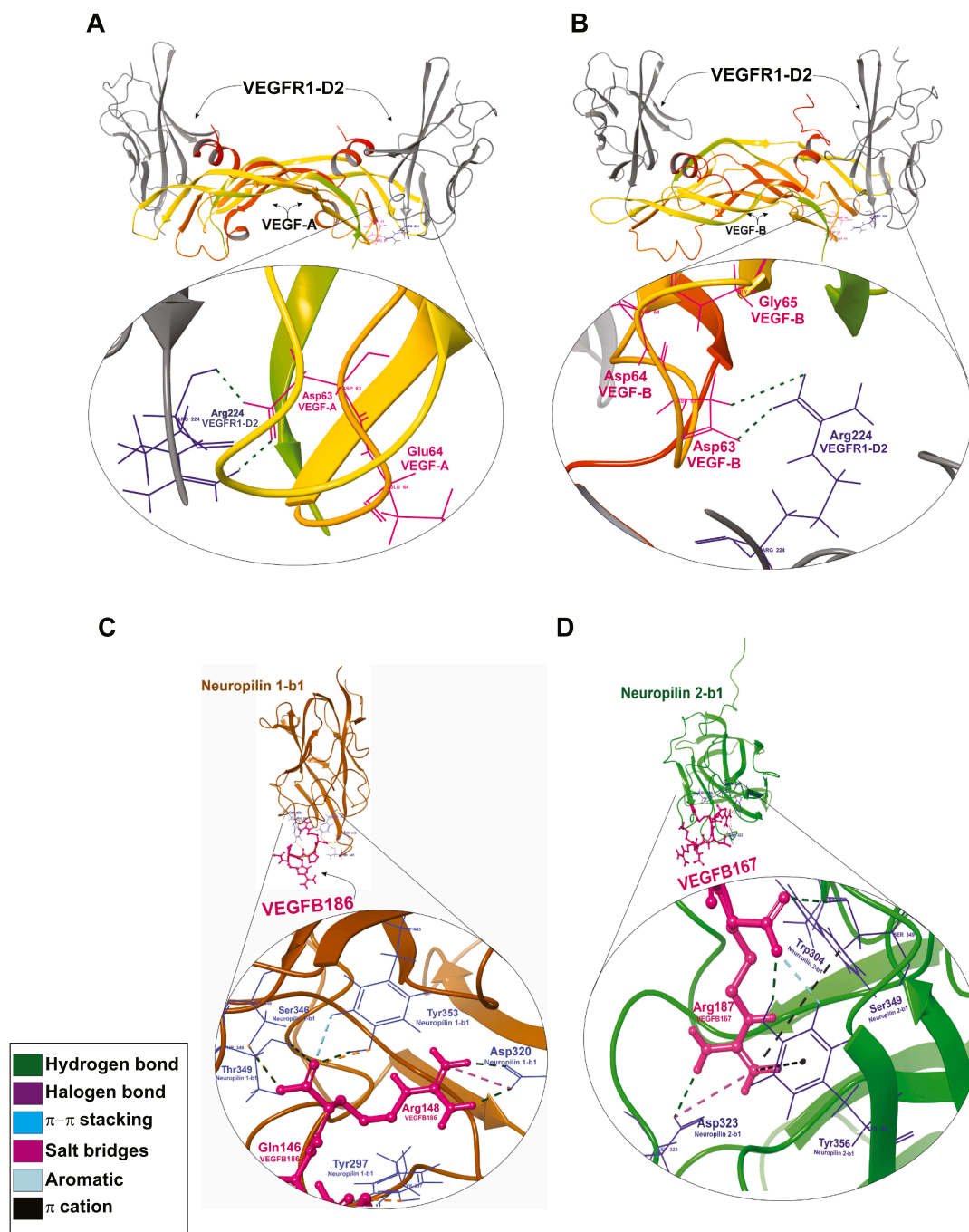


**Fig. 2.** Binding interfaces of VEGF-A and VEGF-B with VEGFR1-D2 and structural interactions of VEGF-B peptides with NRP1 and NRP2. A. Structural image of the VEGF-A/VEGFR1-D2 complex (PDB ID: 1FLT). The zoomed-in view highlights the critical interaction between Asp63 of VEGF-A and Arg224 of VEGFR1-D2. B. Crystal structure of VEGF-B in complex with VEGFR1-D2 (PDB ID: 2XAC). The zoomed-in view highlights the critical interaction between Asp63 of VEGF-B and Arg224 of VEGFR1-D2. C. The VEGF-B186 C-terminus in complex with the NRP1-b1 domain (PDB ID: 6TKK). Key residues such as Arg148 and Gln146 of VEGF-B186 are shown interacting with Asp320, Tyr297, and other residues in the NRP1 binding pocket. D. The VEGF-B167 C-terminus in complex with the NRP2-b1 domain (PDB ID: 6TDB). Arg187 of VEGF-B167 forms salt bridges with Asp323 on NRP2-b1, stabilized by surrounding aromatic residues like Trp304 and Tyr356.

Analysis of VEGF-B mRNA in human tissues from three transcriptomic databases (HPA, GTEx, and FANTOM5) revealed high expression of VEGF-B in adipose tissues, skeletal muscle, heart muscle, and breast (Fig. 3A) [54,55]. These tissues also exhibit high expression of VEGFR1 and NRP1. Single-cell atlases (HCL) show broad but scattered VEGF-B expression, whereas VEGFR1/NRP1 are enriched in EC-rich tissues; notable enrichment occurs in astrocytes and select fetal cell types (Fig. 3B, C) VEGFR1 and NRP1 are not always co-expressed synergistically. VEGFR1 is highly expressed in the placenta and chorionic villus, whereas NRP1 is more expressed in stromal cells and

macrophages. The gene expression pattern of annotated cell types in these two single-cell datasets from multiple tissues consistently showed expression of VEGFR1 and NRP1 in various types of ECs. The expression pattern of VEGFR1 was more restricted to ECs on the current datasets. Intriguingly, in a few cell types, such as astrocytes and intercalated cells, VEGF-B was found to be highly expressed. VEGF-B expression was also detected in fibroblast cells, macrophages, and some fetal cells, such as fetal endocrine cells, fetal fibroblast cells, and fetal enterocytes.

In conclusion, VEGF-B exhibits distinct expression profiles across tissues and cell types, prominently in metabolically active tissues such as

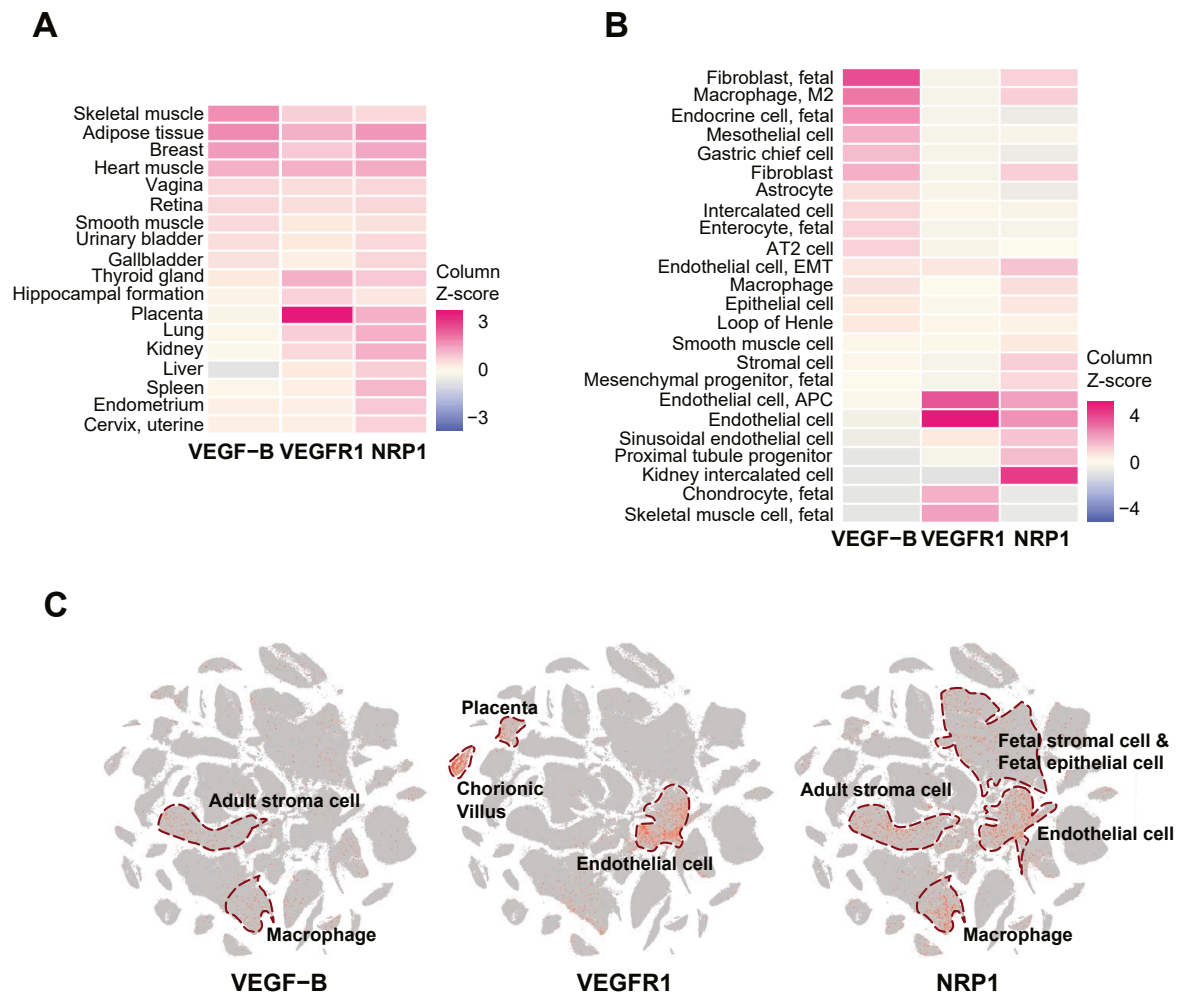


**Fig. 3.** Expression profile of VEGF-B and its receptors, VEGFR1 and NRP1. A. Heatmap displaying the levels of VEGF-B, VEGFR1, and NRP1 mRNA in human tissues that exhibit high expression of these genes. The expression data were obtained from the Human Protein Atlas. B. Heatmap illustrating the gene expression of VEGF-B and its receptors in selected human adult/fetal cell types/subtypes known for their high expression of these genes. The data were extracted from the single-cell Human Cell Landscape (scHCL) available at <http://bis.zju.edu.cn/HCL>. C. The spatial expression patterns of VEGF-B, VEGFR1, and NRP1 in a human tissue section. VEGF-B (left panel) is expressed in adult stroma cells and macrophages. VEGFR1 (middle panel) is expressed in the chorionic villus, placenta, and endothelial cells. NRP1 (right panel) shows expression in adult stroma cells, macrophages, fetal stromal and epithelial cells, and endothelial cells. Gray areas represent the tissue background. This spatial mapping helps in understanding the specific roles and interactions of these markers within the tissue context. The gene expression profiles, and tissue annotations are acquired from single-cell Human Cell Landscape (scHCL, <http://bis.zju.edu.cn/HCL>).

heart, muscle, adipose, kidney, and brain. VEGF-B expression remains stable, unaffected by oxygen or common signaling stimuli; however, exceptions such as hypoxia-induced expression in mouse retina indicate tissue-specific regulation. Furthermore, single-cell analyses show broad, yet dispersed VEGF-B expression compared with endothelial-specific VEGFR1 and NRP1, highlighting notable species differences and underscoring its complex regulatory mechanisms.

### 3. VEGF-B in metabolic disorders

#### 3.1. Fatty acid transport, glucose homeostasis, and insulin resistance

VEGF-B acts as a key regulator of vascular–metabolic coupling, directing endothelial fatty-acid (FA) transport to oxidative tissues such as heart, skeletal muscle, and brown adipose tissue (BAT). Unlike VEGF-A, which primarily promotes angiogenesis, VEGF-B aligns FA delivery with oxidative demand to sustain mitochondrial ATP production [56]. Its expression is co-induced with mitochondrial genes through PGC1 $\alpha$  and ERR $\alpha$  [57], particularly in tissues relying on FA oxidation (Fig. 4A). Mechanistically, VEGF-B binds VEGFR1 and NRP1 on ECs, activating

PI3K/AKT–mTORC1 signaling to upregulate FATP3/4 and trafficking mediators such as calyntenin-1 and RAB proteins [56,58]. In blood endothelial cells, VEGF-B/VEGFR1 signaling upregulates FATP3 and FATP4 to promote long-chain fatty acid (LCFA) uptake across the vascular barrier, thereby maintaining energy balance and facilitating metabolic exchange with surrounding tissues. Furthermore, inhibition of mTORC1 or endothelial RAPTOR diminishes tumor lipid accumulation and improves cytotoxic T cell infiltration, showing how VEGF-B–driven nutrient flux can create an immunosuppressive niche [58].

Loss-of-function studies in *Vegfb* knockout (KO) mice demonstrate that diminished VEGF-B/VEGFR1 signaling reduces endothelial LCFA uptake by over 50 %. This reduction redirects circulating lipids toward white adipose tissue (WAT) for storage [56,59]. Notably, this lipid redistribution may occur independently of VEGF-B, potentially through an alternative pathway involving ANGPT2,  $\alpha 5\beta 1$  integrin, CD36, and FATP3, which collectively enhance FA uptake in WAT [60]. Although this transiently improves glucose tolerance, it compromises oxidative endurance [61,62]. Conversely, *Vegfb* overexpression increases FA uptake but can cause lipotoxicity when excessive [63]. Moreover, in skeletal muscle (Fig. 4B), VEGF-B promotes mitochondrial FA oxidation

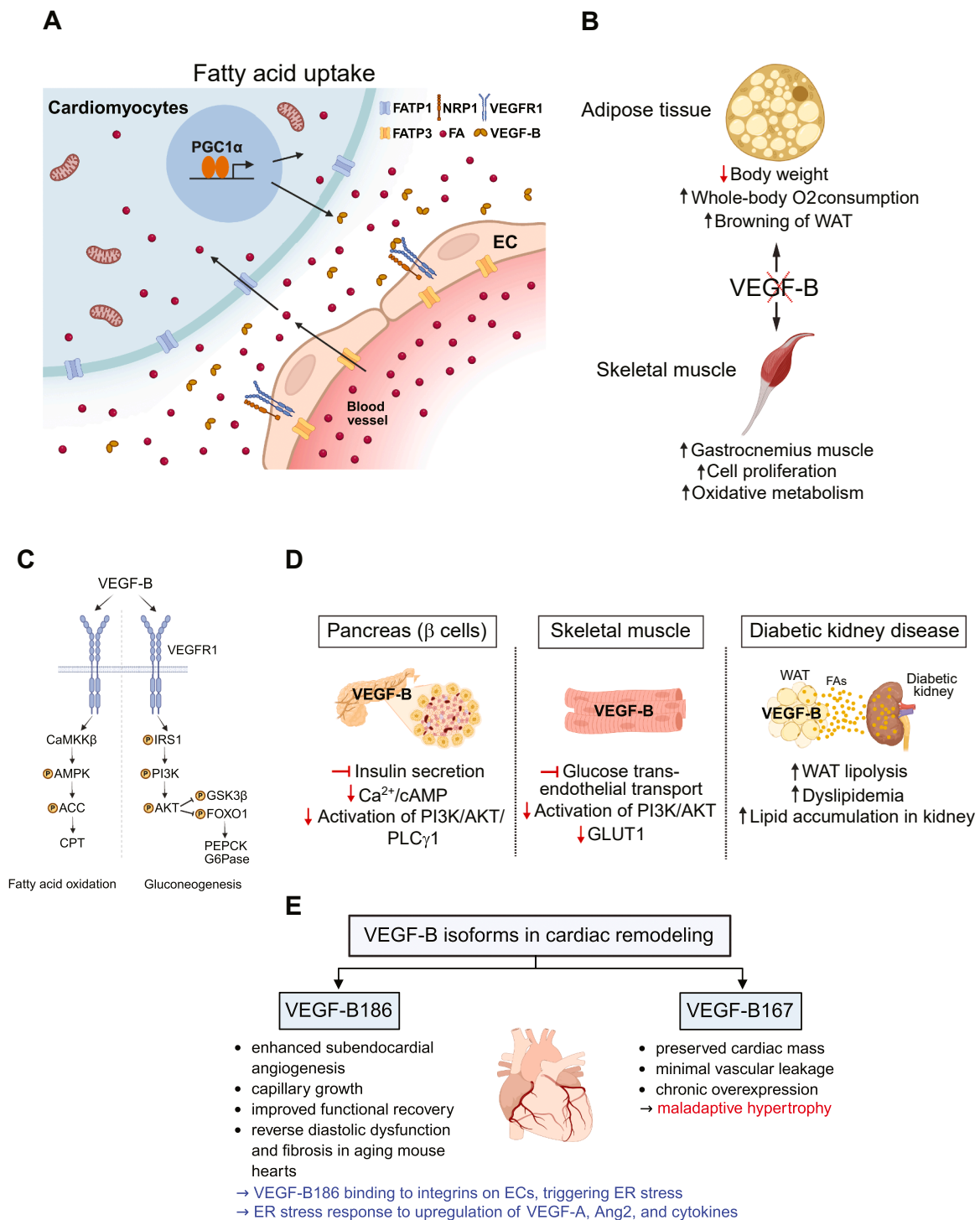


**Fig. 4.** Multifaceted roles of VEGF-B in lipid metabolism and disease. **A.** Schematic of endothelial cell-mediated FA uptake. VEGF-B signaling through VEGFR1/NRP1 induces FATP3 on the endothelial membrane, promoting FA transfer to adjacent cardiac cells. **B.** VEGF-B inhibition is associated with skeletal-muscle metabolic improvement, WAT browning, and lower body weight. **C.** VEGF-B/VEGFR1 signaling regulates FA oxidation (CaMKK $\beta$ -AMPK-ACC-CPT) and gluconeogenesis (IRS1-PI3K/AKT-FOXO1/GSK3 $\beta$ -PEPCK/G6Pase). **D.** VEGF-B reduces insulin secretion, alters Ca<sup>2+</sup>/cAMP signaling and downregulates PI3K/AKT/PLC $\gamma$ 1 activation in  $\beta$  cells. In muscle, VEGF-B decreases glucose trans-endothelial transport and GLUT1 expression. In diabetic kidney disease, VEGF-B increases WAT lipolysis, promotes dyslipidemia, and enhances lipid accumulation in the kidney. **E.** Isoform-specific functions in cardiac remodeling. VEGF-B186 (diffusible) promotes angiogenesis and metabolic recovery; VEGF-B167 (matrix-bound) maintains local trophic signaling. VEGF-B186 promotes enhanced subendocardial capillary growth and improved functional recovery with reduced fibrosis in aging mouse hearts. VEGF-B167 preserves cardiac mass but induces vascular leakage under chronic overload and maladaptive hypertrophy. Abbreviations: FA, fatty acid; WAT, white adipose tissue; VEGF-B, vascular endothelial growth factor B; FATP, fatty acid transport protein; NRP1, neuropilin-1; VEGFR1, vascular endothelial growth factor receptor 1; PGC1 $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  coactivator 1- $\alpha$ ; CaMKK $\beta$ , calcium/calmodulin-dependent protein kinase kinase  $\beta$ ; AMPK, AMP-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B. Created in BioRender.com.

and reduces glycolytic dependence [56,61,64] but in catch-up-growth models, epigenetic upregulation of *Vegfb* (H3K9me1, H3K14ac, H3K18ac) drives FA overload, insulin resistance, and lipid deposition [65].

VEGF-B also integrates adipose–muscle signaling and thermogenesis. AAV-mediated suppression of VEGF-B/VEGFR1 promotes WAT browning, oxygen consumption, and beige-cell formation [66]. VEGF-B knockdown increases gastrocnemius mass (Fig. 4B) but impairs differentiation, emphasizing its fine-tuned role in muscle development. Through an adipocyte–macrophage axis, VEGF-B preserves norepinephrine levels by limiting p38 MAPK-dependent SLC6A2 and MAOA signaling during cold or  $\beta$ 3-adrenergic stimulation [67]. Its expression rises with exercise-mimetic stimulation and declines under TNF $\alpha$ -driven inflammation [68]. In combination therapy, VEGF-B plus myostatin-propeptide gene delivery enhances muscle hypertrophy and capillary density via IGF and agrin-YAP pathways [69], highlighting potential for muscle-wasting and metabolic disorders.

### 3.2. Roles in NAFLD, diabetes, and renal lipotoxicity

VEGF-B-mediated endothelial FA transport extends to systemic metabolism, affecting the liver, pancreas, muscle, and kidney. In non-alcoholic fatty-liver disease (NAFLD), circulating VEGF-B correlates with insulin resistance and hepatic steatosis [70–72]. By promoting WAT lipolysis and endothelial FATP3/4 expression, VEGF-B enhances free FA flux to the liver [71], whereas its role in lipoprotein metabolism or atherosclerosis remains unestablished. In high-fat-diet models, *Vegfb* deletion or neutralization reduces hepatic lipid accumulation, improves insulin sensitivity, and suppresses inflammation [71]. However, human data remain limited to correlative findings that have not yet established causality. Conversely, recombinant or AAV-delivered VEGF-B has been reported to activate hepatic AMPK and PI3K/AKT signaling to enhance FA oxidation (Fig. 4C), glycogen synthesis, and suppression of gluconeogenic enzymes (PEPCK, G6Pase), although the biological activity of the VEGF-B preparations used in these studies were not been fully validated [73,74]. In contrast, *Vegfb* deficiency lowers AMPK activity while increasing SREBP1, ACC1, and FAS expression, worsening hepatic steatosis and insulin resistance [75].

In type 2 diabetes mellitus, VEGF-B affects both pancreatic  $\beta$ -cell and peripheral insulin sensitivity. Plasma VEGF-B inversely correlates with first-phase insulin secretion [76]. In MIN6- $\beta$  cells, exogenous VEGF-B suppresses glucose-stimulated insulin release via PI3K/AKT-mediated  $\text{Ca}^{2+}$  and cAMP inhibition (Fig. 4D), whereas *Vegfb* knockdown restores it [77].  $\beta$ -cell-specific *Vegfb* deletion elevates Ins2 expression but leaves systemic glucose tolerance unchanged under high-fat feeding [77, 78]. *Vegfb* deficiency also increases glucagon secretion and hyperglycemia, while pancreatic *Vegfb* overexpression normalizes glucose tolerance via insulin-mediated glucagon suppression [76,79]. VEGF-B also limits glucose trans-endothelial transport by down-regulating GLUT1 through VEGFR1–PI3K/AKT (Fig. 4D), and its knockdown reverses diet-induced insulin resistance [80]. Collectively, these findings identify VEGF-B as a dual regulator of insulin–glucagon balance critical for metabolic stability. Moreover, VEGF-B further affects renal lipid metabolism in diabetic-kidney disease (DKD). Mesangial VEGF-B expression correlates with renal dysfunction in human DKD biopsies [81]. Adipocyte-specific VEGF-B promotes WAT lipolysis, dyslipidemia, and lipid deposition in kidneys, accelerating disease progression (Fig. 4D), whereas VEGF-B inhibition preserves podocyte insulin sensitivity and mitigates DKD [82].

Overall, VEGF-B maintains metabolic homeostasis but can become pathogenic when overactivated, emphasizing the need for context- and stage-specific therapeutic consideration.

### 4. VEGF-B in cardiac functions

Although *Vegfb* deletion does not affect embryonic development or

postnatal survival, it reveals critical functions under stress [83,84]. In coronary-occlusion models, *Vegfb* KO mice exhibit smaller hearts, reduced vascularization, and poor recovery, emphasizing VEGF-B's role in maintaining myocardial integrity during ischemia [83,84].

Isoform-specific gene therapy demonstrates distinct outcomes (Fig. 4E). AAV-VEGF-B186 promotes subendocardial angiogenesis, capillary growth, and myocardial repair without excessive leakage, whereas AAV-VEGF-B167 preserves cardiac mass more effectively than VEGF-A165 but induces maladaptive hypertrophy, ceramide accumulation, mitochondrial dysfunction, and early mortality when chronically expressed [37,63,85,86]. In contrast, Bry *et al.* generated  $\alpha$ -MHC-VEGF-B transgenic mice and rats using a full-length genomic construct that produced both VEGF-B167 and VEGF-B186 isoforms, resulting in combined physiological effects not attributable to a single variant [36], demonstrating that VEGF-B acts as a coronary growth factor that expands large coronary arteries without inducing capillary angiogenesis, vascular leak, or inflammation. Moreover, recent work clarifies these isoform-specific effects. Sultan *et al.* identified an endocardial EC population responsive to paracrine VEGF-B186 [86]. Consequently, this pathway promotes organized vascular regeneration and myocardial repair without aberrant angiogenesis. In contrast, endothelial overexpression of VEGF-B167, as opposed to cardiomyocyte-derived paracrine signaling, results in disorganized vasculature and pathological hypertrophy, suggesting that differences in the spatial or contextual mode of VEGF-B signaling may affect cardiac remodeling outcomes. Clinically, a recent study showed that anthracycline- and anti-HER2-based chemotherapy in breast-cancer patients leads to persistent microvascular endothelial dysfunction characterized by reduced nitric oxide production and diminished VEGF-B expression. Notably, *ex vivo* supplementation with VEGF-B restored vasodilatory function in healthy human arterioles exposed to doxorubicin or trastuzumab, highlighting its potential as a vascular-protective factor against chemotherapy-induced injury [87].

Additionally, in patients with acute myocardial infarction, elevated VEGF-B186 associates with improved collateral growth, limited remodeling, and better prognosis [88]. Furthermore, in aging-heart models, AAV9-VEGF-B186 reverses diastolic impairment, fibrosis, and sympathetic-nerve loss without inducing pathological angiogenesis or inflammation; the mild concentric hypertrophy observed is compensatory and STAT3-dependent [89]. In addition, VEGF-B confers cytoprotection to ECs, pericytes, and smooth-muscle cells via VEGFR1/NRP1-mediated PI3K/AKT and MAPK/ERK activation [90, 91]. It also engages integrins and matrix components to facilitate migration and remodeling [4,92]. **However, excessive or prolonged delivery particularly of the VEGF-B127 fragment can provoke arrhythmias and cardiomyocyte stress under adrenergic stimulation [86].**

A novel mechanism involves VEGF-B186-driven angiogenesis independent of VEGFR1 and NRP1, mediated by ER-stress signaling and RGD-binding integrins. In VEGFR1 tyrosine kinase-deficient mice (*Flt1*  $tk^{-/-}$ ), both VEGF-B186 and its NRP-binding-deficient variant (R127S) stimulate microvascular growth and EC activation [5]. These effects rely on selective ER-stress activation (BiP, ATF6, IRE1 $\alpha$ , PERK). Furthermore, proteomics identified integrins  $\alpha$ V and  $\alpha$ 5 as new VEGF-B186 receptors initiating this response, while the transcription factor XBP1 links ER stress to increased VEGF-A, ANGPT2, and cytokine expression, defining an integrin–ER-stress axis for VEGF-B-mediated remodeling. This signaling may be protective or detrimental: in diabetic cardiomyopathy, VEGF-B enhances GRP78/PERK-dependent autophagy, yet protection is lost when PERK is blocked or signaling becomes dysregulated [93].

Overall, VEGF-B orchestrates myocardial remodeling through isoform-specific and context-responsive signaling networks. Therapies that emphasize VEGF-B186's reparative profile while limiting VEGF-B167-driven hypertrophic signaling appear most promising.

## 5. Neuroprotective roles of VEGF-B

VEGF-B has emerged as a pivotal neurotrophic factor with broad relevance to neuronal survival across neurodegenerative disorders [15]. Because it exhibits minimal angiogenic activity, VEGF-B represents an attractive target for neuroprotective therapy. Its effects are mediated mainly through VEGFR1 and NRP1, which activate pro-survival PI3K/AKT and ERK1/2 signaling [94]. These cascades inhibit apoptosis and promote neuronal viability under stress. In cultured cortical neurons (Fig. 5A), VEGF-B enhances survival in a dose-dependent manner during hypoxia [90]. In primary spinal motor-neuron cultures, the VEGF-B186 isoform protects against degeneration through VEGFR1-dependent kinase activity without angiogenic effects [95]. This low-permeability profile offers an advantage for CNS indications [90].

VEGF-B also protects neurons in acute ischemic injury (Fig. 5A). In murine middle-cerebral-artery-occlusion models, administration of VEGF-B reduces infarct volume and neuronal loss via VEGFR1/NRP1 signaling [90], supporting its potential in stroke. To date, such neuroprotective effects have been documented only in rodent models; human validation remains lacking. Furthermore, in amyotrophic lateral sclerosis (ALS), VEGF-B186 delays disease progression and preserves spinal motor neurons in SOD1 transgenic rodents [15,95,96]. These effects depend on neuronal VEGFR1 and occur without vascular changes, highlighting a neuron-intrinsic mechanism and a safety advantage over VEGF-A.

In peripheral neuropathies, including diabetic peripheral neuropathy (DPN), VEGF-B maintains neuronal integrity [97]. Deficient mice of *Vegfb* or *Flt1* show retrograde degeneration and dorsal-root-ganglion (DRG) vulnerability to paclitaxel-induced damage, whereas neuron-specific VEGF-B186 overexpression preserves mitochondrial potential and limits apoptosis [98] (Fig. 5A). Consistently, in type 2 diabetes, elevated serum VEGF-B and VEGFR1 up-regulation in peripheral nerves further implicate this pathway in neuropathic injury [99].

In Parkinson's disease (PD), VEGF-B acts as a stress-inducible trophic factor [100]. Rotenone-treated midbrain cultures show up-regulated VEGF-B but unchanged VEGF-A; exogenous VEGF-B improves dopaminergic-neuron survival, suggesting a role in countering neurotoxic stress. Moreover, in Alzheimer's disease (AD), VEGF-B shows cell-type-specific activity (Fig. 5A) with higher microglial/oligodendrocyte expression tracking amyloid burden and inhibitory-neuron expression associating with lower amyloid [96], whereas expression in inhibitory neurons relates to reduced amyloid load, suggesting context-dependent protection. Further study is needed to resolve these divergent effects. Complementarily, in Purkinje-cell-degeneration (PCD) models of childhood cerebellar atrophy, recombinant VEGF-B prevents neuronal loss and restores motor and cognitive functions [101]. These benefits follow an inverted U-shaped dose-response, with moderate dosing optimal and high levels detrimental [102], underscoring the importance of dose optimization.

Collectively, current evidence defines VEGF-B as a multifaceted neurotrophic modulator with therapeutic promise across acute and chronic neurodegenerative settings including stroke, ALS, PD, AD, and cerebellar disorders. By activating VEGFR1/NRP1 pro-survival signaling while avoiding the vascular permeability associated with VEGF-A, VEGF-B offers a safer neuroprotective strategy. Nonetheless, its actions remain context-dependent, as seen in AD cell-type variation and the inverted U-shaped dose curve [102]. Future progress will require identifying precise cellular targets, refining delivery and dosing, and validating VEGF-B-based interventions through well-designed clinical trials.

## 6. Immunometabolic regulation and potential biomarker

VEGF-B, largely unknown in immune regulation until recently, has emerged as a key metabolic and survival factor for T cells and a clinically

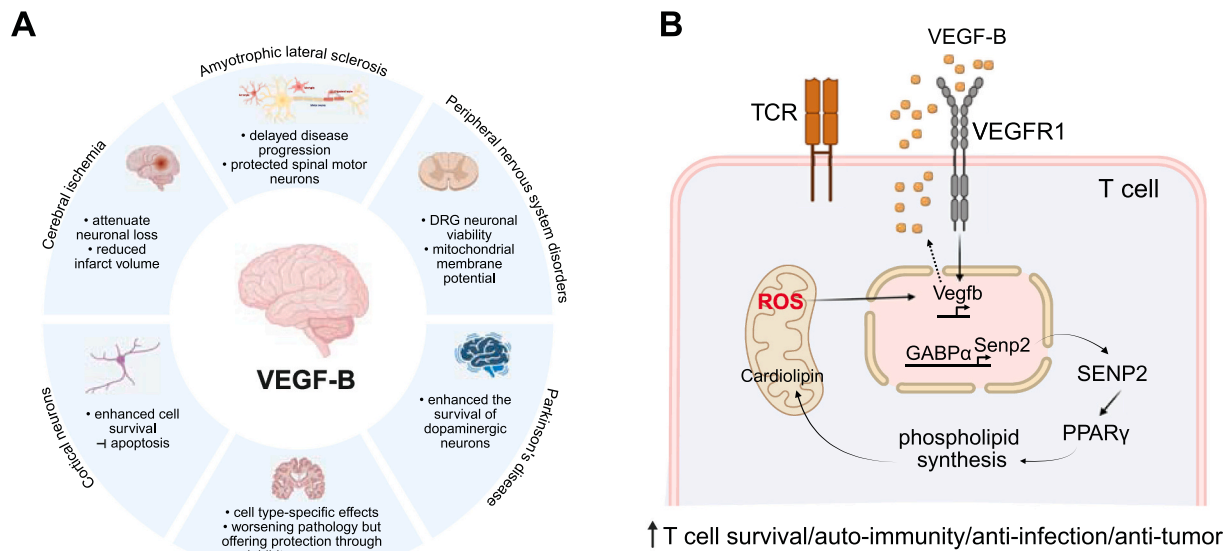
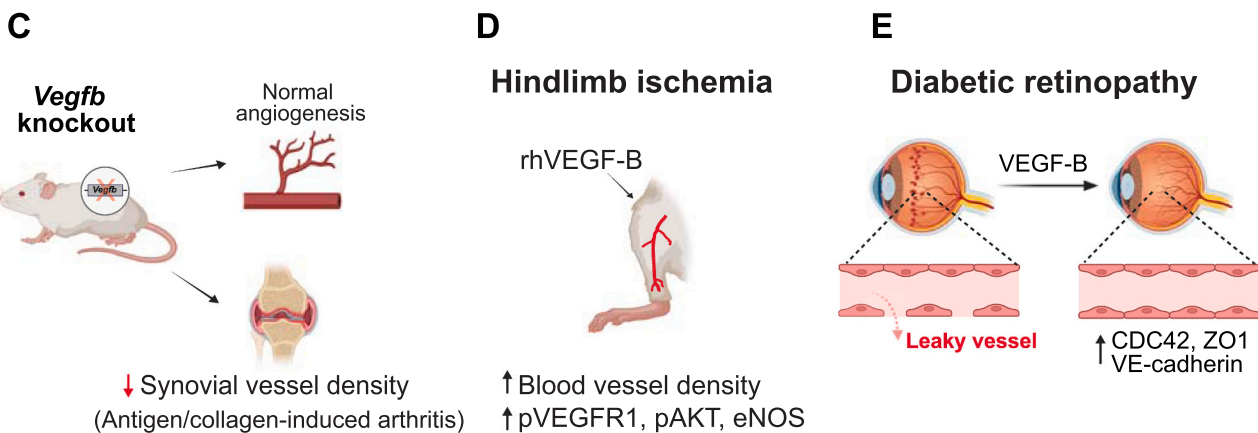
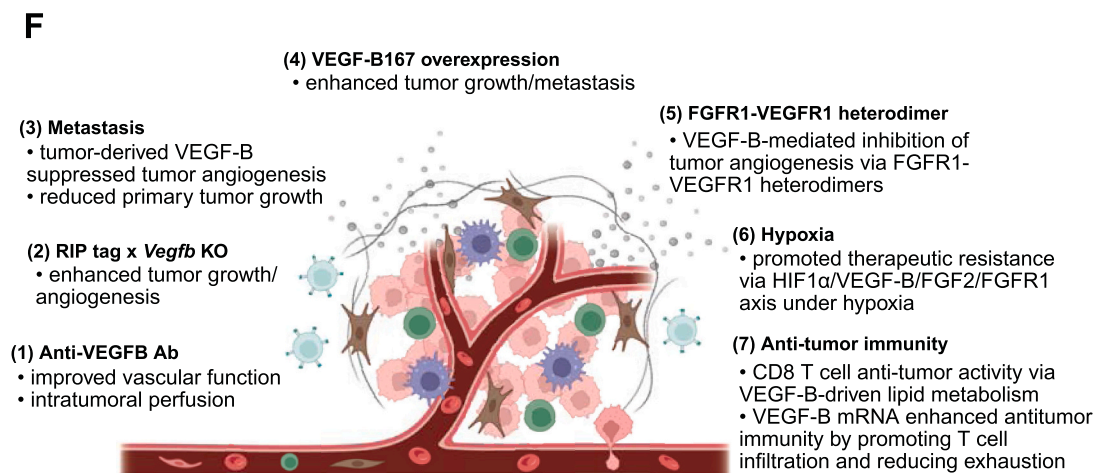
relevant biomarker in cancer immunotherapy. T cell receptor (TCR) stimulation induces VEGF-B expression and secretion in both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, where it functions in an autocrine manner to maintain mitochondrial integrity and support cell survival [103]. This autocrine signaling is initiated by mitochondrial reactive oxygen species (ROS), which serve as a trigger for VEGF-B upregulation during T cell activation. Once secreted, VEGF-B binds to VEGFR1 on the surface of T cells and activates downstream signaling pathways including PI3K and ERK1/2, thereby promoting phospholipid synthesis through the GABP $\alpha$ -SENP2-PPAR $\gamma$  axis (Fig. 5B). This cascade enhances the production of cardiolipin, a key mitochondrial phospholipid required for cristae integrity and oxidative phosphorylation. Disruption of VEGF-B or VEGFR1 signaling results in reduced mitochondrial membrane potential, increased apoptosis, and impaired formation of memory T cells. Supplementation with cardiolipin or activation of PPAR $\gamma$  restores mitochondrial function and rescues T cell viability, indicating that VEGF-B is indispensable for sustaining the metabolic fitness of activated T cells and their long-term immune function.

Parallel clinical findings have demonstrated that VEGF-B may also predict overall survival in immune checkpoint blockade therapy [6]. In patients with advanced non-small cell lung cancer (NSCLC) treated with pembrolizumab, higher post-treatment serum VEGF-B levels were independently associated with poor overall, but not disease-specific, survival. While VEGF-B levels declined following therapy, higher post-treatment levels correlated with worse prognosis, irrespective of tumor PD-L1 expression or initial treatment response. Notably, VEGF-B also showed diagnostic potential in distinguishing NSCLC patients from healthy controls, supporting its utility as a blood-based biomarker, suggesting that VEGF-B may reflect broader systemic or tumor-intrinsic processes that affect therapeutic outcomes in cancer immunotherapy. Together, this duality underscores the need to further investigate the temporal and cellular contexts of VEGF-B signaling in immune responses and its potential as both a therapeutic target and biomarker across disease states.

## 7. VEGF-B in vascular and tumor biology

VEGF-B shows context-dependent actions in vascular biology, with far weaker vessel-forming capacity than VEGF-A. Because it does not cause vascular leakage, it is considered a promising target for revascularization therapies that avoid edema-related side effects [36,40,83]. Developmental studies in *Vegfb* KO mice reveal no angiogenic defects under normal or stress conditions (Fig. 5C), indicating that VEGF-B is not required for embryonic vessel formation [83,84]. Yet endothelial overexpression enhances postnatal vascular growth and accelerates wound healing through VEGFR1 signaling [104]. Consistent with the weak kinase activity of VEGFR1, VEGF-B induces only limited endothelial proliferation [28], likely by occupying VEGFR1 and indirectly facilitating VEGF-A/VEGFR2 signaling. Although VEGFR1/VEGFR2 heterodimer formation is theoretically supported by computational studies [105], its physiological occurrence appears to be primarily driven by ligands such as VEGF-A [106,107].

By contrast, under pathological conditions, VEGF-B can either promote or suppress angiogenesis. In arthritis models (Fig. 5C), *Vegfb* deletion reduces synovial vessel density, indicating a pro-angiogenic role [108]. Moreover, in ischemic tissues (Fig. 5D), VEGF-B enhances vascular density through VEGFR1-AKT-eNOS signaling [109]. AAV-mediated expression of VEGF-B isoforms increases retinal and choroidal neovascularization without inflammation, although VEGF-B186 can disturb the blood-retinal barrier because of its higher diffusibility [110]. Conversely, in diabetic retinopathy, VEGF-B expression declines during early disease, contributing to vascular leakage (Fig. 5E). Mechanistically, VEGF-B stabilizes endothelial junctions by up-regulating CDC42, ZO-1, and VE-cadherin, thereby reducing hyperglycemia-induced leakage without stimulating angiogenesis [111]. Additionally, in hypoxic lung endothelium, VEGF-B can suppress



(caption on next page)

**Fig. 5.** Diverse roles of VEGF-B in neuronal protection, immunometabolic, and tumor progression. A. VEGF-B regulates across neurological disease models, including cerebral ischemia (attenuated neuronal loss, reduced infarct volume), amyotrophic lateral sclerosis (delayed disease progression, motor neuron protection), peripheral nervous system disorders (improved DRG neuron viability and mitochondrial function), Parkinson's disease (enhanced survival of dopaminergic neurons), Alzheimer's disease (cell type-specific effects), and cortical neurons (enhanced survival and reduced apoptosis). B. Mechanism of VEGF-B action in T cell function. VEGF-B binding to VEGFR1, affects GABP $\alpha$  and SENP2 signaling, regulates phospholipid synthesis via PPAR $\gamma$ , and enhances T cell survival, autoimmunity, anti-infection, and anti-tumor responses through modulation of ROS and cardiolipin metabolism. C. Effects of *Vegfb* KO on synovial angiogenesis in mice, demonstrating reduced synovial vessel density in antigen/collagen-induced arthritis despite normal systemic angiogenesis. D. Administration of recombinant human VEGF-B (rhVEGF-B) in hindlimb ischemia increases blood vessel density and activation of molecular pathways (pVEGFR1, pAKT, eNOS). E. Role of VEGF-B in diabetic retinopathy. VEGF-B exacerbates vascular leakage in the retina, involving CDC42, ZO1, and VE-cadherin signaling, contributing to disease pathology. F. Summary of VEGF-B functions in cancer models. Anti-VEGF-B antibodies enhance vascular function and intratumoral perfusion, while *Vegfb* knockout in RIP1-Tag2 models increases angiogenesis and tumor growth. Conversely, tumor-derived VEGF-B suppresses angiogenesis and limits tumor expansion. Overexpression of VEGF-B167 promotes metastasis. Furthermore, FGFR1-VEGFR1 heterodimerization inhibits angiogenesis through coordinated VEGF-B, FGF2, and hypoxia signaling. VEGF-B-driven lipid metabolism in hypoxic tumors contributes to therapeutic resistance. Finally, VEGF-B mRNA has been reported to enhance CD8 $^{+}$  T-cell-mediated anti-tumor immunity by preventing T cell exhaustion. Abbreviations: RIP, rat insulin promoter; DRG, dorsal root ganglion; ROS, reactive oxygen species; GABP $\alpha$ , GA-binding protein alpha; SENP2, SUMO-specific protease 2; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; CDC42, cell division cycle 42; ZO1, zonula occludens-1; eNOS, endothelial nitric oxide synthase; FGFR1, fibroblast growth factor receptor 1; HIF1 $\alpha$ , hypoxia-inducible factor 1-alpha. Created in Bio-Rendender.com.

VEGF-A-driven migration and wound closure, an effect reversible by PlGF, suggesting ligand competition [112]. It also acts as a negative regulator of  $\beta$ 1 integrin activation; loss of VEGF-B promotes focal adhesion formation and cytoskeletal remodeling via SHANK3 and MICAL3 phosphorylation, whereas exogenous VEGF-B reverses these changes [4]. Moreover, interactions with ECM proteins further modulate its activity, for example, tenascin-X binds VEGF-B through the FNIII13–25 region and N-terminal 115 amino acids, enhancing VEGFR1 phosphorylation and EC proliferation [113]. Collectively, these findings suggest that isoform and context difference underlie the variable angiogenic responses to VEGF-B.

In addition to VEGFR1, VEGF-B167 interacts with FGFR1 to form VEGFR1-FGFR1 complexes that compete with FGF2 and attenuate FGF2-induced ERK1/2 signaling, thereby limiting endothelial migration, sprouting, and tumor angiogenesis [2]. This mechanism likely depends on local ligand concentration, receptor ratios, and co-receptors such as NRP1. Because VEGFR1 has low kinase activity, VEGFR1-FGFR1 heterodimers may act in a dominant-negative fashion to restrain FGF2 signaling. Moreover, synthetic peptides mimicking VEGF-B loop regions similarly inhibit VEGF-A/VEGFR2-mediated angiogenesis and suppress tumor growth *in vivo* [114–116].

VEGF-B regulates angiogenesis, vessel remodeling, immune balance, metabolism, and metastasis, often independently of VEGF-A. It is broadly expressed in malignant and benign tumors, in both cancer cells and associated vasculature [31,117]. In breast and colorectal cancer, antibody blockade improves vascular function, enhances perfusion, and sensitizes tumors to chemotherapy without excessive vessel pruning [117] (Fig. 5F). Conversely, in a mouse model of pancreatic neuroendocrine tumors, *Vegfb* deletion enhances angiogenesis and growth, whereas overexpression inhibits both, suggesting an anti-angiogenic role [118].

VEGF-B may also promote metastasis while reducing primary tumor angiogenesis [119]. It remodels tumor vessels into leaky, hypoxic structures with poor pericyte coverage, facilitating dissemination and M2-like macrophage polarization through VEGFR1/STAT3 signaling [120]. This pathway suppresses inflammatory cytokines, inhibits apoptosis, and favors tumor progression, whereas *Vegfb* loss skews macrophages toward the M1 phenotype, enhancing tumor control. At the signaling level, cross-talk with FGFR1 further modifies angiogenic and therapeutic responses. Notably, in ovarian cancer, a HIF1 $\alpha$ /VEGF-B/FGF2/FGFR1 cascade (Fig. 5F) promotes gemcitabine resistance, reversible by FGFR1 silencing [121]. Moreover, epigenetic mechanisms such as promoter methylation and non-coding RNAs also regulate VEGF-B expression and impact tumor proliferation, migration, and immune evasion [122]. In addition, isoform differences may be critical: VEGF-B186 is frequently upregulated in aggressive tumors, whereas VEGF-B167 mRNA appears more abundant in normal tissues [29,31], although this pattern is solely supported on mRNA data rather

than isoform-specific protein level analyses. This apparent duality - anti-angiogenic in some contexts yet pro-metastatic in others - illustrates the context-dependency of VEGF-B signaling and underscores the need for systematic isoform-specific and dose-controlled investigations in both mouse and human systems.

VEGF-B also shapes the immune tumor microenvironment. Loss of *Vegfb* or *Flt1* reduces T-cell persistence and memory formation. VEGF-B mRNA delivery via lipid nanoparticles (LNP) increases CD4 $^{+}$ /CD8 $^{+}$  infiltration, enhances CD8 $^{+}$  cytotoxicity, and lowers PD-1 expression, reducing T-cell exhaustion [123]. Combined with PD-1 blockade, this approach can induce complete regression in metastatic lung cancer models by enhancing T cell activation and antitumor responsiveness (Fig. 5F). The above mechanisms are consolidated in Fig. 5F, which illustrates how VEGF-B modulates angiogenesis, metastasis, immunometabolism, and immune activity across tumor models.

From a therapeutic perspective, VEGF-B targeting should follow a precision-medicine framework. In ischemic heart disease, diabetic microvascular disorders, and chronic inflammation, VEGF-B augmentation may stabilize vasculature and improve perfusion without the leakage linked to VEGF-A. Conversely, in metastatic cancer with high VEGF-B186 and M2 macrophage infiltration, VEGF-B inhibition - alone or combined with immune checkpoint blockade - could restrain metastasis and reprogram the tumor microenvironment. Patient stratification based on VEGF-B isoform levels, receptor profiles, and microenvironmental cues will be essential to harness its vascular-protective and immunostimulatory benefits while minimizing pro-metastatic risk [91, 124,125].

## 8. Therapeutic targeting

Therapeutic modulation of the VEGF pathway has historically focused on VEGF-A. Bevacizumab remains a mainstay in oncology for colorectal, lung, and renal cancers, while ranibizumab and faricimab are established for ocular neovascular disease [9,10,126]. Aflibercept, a VEGFR1/VEGFR2-based decoy receptor that sequesters VEGF-A, VEGF-B, and PlGF, is widely used for ocular neovascular diseases such as age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity, as well as for certain tumor types [9,127]. These agents confirm the feasibility of VEGF inhibition but highlight a limitation: broad suppression may also neutralize VEGF-B's protective roles in metabolism, neuroprotection, and vascular homeostasis.

Accordingly, two complementary therapeutic strategies have emerged: (1) inhibition to restrict excessive endothelial lipid transport, and (2) augmentation to restore oxidative metabolism and vascular support. Blocking VEGF-B-VEGFR1 signaling limits endothelial LCFA transport and lipid accumulation. Ligand-neutralizing antibodies and soluble decoy receptors exemplify this approach. Among them, the anti-VEGF-B antibody CSL346 was evaluated in a phase 2a trial in patients

with type 2 diabetes and DKD. Doses of 8 or 16 mg/kg every four weeks for 12 weeks failed to significantly reduce albuminuria versus placebo and, at the higher dose, increased diastolic pressure and tubular-injury biomarkers (KIM1, MCP1) without clear renal or metabolic benefit [3, 82]. Although the mechanistic rationale remains strong in lipid-overloaded vascular beds, these findings emphasize biological heterogeneity and the need for refined patient selection.

Peptide inhibitors mimicking VEGF-B loop domains offer a more selective alternative, attenuating ERK1/2 and PI3K/AKT/mTOR signaling while reducing off-target interference [114,116]. Conversely, in conditions characterized by inadequate oxidative substrate supply such as myocardial ischemia or impaired thermogenic adipose activity VEGF-B augmentation can be beneficial. Gene-transfer studies show that AAV-mediated *Vegfb* expression enhances mitochondrial efficiency and FA oxidation in target tissues, although effects are strongly dose- and tissue-dependent [85,128]. Emerging mRNA platforms in LNP extend this approach by enabling transient, adjustable expression with isoform flexibility. Additionally, in tumor models, VEGF-B mRNA increased CD4<sup>+</sup>/CD8<sup>+</sup> T cell infiltration, reduced PD-1 expression, and improved metabolic fitness, yielding durable tumor control when combined with PD-1 blockade [123]. Conversely, cardiac data favor VEGF-B186 for reparative angiogenesis and flag uncontrolled VEGF-B167 for hypertrophy [85,86].

Combining modalities may further optimize outcomes. Pairing VEGF-B inhibition with agents that stimulate mitochondrial FA oxidation can prevent lipid diversion to non-target tissues, whereas coupling VEGF-B augmentation with angiogenic or mitochondrial-biogenesis stimuli enhances oxidative capacity in muscle and BAT while minimizing lipotoxicity. In diabetic models, co-delivery of VEGF-B with myostatin inhibitors restored capillary density, improved myofiber regeneration, and enhanced strength through IGF- and agrin-YAP-linked vascular–myogenic signaling, supporting their potential for therapeutic muscle regeneration [69].

Ultimately, the clinical success of VEGF-B–targeted therapy will rely on precision implementation guided by validated biomarkers. Integrating isoform and receptor profiling with indicators of endothelial FA transport, imaging of organ lipid content, and disease-stage assessment can refine therapeutic decisions. Such a framework would enable appropriate selection between VEGF-B inhibition and augmentation, inform isoform choice, and allow dynamic adjustment of delivery. This precision strategy should make it possible to capture the vascular-metabolic benefits of VEGF-B while minimizing disruption of its physiological homeostatic roles.

## 9. Conclusion and future perspectives

Advances in VEGF-B biology over the past decade have reframed it from a relatively minor member of the VEGF family into a multifunctional regulator at the crossroads of vascular, metabolic, neural, and immune system. This broadened perspective has opened new therapeutic horizons while also exposing the complexity of safely manipulating the pathway in disease.

### 9.1. Mechanistic and systems-level integration

Recent studies reveal that VEGF-B interacts not only with VEGFR1 and NRP1 but also with non-canonical partners such as FGFR1 and integrins, establishing a multilayered receptor network that coordinates

endothelial metabolism, stress adaptation, and inter-organ communication [2,4,5,10]. Comprehensive mapping of these receptor complexes using structural and proteomic approaches will be essential to clarify how VEGF-B integrates signaling across vascular, neural, and immune compartments.

Future research should define how VEGF-B regulates lipid trafficking, mitochondrial homeostasis, and redox balance under physiological and pathological conditions. Integrating transcriptomic, proteomic, and lipidomic datasets with single-cell and spatial profiling will help identify tissue- and stage-specific signaling logic. Understanding how nutritional state, hypoxia, or inflammation modulates VEGF-B transcription and splicing will further explain its tissue-restricted actions that diverge from VEGF-A's classical angiogenic profile [56,57].

Furthermore, to complement these mechanistic studies, systems-biology approaches will be valuable for capturing the complex roles of VEGF-B across tissues. Computational models integrating receptor-binding kinetics, endothelial FA flux, and hemodynamic parameters may help predict pharmacodynamic outcomes under different metabolic conditions. Machine-learning analyses based on VEGF-B expression and lipidomic data could identify biomarkers and guide rational therapy design. AI-driven simulations may also help evaluate off-target or adaptive responses, thereby improving translational prediction and safety assessment [58].

### 9.2. Precision therapeutics and patient stratification

The clinical failure of CSL346 in DKD underscores that context blindness rather than target inadequacy is what truly limits translation success [3]. Dualistic effects of VEGF-B – protective in oxidative tissues but pathogenic in lipid-overloaded states – highlight the need for carefully tailored, patient-specific therapeutic strategies. Accordingly, clinical translation will require stratification by isoform profile, receptor context, and FA-transport activity, as outlined in Section 8.

To support this personalized framework, PET-based VEGF-B tracers and metabolic MRI, together with circulating biomarkers of endothelial integrity and lipid metabolism, could enable real-time response monitoring and dose adjustments. This integrated approach could help identify patient subgroups more likely to benefit from VEGF-B inhibition (e.g., DKD, NAFLD) versus augmentation (e.g., ischemic cardiomyopathy, muscle atrophy) [70,74].

### 9.3. Technological innovation in drug delivery

Emerging nucleic-acid and gene-editing technologies now offer unprecedented spatiotemporal precision in controlling VEGF-B activity. Particularly, LNP-mRNA delivery systems enable transient, organ-specific modulation of VEGF-B signaling, while complementary base-editing tools can correct pathogenic mutations such as p.L10F or p.AA193del [129], as well as loss-of-function frameshift variants (c.385delA, c.385\_386delAA) found in microsatellite instability-high colorectal cancers that truncate VEGF-B and abolish its angiogenic activity [130], with high fidelity and minimal off-target effects. Together, these innovative modalities hold the potential to restore physiological VEGF-B signaling across a range of contexts including congenital vascular disorders, ischemic injury, and degenerative diseases.

Beyond conventional gene therapy, immuno-oncology provides another frontier for VEGF-B modulation. For example, synthetic-biology

frameworks could be engineered so that CAR-T cells express VEGF-B-responsive circuits, activating downstream metabolic effectors (e.g., SENP2) to maintain mitochondrial fitness under nutrient-deprived and oxidative stress conditions. Conversely, CAR-T cells designed to secrete anti-VEGF-B single-chain variable fragments (scFvs) may achieve tumor-localized vascular normalization, mirroring the success of VEGF-A-blocking constructs while minimizing systemic exposure [67,69]. Together, these next-generation strategies exemplify how precise VEGF-B modulation could be integrated into precision immunometabolic therapies, bridging vascular, metabolic, and immune engineering.

#### 9.4. Vascular-metabolic regulation in cancer

In the context of cancer, VEGF-B functions as a metabolic modulator rather than a conventional angiogenic driver. Through this role, it fine-tunes endothelial FA transport and mitochondrial respiration, thereby affecting tumor perfusion, hypoxia tolerance, and immune infiltration. Consequently, normalizing tumor vasculature via VEGF-B may improve drug delivery and immune entry [81].

Beyond its vascular effect, VEGF-B also contributes to maintaining metabolic niches that sustain cancer stem-cell quiescence and therapy resistance. Its regulation of lipid availability and mitochondrial dynamics warrants systematic investigation to uncover metabolic vulnerabilities that could be exploited to prevent relapse or metastatic outgrowth. Moreover, extending this inquiry beyond cytotoxic T cell metabolism to encompass other immune populations such as regulatory T cells, natural killer cells, and dendritic cells will be critical. Such understanding could inform the design of next-generation vascular-immunometabolic therapies capable of transforming “immune-cold” tumors into treatment-responsive environments [76,79].

#### 9.5. Regenerative applications and emerging therapeutic opportunities

VEGF-B's unique vascular stabilizing properties position it as an attractive candidate for regenerative medicine applications. Future research should explore its therapeutic potential in tissue engineering, where controlled vascularization without excessive leakage remains a critical determinant of successful organ construction. By promoting stable endothelial networks, VEGF-B may facilitate the development of more physiologically relevant vasculature in bioengineered tissues. In addition, the tumor microenvironment provides another instructive model for understanding VEGF-B-mediated vessel remodeling. Particularly, extrinsic physical cues such as biomechanical forces and the ECM composition affect cell signaling and can promote cancer progression and drug resistance [131]. Similarly, the activity of VEGF-B to promote vessel remodeling and maturation without inducing pathological angiogenesis suggests that it could be harnessed for wound healing and tissue repair where excessive scarring remains a major clinical challenge. Further investigation into its interactions with pericytes, smooth muscle cells, and ECM components may uncover strategies for promoting functional rather than merely structural vascular repair, advancing both regenerative and anti-fibrotic therapies.

#### 9.6. Translational challenges

Although VEGF-B-targeted interventions remain in their infancy compared with the extensively studied VEGF-A pathway, several translational challenges must be addressed to realize their therapeutic potential. Early clinical attempts, including an anti-VEGF-B trial in DKD [3], have underscored the complexity of modulating this factor safely and effectively. Current evidence suggests that VEGF-B does not operate through a single systemic therapeutic window; rather, its effects are highly tissue-specific, reflecting its diverse physiological roles. Consequently, the development of strategies enabling precise, targeted delivery will be essential to achieve efficacy while minimizing unintended effects in non-target tissues. At the same time, rigorous long-term safety

assessment remains critical, given VEGF-B's fundamental involvement in vascular and metabolic homeostasis.

Developing reversible VEGF-B modulators such as small molecules could offer greater flexibility than long-lived biologics. These agents would enable adaptive dosing and rapid withdrawal if adverse effects occur. Incorporating advanced delivery technologies, including nanoparticle carriers or tissue-specific ligands, may further enhance control and safety. Furthermore, VEGF-B's therapeutic potential appears broader. Its neuroprotective properties merit investigation in neurodegenerative diseases where vascular and metabolic dysfunctions intersect. Likewise, its effect on immune cell metabolism suggests applications in autoimmune disease, transplantation, and vaccine modulation. Moreover, the link between VEGF-B signaling and aging biology presents an opportunity to counter age-related declines in vascular and metabolic resilience, thereby supporting healthy aging.

From a broader perspective, translating VEGF-B biology into clinical practice will require sustained mechanistic research and continued innovation in delivery technologies that allow precise, context-dependent modulation. A deep understanding of VEGF-B's tissue-specific and condition-dependent functions rather than reliance on oversimplified therapeutic paradigms will be essential to fully harness its therapeutic potential while preserving physiological balance.

#### CRediT authorship contribution statement

**Yonghwan Kim:** Writing – review & editing, Funding acquisition, Conceptualization. **Han-Woong Lee:** Visualization, Validation. **Xuri Li:** Writing – review & editing, Validation, Supervision. **Nayoung Oh:** Writing – review & editing. **Anil Kumar:** Writing – review & editing. **Vivek Hamse Kameshwar:** Writing – review & editing. **Eunyoung Jung:** Writing – review & editing. **Jianing Zhang:** Writing – review & editing. **Chunsi Lee:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Myung-Jin Kim:** Writing – review & editing.

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#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Data availability

No data was used for the research described in the article.

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