

Key References

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Overview

The vascular endothelial growth factor receptor (VEGFR) family comprises in humans three endothelial cell (EC) specific tyrosine kinase receptors (VEGFR-1, VEGFR-2 and VEGFR-3). VEGFRs are the major direct mediators of proliferation of blood vascular endothelial cells (BECs) and lymphatic endothelial cells (LECs). Individual VEGFRs become activated by different subsets of the vascular endothelial growth factor (VEGF) family.

VEGFR-2 is the central mediator of the formation (vasculogenesis), growth (angiogenesis) and maintenance of blood vessels. It is also a marker for the common precursors of blood and endothelial cells (hemangioblasts). VEGFR-2 continues to be expressed in the differentiated endothelial lineage, but is downregulated by hematopoietic cells. The importance of VEGFR-2 for vasculogenesis and hematopoiesis is seen in knock-out mice which fail to develop both blood islands and blood vessels.

In contrast to VEGFR-2, VEGFR-1 has a more limited scope of action. In fact, it was thought that all functions of VEGF except for its chemoattractive role for monocytes were mediated exclusively by VEGFR-2. VEGFR-2 selective VEGF mutants or viral homologues are fully active EC mitogens, whereas VEGF family members or mutants which bind only to VEGFR-1 largely lack the ability to promote EC growth. Mice lacking the tyrosine kinase domain of VEGFR-1 are normal; only the VEGF-induced migration of their macrophages is reduced in vitro. However, complete ablation of VEGFR-1 results in embryonic lethality because increased endothelial precursor proliferation leads to a disorganized vasculature. Based on these results, VEGFR-1 was regarded as a decoy receptor with negligible signaling properties. However, recent reports indicate that there is a more complex interplay between VEGFR-1

and VEGFR-2 including heterodimerization in pathological angiogenesis.

In early embryogenesis all three VEGFRs are expressed in endothelial cells. Concomitantly with the development of the lymphatic vessels VEGFR-3 becomes restricted to the lymphatic endothelium. While the ligand binding characteristics of VEGFR-1 and VEGFR-2 are conserved between humans and mice, VEGFR-3 shows more interspecies variability: in humans both VEGFR-3 ligands (VEGF-C and VEGF-D) are also capable of activating VEGFR-2 and are therefore potentially angiogenic, whereas mouse VEGF-D can only activate VEGFR-3. Moreover, in higher primates a retroviral insertion into the VEGFR-3 gene has led to the emergence of two splice isoforms, which differ in their signaling properties.

Of the seven extracellular Ig-like domains of VEGFRs, the three N-terminal ones are responsible for ligand binding; further deletion of at least one domain is tolerated without significant loss of affinity. The functions of the remaining extracellular domains are less well defined; however a duplication event within these domains marks the evolutionary segregation between the VEGF and the PDGF/CSF-1/SCF receptor families.

Due to the central role of endothelial cells in both cardiovascular and neoplastic disease VEGFRs have been used as targets for both pro- and antiangiogenic therapy. Proangiogenic therapy has mostly employed various VEGFs or modified versions thereof to stimulate VEGFR signaling. Antiangiogenic therapy can target VEGFRs at three different levels: 1. Soluble forms of the receptor ("ligand traps") can sequester receptor agonists (a method that nature itself uses to downregulate VEGF signaling), 2. Molecules (antibodies, aptamers, small peptides, dominant negative receptors,

synthetic compounds) can block agonist binding or receptor dimerization, 3. Specific inhibitors can block the tyrosine kinase activity (ATP analogues) or critical transphosphorylation sites (small peptides, nonphosphorylatable peptide analogs). While angiogenesis can also be suppressed using other targets than VEGFRs, VEGFRs seem to be among the most promising drug targets with several compounds in clinical trials.

VEGFR

FAMILY MEMBERS	VEGFR-1	VEGFR-2	VEGFR-3
OTHER NAMES	Flt-1, Fms-like tyrosine Kinase 1	KDR, Flk-1, kinase insert domain containing receptor, fetal liver kinase 1	Flt-4, fms-like tyrosine kinase 4
MOLECULAR WEIGHT/ STRUCTURAL DATA	~180 kDa 1312 aa (VEGFR-1); 661 aa (sVEGFR-1)	200-230 kDa 1337 aa	195 kDa (120+75 ^a ; VEGFR-3s) 1340 aa (VEGFR-3l); 1275 aa (VEGFR-3s)
ISOFORMS	VEGFR-1, sVEGFR-1 (soluble form)	Not known	VEGFR-3l; VEGFR-3s
SPECIES	Presumed ubiquitous in vertebrates, invertebrate homologs exist	Presumed ubiquitous in vertebrates, invertebrate homologs exist	Presumed ubiquitous in vertebrates, invertebrate homologs exist
DOMAIN ORGANIZATION	7 extracellular IgSF domains, single transmembrane domain, split intracellular tyrosine kinase domain	7 extracellular IgSF domains, single transmembrane domain, split intracellular tyrosine kinase domain	7 extracellular IgSF domains, single transmembrane domain, split intracellular tyrosine kinase domain
PHOSPHORYLATION SITES	Tyr ⁷⁹⁴ , Tyr ¹¹⁶⁹ , Tyr ¹²¹³ , Tyr ¹²⁴² , Tyr ¹³²⁷ , Tyr ¹³³³	Tyr ⁸⁰¹ , Tyr ⁹⁵¹ , Tyr ¹⁰⁵⁹ , Tyr ¹⁰⁵⁴ , Tyr ¹¹⁷⁵ , Tyr ¹²¹⁴ , Tyr ¹²²³ , Tyr ¹³⁰⁵ (minor), Tyr ¹³⁰⁹ (minor), Tyr ¹³¹⁹ (minor)	Tyr ¹⁰⁶³ , Tyr ¹⁰⁶⁸ , Tyr ¹²³⁰ , Tyr ¹²³¹ , Tyr ¹²⁶⁵ , Tyr ¹³³⁷ , Tyr ¹³⁶³
TISSUE DISTRIBUTION	BECs, Hematopoietic stem cells, monocytes/macrophages, osteoclasts, spermatogenic and Leydig cells	BECs, LECs, hematopoietic stem cells, megakaryocytes	LECs, fenestrated BECs, HEVs, tumor endothelium
SUBCELLULAR LOCALIZATION	Plasma membrane	Plasma membrane	Plasma membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	NRP-1, NRP-2, VEGFR-2	NRP-1, NRP-2, α v β 3 integrin, VE-cadherin, VEGFR-1, VEGFR-3, VRAP, Sck, PLC γ	Shc, Sos, SHP-2, p85, PLC γ , VEGFR-2, Grb2
UPSTREAM ACTIVATORS	VEGF ^{b,g} , PIGF, VEGF-B ^{b,c}	VEGF, VEGF-C ^{d,e} , VEGF-D ^{d,f} , VEGF-E, svVEGF	VEGF-C ^e , VEGF-D ^f
DOWNSTREAM ACTIVATION	NO release, STATs	Erk, Akt/PKB, MAPK, Src, FAK, STATs, NO	Erk, Akt/PKB, MAPK
ACTIVATORS	Not known	Not known	Not known
INHIBITORS ^h	SU5416/semaxinib (S8442), SU6668, SU11657, SU11248, ZD6474, PTK787/ ZK222584/vatalanib, AAL993/ ZK260255, SU10944, CP-547,632	SU5416/semaxinib (S8442), SU6668, SU11657, SU11248, ZD6474, PTK787/ ZK222584/vatalanib, AAL993/ ZK260255, SU10944, CP-547,632	SU5416/semaxinib (S8442), SU6668, SU11657, SU11248, ZD6474, PTK787/ ZK222584/vatalanib, AAL993/ ZK260255, MAZ51 ⁱ
SELECTIVE INHIBITORS	Bevacizumab (VEGF monoclonal antibody, Avastin), VEGF-TRAP (soluble chimeric VEGFR), VGA1102 (ligand binding inhibitor)	Bevacizumab (VEGF monoclonal antibody, Avastin), VEGF-TRAP (soluble chimeric VEGFR), VGA1102 (ligand binding inhibitor)	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known

PHYSIOLOGICAL FUNCTION	Vascular development, vascular permeability, receptor for VEGF, PlGF and VEGF-B	Vascular development, vascular permeability, receptor for VEGF, VEGF-C, VEGF-D, VEGF-E, and svVEGF, critical role in tumor-associated angiogenesis	Receptor for VEGF-C and VEGF-D, lymphangiogenesis, embryonic angiogenesis/vasculogenesis
DISEASE RELEVANCE	Not known	Angiogenesis (or lack thereof) in diabetic retinopathy, psoriasis, rheumatoid arthritis, tumor growth, cardiovascular disease	Tumor metastasis, germ line mutations in some families of type I hereditary lymphedema

Abbreviations

BEC: Blood vascular endothelial cell

CSF-1: Colony-stimulating factor-1

FIGF: c-fos induced growth factor

HEV: High endothelial venules

LEC: Lymphatic endothelial cell

NRP: Neuropilin

PDGF: Platelet-derived growth factor

PlGF: Placenta growth factor

SCF: Scatter factor

svVEGF: Snake venom VEGF

VEGF: Vascular endothelial growth factor

VEGFR: VEGF receptor

VPF: Vascular permeability1 factor (VEGF)

VRF: VEGF-Related factor (VEGF-B)

VRP: VEGF-Related protein (VEGF-C)

FOOTNOTES

a The extracellular domain is cleaved into two polypeptides but remains connected via a disulfide bridge.

b Splice isoforms differ in their ability to bind heparane sulfate proteoglycans, distribution and biological function.

c Also called VRF (VEGF-related Factor)

d High affinity binding requires proteolytic processing.

e Also called VRP or VEGF-2.

f Also called FIGF.

g Also called VEGF-A or VPF.

h Due to the large number of different tyrosine kinases, the specificity of TK inhibitors cannot be tested exhaustively; tyrosine kinases known to be affected are given in brackets; for several inhibitors, differences between assays have been reported (isolated kinase assays versus cell-based assays versus in-vivo assays).

i Inhibits also other not yet identified kinase(s).