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Gene Section
Short Communication

KDR (kinase insert domain receptor)/Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)

Noah Sorrelle, Rolf Brekken

University of Texas Southwestern Medical Center noah.sorrelle@utsouthwestern.edu, rolf.brekken@utsouthwestern.edu

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Abstract

This is a concise review of the KDR/VEGFR2 gene, including expression, function, and implications of VEGFR2 expression in cancer.

Keywords
CD309, Kdr, Flk-1, VEGFR2, Angiogenesis, Vascular Endothelial Growth Factor Receptor 2, Tumor Angiogenesis

Identity

Other names: CD309, Flk1, VEGFR, VEGFR2

HGNC (Hugo): KDR

Location: 4q12

DNA/RNA

Description

The human KDR/VEGFR2 gene was cloned in 1991 and mapped in 1992 (Terman BI et al., 1991, Terman BI et al., 1992). The human gene (Kdr/VEGFR2) maps to human chromosome 4. The mouse gene (Kdr/Vegfr2/Flk-1) was cloned in 1991(Matthews W et al., 1991). The mouse gene (Flk-1/Vegfr2) is located on mouse chromosome 5.

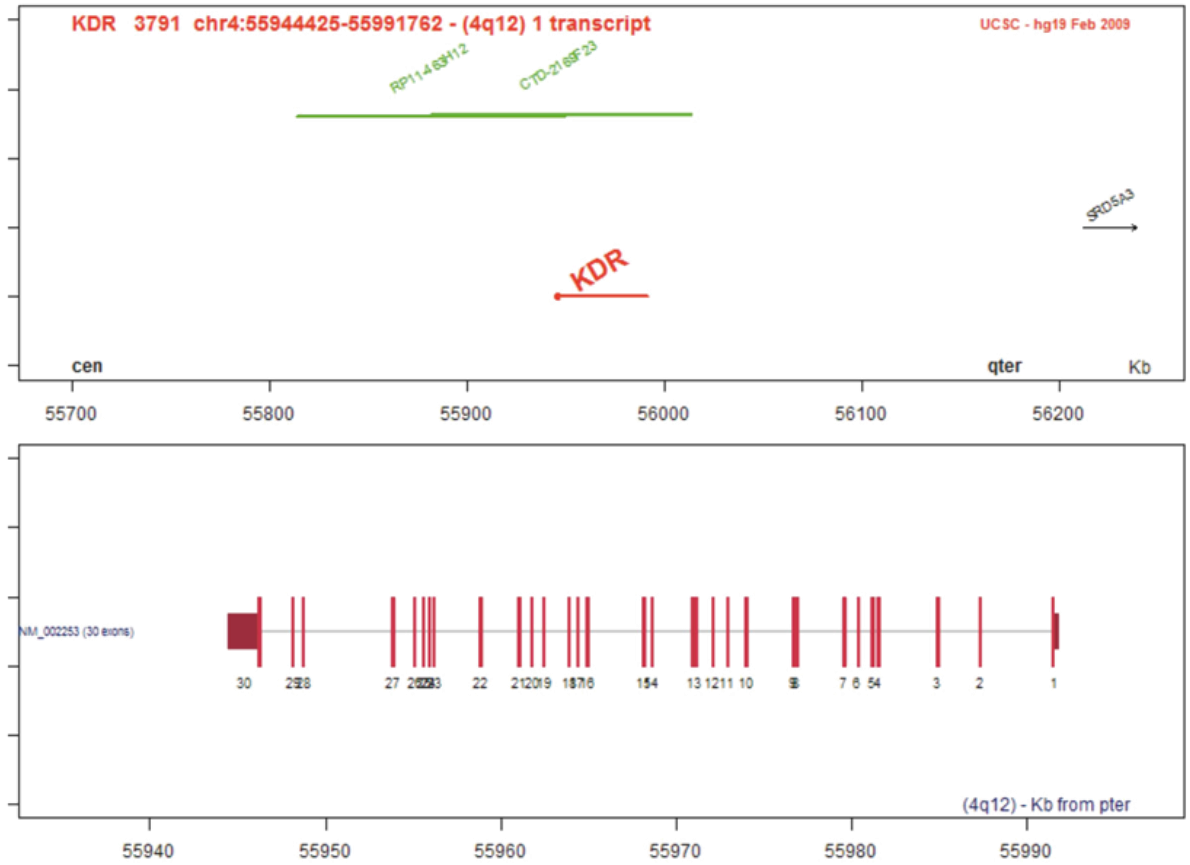
Transcription

In humans, the KDR gene consists of 30 exons, spanning 47,337 bp of DNA on the reverse strand of Chromosome 4. Exon 1 contains 5' UTR and exon 30 contains 3' UTR. All 30 exons contain translated sequence. Three splice variants have been reported in Ensembl. Alternative splicing results in partial retention of intron 13 and an alternative stop codon, encoding a unique C-terminal sequence. Transcription factors regulating Vegfr2 expressing include ETS1 and ETS2 (Elvert G et al., 2003, Kappel A et al., 2000), EPAS1 (hypoxia inducible factor 2 alpha) (Elvert G et al., 2003), ETV2 (ER71/etsrp) (Lee D et al., 2008), and OVOL2 (Kim JY et al., 2014).

Protein

Description

The canonical form of VEGFR2 comprises 1356 amino acids in humans and 1345 in mice. VEGFR2 is translated into a 150 kDa protein. Glycosylation of the extracellular domain results in the mature form at the cell surface which migrates at 230 kDa via western blot.
VEGFR2 is composed of three domains: an extracellular domain, transmembrane domain, and a cytosolic domain. The extracellular domain (including N-terminus) is composed of a signal peptide (aa: 1-20) and seven Ig-like subdomains (aa: 20-764).
The second and third Ig-like subdomains (aa: 141-207, 224-320) facilitate binding of the principal VEGFR2 ligand, VEGFA (Fug G et al., 1998, Shinkai A et al., 1998). This is followed by a single-pass type I transmembrane domain (aa: 765-785).



The intracellular region (aa: 786-1356) consists of a juxtamembrane domain (JMD) and kinase domain. Biochemical analyses by Solowiej et al. (2009) determined that the JMD promotes autophosphorylation of the kinase domain, which is preceded by phosphorylation of the JMD residue, Y801(Solowiej J et al., 2009).

Replacing the VEGFR2 JMD with the VEGFR1 JMD reduces the kinase activity of VEGFR2 in vitro. Conversely, replacing the VEGFR1 JMD with the VEGFR2 JMD increases the kinase activity of VEGFR1(Gille H et al., 2000).

These data suggest that the higher kinase activity of VEGFR2 relative to VEGFR1 may be partially explained by differences in the JMD.

The kinase domain (KD; aa: 834-1162) is split by a 70 amino acid insert (aa: 930-1000).

Phosphorylation of the KD activation loop residues Y1054 and Y1059 is required for kinase activity(Kendall RL et al., 1999).

Additional phosphorylation sites in the intracellular domain facilitate specific interactions of between VEGFR2 and signaling mediators, including PLC gamma, SHB, SCK, SHCA, GRB2, son of sevenless (SOS), and NCK. For further review, see S. Koch and L. Claesson-Welsh, 2012, and Claesson-Welsh and Welsh, 2013 (Claesson-Welsh L et al., 2013, Koch S et al., 2012).

Co-receptors:

Integrins, neuropilin-1, and CD146 promote VEGFR2 activation, and mediate VEGFR2 activities, including endothelial cell migration, permeability, and angiogenesis.

For more information, see Table 1 and Koch and Claesson-Welsh, 2012.

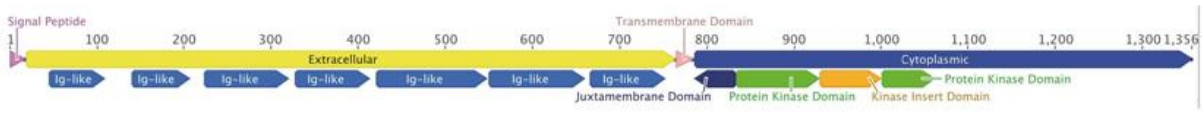


Figure 1: Annotated VEGFR2 Protein. The figure was constructed using Geneious v8.0, (http://www.geneious.com).

Table 1: VEGFR2 Co-receptors

Co-receptor	Association and Function with VEGFR2	Reference(s)
CD146	Interacts with directly with VEGFR2 upon Nrp1-binding of VEGF-A	Jiang et al., 2012
	Mediates endothelial cell migration and microvascular formation	
	Mediates VEGFR2-dependent tumor angiogenesis	
Neuropilin-1	Mediates VEGFR2-dependent permeability	Becker et al., 2005
	Binds VEGF-A, allowing formation of a VEGFR2/ Nrp-1 complex that increases VEGF-A affinity for VEGFR2	Soker et al. 1998, 2002
	Mediates endothelial cell migration	Wang et al., 2003
	Nrp1 knockout mice die at E14 and display severe vascular and nervous system defects	Kawasaki et al, 1999; Gu et al., 2003
alpha V beta 3 Integrin	Mediates in VEGFR2-dependent tumor angiogenesis	Mahabelesh war et al., 2006
	Binds VEGFR2 through its extracellular domain	Borges et al. 2000; Liu et al. 2009
	May be required for full VEGF-dependent phosphorylation of VEGFR2 and angiogenesis	Masson-Gadais et al., 2003; Mahabelesh war et al., 2008

Table 2: Effect of VEGFR2 signalling by cell type

Cell Type	Function of VEGFR2	Reference(s)
B cells	Selective ligation of VEGFR2 in vivo reduces bone marrow pro-B cells and splenic B cells	Huang et al., 2007
Endothelial cells	Promotes survival, proliferation, and migration	Terman et al., 1992a; Waltenberger et al., 1994; Gerber et al., 1998; Jia et al., 2004
Hemangioblasts	Development of hemangioblasts	Shalaby et al., 1995
Myeloid-Derived Suppressor Cells	Promotes MDSC expansion in spleen, which is associated with splenomegaly	Huang et al., 2007
	chemotaxis	Dineen et al., 2008; Roland et al., 2009
Hematopoietic stem cells	Functions in the generation and survival of HSCs	Larrivée et al., 2003
T cells	Selective ligation of VEGFR2 in vivo inhibits thymic T cell differentiation, results in thymic atrophy, and reduces splenic T cells.	Huang et al., 2007
Dendritic cells	VEGF inhibits splenic dendritic cells and dendritic cell maturation through activation of VEGFR2	Gabrilovich et al., 1996, 1998, 1999
	VEGFR2 activation inhibits dendritic cell-driven allogeneic T-cell proliferation in vitro	Huang et al., 2007
	Dendritic cell-speficic deletion of VEGFR2 diminishes the type I interferon response in plasmacytoid dendritic cells	Agudo et al., 2014

Alternative Isoforms:

In 2009, Albuquerque et al. discovered that alternative splicing produces a soluble form of VEGFR2, present in mouse and human cornea (Albuquerque RJ et al., 2009). This isoform results from inclusion of the intron following exon 13 and results in a truncated product which migrates at 75 kDa via western blot. This isoform contains only the extracellular domain of VEGFR2 and a unique C-terminal sequence. Characterization of sVEGFR2 revealed that it may play a role as an endogenous inhibitor of lymphoangiogenesis via antagonizing VEGF-C/VEGFR3 signaling (Albuquerque RJ et al., 2009).

Ligands:

VEGF-A (Terman BI et al., 1992), VEGF-C (Joukov V et al., 1996), VEGF-D (Achen MG et al., 1998), and VEGF-E (M Meyer et al., 1999, Ogawa S et al., 1998). VEGF-A is the primary endogenous ligand activating VEGFR2 signaling, while VEGF-C and VEGF-D signal mostly through VEGFR3. VEGF-E is encoded by the Orf virus and activates VEGFR2 similarly to VEGF-A. Unlike VEGF-A, however, VEGF-E is a VEGFR2-exclusive ligand.

Expression

VEGFR2 is the principal VEGF receptor expressed on blood endothelial cells. Vegfr2-null mice die at E8.5 due to inadequate development of endothelial and hematopoietic cells(Shalaby F et al., 1995). Vegfr2 expression levels peak during embryonic angiogenesis and vasculogenesis (Millauer B et al., 1993, Oelrichs RB et al., 1993). In adults, VEGFR2 is expressed prominently on vascular endothelial cells, where it's expression is, in part, regulated by fibroblast growth factor signaling(Michael S. Pepper et al., 1998, Murakami M et al., 2011). Expression is also observed on hematopoietic stem cells and megakaryocytes(Casella I et al., 2003, Katoh O et al., 1995, Larrivée B et al., 2003).

Table 3: VEGF Family Inhibitors: Recombinant Protein and Monoclonal Antibodies

Drug	Type	Target	Mechanism of Inhibition	Clinical Status
bevacizumab (Avastin)	Humanized monoclonal antibody	Human VEGF-A	Prevents VEGF-A from binding VEGFR1 or VEGFR2	Approved for cervical, colorectal, glioblastoma, NSCLC, ovarian, and renal cell cancer
2C3	Mouse monoclonal antibody	Human VEGF-A	Specifically prevents VEGF-A from binding VEGFR2	Useful tool for preclinical studies to specifically block VEGF-A produced by human cancer cells
r84	Human monoclonal antibody	Human, Mouse VEGF-A	Specifically prevents VEGF-A from binding VEGFR2	Effective in preclinical studies; candidate for clinical trial
mcr84	Mouse chimeric monoclonal antibody	Human, Mouse VEGF-A	Specifically prevents VEGF-A from binding VEGFR2	Useful tool for preclinical studies in immunocompetent murine models of cancer
aflibercept (VEGF-Trap)	Recombinant protein consisting of human VEGFR1 and VEGFR2 extracellular domains fused to human IgG1 FC domain	VEGFR1 and VEGFR2 ligands	Acts as a decoy for VEGFR1 and VEGFR2 ligands	Approved for treatment of wet macular degeneration and metastatic colorectal cancer
icrucumab (IMC-18F1)	Human monoclonal antibody	Human VEGFR1	Blocks ligand-dependent signalling	In Phase II for Breast Cancer (AUG2015)
DC101	Rat monoclonal antibody	Mouse VEGFR2	Blocks ligand-dependent signalling	Useful tool for preclinical studies
ramucirumab (IMC-1121B)	Human monoclonal antibody	Human VEGFR2	Blocks ligand-dependent signalling	Approved for gastric adenocarcinoma, metastatic NSCLC, and metastatic colorectal cancer

Table 4: Small Molecule Inhibitors of VEGF Receptors

Drug	Specificity	Targets	Mechanism of Inhibition	Clinical Status
sorafenib	Multi-RTK Inhibitor	KIT, Flt3, PDGFR-B, VEGFR2, VEGFR3, Raf kinases	ATP-binding site competitive inhibitor	Approved for advanced renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer
pazopanib	Multi-RTK Inhibitor	FGFR1, VEGFR1-3, PDGFR, KIT, c-Fms	ATP-binding site competitive inhibitor	Approved for advanced renal cell carcinoma and soft tissue sarcoma
sunitinib	Multi-RTK Inhibitor	PDGF-Rs, VEGFR1-3, KIT, RET, CSF-1R, Flt3	ATP-binding site competitive inhibitor	Approved for renal cell carcinoma, gastrointestinal stromal tumors, and well-differentiated pancreatic neuroendocrine tumors
nintedanib	Multi-RTK Inhibitor	VEGFR1-3PDGFRa and B, FGFR1-3	ATP-binding site competitive inhibitor	Approved for idiopathic pulmonary fibrosis. Approved for NSCLC in the EU. Clinical trials ongoing for a variety of solid tumors.
apatinib	Exhibits higher selectivity for VEGFR2	VEGFR2, RET; lesser activity on cKIT, c-Src	ATP-binding site competitive inhibitor	Clinical trials ongoing for a variety of solid tumors; approved for late stage gastric cancer in China

Table 5: VEGFR2 point mutations and associated phenotype

Mutation	Amino Acid Change	Codon #	Affected Domain	Phenotype	Reference(s)
GTA -> ATA	Val-Ile	297	Ig-Like Domain 3	Associated with cornory heart disease	Wang et al., 2007
CAT -> CAA	His-Gln	472	Ig-Like Domain 5	Associated with cornory heart disease	Wang et al., 2007
TGT -> CGT	Cys-Arg	482	Ig-Like Domain 5	Associated with Hemangioma; affects VEGFR2's ability to regulate VEGFR1 expression	Jinnin et al., 2008
CCC -> TCC	Pro-Ser	1147	Kinase Domain	Associated with Hemangioma	Walter et al., 2002
Unreported	Asp-Val	717	Ig-Like Domain 7	Identified in angiosarcoma; results in ligand-indepedent activation of VEGFR2	Antonescu et al., 2009
Unreported	Thr-Arg	771	Transmembrane Domain	Identified in angiosarcoma	Antonescu et al., 2009
Unreported	Ala-Thr	1065	Kinase Domain	Identified in angiosarcoma; results in ligand-indepedent activation of VEGFR2	Antonescu et al., 2009

Table 6: Characterized VEGFR2 Single Nucleotide Polymorphisms (SNP)

SNP Position	Chromosome 4 Position	Sequence	Phenotype
-2854	55835242	tacatgcagt(A-C)actcctttaa	(-2854C) Increased VEGFR2 expression in vitro; correlates with increased VEGFR2 mRNA in patient tumors
-2766	55835154	gtaagttggt(A-T)aagatcacac	(-2766T)No change in vitro; correlates with increased VEGFR2 mRNA in patient tumors
-2455	55834843	gaatgtggta (G-A)actgatttca	(-2455A) Increased VEGFR2 expression in vitro; correlates with increased VEGFR2 mRNA in patient tumors
-906	55833294	agcgggaatg(T-C)tggcgaactg	(-906C) Increased VEGFR2 expression in vitro; correlates with increased VEGFR2 mRNA in patient tumors
-271	55832659	agagcggtca(G-A)tgtgtggtcg	(-271A) Reduced VEGFR2 expression in vitro; correlates with decreased VEGFR2 protein in patient tumors
18487	55813902	cttatagcca(A-T)gctgtctcag	(18487T) Q472H; Increased VEGF-A binding and VEGF-A-dependent VEGFR2 phosphorylation; correlates with increased microvessel density in patient tumors
23408	55808981	gtcagtggga(T-G)aaaaaaaaat	(23408G) correlates with increased VEGFR2 mRNA in patient tumors

ATG = Position "1"

SNP in paranthesis

Localisation

Full length VEGFR2 is localized on the plasma membrane and is internalized in a VEGF binding-dependent manner (Koch S et al., 2012, Waltenberger J et al., 1994). Soluble VEGFR2 is secreted from the cell.

Function

VEGFR2 is the premier receptor mediating VEGF-A activity on endothelial cells, where it functions to enhance proliferation, migration, and survival(Gerber HP et al., 1998, Jia H et al., 2004, Terman BI et al., 1992, Waltenberger J et al., 1994). Vegfr2 also promotes the survival of hematopoietic stem cells(Larrivée B et al., 2003).

VEGFR2 is the principal VEGF receptor involved in vascular angiogenesis and the regulation of vascular permeability(Kowanetz M et al., 2006, Terman BI et al., 1992). VEGFR2 activity on vascular endothelial cells in tumors promotes tumor angiogenesis(K. H. Plate et al., 1993, Millauer B et al., 1994). For the effects of VEGFR2 signaling on different cell types, see Table 2.

VEGF Signaling Inhibitors:

Strategies employed to target VEGF signaling are multifocal, consisting of monoclonal antibodies for both the ligands and VEGFRs, recombinant VEGFR extracellular domain fusion proteins (Table 3), and small molecule receptor tyrosine kinase inhibitors (Table 4)

Mutations

Somatic

Increased VEGFR2 copy number has been identified in breast(Johansson I et al., 2012), non-small cell lung cancer (Yang F et al., 2011), and neurological malignancies (Blom T et al., 2010, Puputti M et al., 2006).

Missense mutations have been identified in hemangioma, leading to constitutive activation of VEGFR2 (Antonescu CR et al., 2009, Jinnin M et al., 2008, Walter JW et al., 2002). Wang et al., 2007, identified that polymorphisms in the VEGFR2 were associated with coronary heart disease (Wang Y et al., 2007) (Table 5).

Glubb et al., 2011, characterized the significance of selected single nucleotide polymorphisms on VEGFR2 function and expression (Table 6).

Of particular note, Glubb et al., 2011, identified that a SNP that results in the amino acid change Q472H, which was associated with increased VEGFR2 activity, and was correlated with increased microvessel density in non-small cell lung cancer patients (Glubb DM et al., 2011) (Table 6).

Table 7: Reports and Characterization of VEGFR2 Expression by Tumor Cells

Cancer Type	Reference(s)	Cancer Type	Reference(s)
Angiosarcoma	Antonescu et al., 2009	Melanoma	Straume et al., 2003
Bladder	Xia et al., 2006	Mesothelioma	Strizzi et al., 2001
Brain/ Neurological	Knizetova et al., 2008; Nobusawa et al., 2011; Puputti et al., 2006; Yao et al., 2013; Blom et al., 2010	Multiple Myeloma	Giatromanolaki et al., 2010
Breast	Ghosh et al., 2008; Nakopoulou et al., 2002; Yan et al., 2015; Johansson et al., 2012	Myeloid Leukemia	Padró et al., 2002
Carcinoid	Silva et al., 2011	Ovarian	Spannuth et al., 2009; Chen et al., 2004
Cervical	Longatto-Filho et al., 2009	Pancreatic	Itakura et al., 2000; von Marschall et al., 2000; Chung et al., 2006
Colon	Takahashi et al., 1995, Giatromanolaki et al., 2007	Prostate	Köllermann et al., 2001; Jackson et al., 2002
Endometrial	Giatromanolaki et al., 2006	Renal Cell Carcinoma	Badalian et al., 2007
Esophageal	Gockel et al., 2008	Squamous (oral)	Sato et al, 2009
Gastric	Ozdemir et al., 2006	Thyroid	Rodríguez-Antona et al., 2010
Head and Neck	Lalla et al., 2003; Neuchrist et al., 2001	Lung	Carrillo de Santa Pau et al, 2009; Decaussin et al., 1999; Seto et al., 2006, Yang et al., 2011; Chatterjee et al., 2013

Implicated in

Various Cancers (see Table)

The expression VEGFR2 is increased by endothelial cells during tumor angiogenesis (K. H. Plate et al., 1993, Millauer B et al., 1994). VEGFR2 expression has also been identified on myeloid-derived suppressor cells, where it functions in splenic MDSC expansion and the chemotaxis of MDSCs into tumors (Dineen et al., 2008, Huang Y et al., 2007, Roland CL et al., 2009).

In addition to stromal cells, VEGFR2 expression by tumor cells has been identified in a variety of cancers, including bladder (Xia G et al., 2006), brain (Knizetova P et al., 2008, Nobusawa S1 et al., 2011, Puputti M et al., 2006, Yao X et al., 2013), breast (Ghosh S et al., 2008, Nakopoulou L et al., 2002, Yan JD et al., 2015), carcinoid (Silva SR et al., 2011), cervical (Longatto-Filho A et al., 2009), colon (Giatromanolaki A et al., 2007, Takahashi Y et al., 1995), endometrial ID: 5045> (Giatromanolaki A et al., 2006), esophageal (Gockel I et al., 2008), gastric (Ozdemir F et al., 2006), head and neck (Lalla RV et al., 2003, Neuchrist C et al., 2001), lung (Carrillo de Santa Pau E et al., 2009, Chatterjee S et al., 2013, Decaussin M et al., 1999, Seto T et al., 2006, Yang F et al., 2011), melanoma (Straume O et al., 2003), mesothelioma (Strizzi L et al., 2001), multiple myeloma (Giatromanolaki A et al., 2010), myeloid leukemia (Padró T et al., 2002), ovarian (Chen H et al., 2004, Spannuth WA et al., 2009), pancreatic (Chung GG et al., 2006, Itakura J et al., 2000, von Marschall Z et al., 2000), prostate (Jackson MW et al., 2002, Köllermann J et al., 2001), renal cell carcinoma (Badalian G et al., 2007), squamous (Sato H et al., 2009), and thyroid (Rodrèguez-Antona C et al., 2010), (Table 7).

In some cases, tumor cell expression of VEGFR2 appears to play an important function in tumor progression and correlates with worse prognosis. For example, Yang et al. (2011) identified VEGFR2 copy number gains (CNG) in 32% of tumors, which was associated with increased VEGFR2 protein, tumor angiogenesis, and correlated with poor prognosis(Yang F et al., 2011). Furthermore, Chatterjee et al. (2013) identified that the levels of VEGF/VEGFR2 binding on tumor cells strongly

correlated with tumor angiogenesis, and selective VEGFR2 inhibition had a significant combinatorial effect with MEK inhibitors in reducing tumor growth in preclinical models of NSCLC(Chatterjee S et al., 2013).
Yan et al. (2015) found that VEGFR2 expression by breast tumor cells was significantly correlated with increased lymph node metastasis, epithelial to mesenchymal transition (EMT) marker expression, and reduced overall survival(Yan JD et al., 2015).
For further review of expression and function of VEGFR2 in different cancers, see Table 7 and Goel and Mercurio, 2013(Goel HL et al., 2013).

Coronary Heart Disease

Wang et al., 2007, identified that polymorphisms in the VEGFR2 were associated with coronary heart disease (Wang Y et al., 2007) (Table 5).

Hemangioma

Missense mutations have been identified in hemangioma, leading to constitutive activation of VEGFR2 (Antonescu CR et al., 2009, Jinnin M et al., 2008, Walter JW et al., 2002).

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