VEGFA-VEGFR2 Pathway


European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

25/09/2019
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 70

This document contains 3 pathways and 50 reactions (see Table of Contents)
VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-4420097

Compartments: plasma membrane

Angiogenesis is the formation of new blood vessels from preexisting vasculature. One of the most important proangiogenic factors is vascular endothelial growth factor (VEGF). VEGF exerts its biologic effect through interaction with transmembrane tyrosine kinase receptors VEGFR, selectively expressed on vascular endothelial cells. VEGFA signaling through VEGFR2 is the major pathway that activates angiogenesis by inducing the proliferation, survival, sprouting and migration of endothelial cells (ECs), and also by increasing endothelial permeability (Lohela et al. 2009, Shibuya & Claesson-Welsh 2006, Claesson-Welsh & Welsh, 2013). The critical role of VEGFR2 in vascular development is highlighted by the fact that VEGFR2-/- mice die at E8.5-9.5 due to defective development of blood islands, endothelial cells and haematopoietic cells (Shalaby et al. 1995).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
VEGFR2 autophosphorylates

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-4420117

Type: transition

Compartments: plasma membrane, cytosol

Binding of VEGFA to VEGFR2 induces receptor dimerization and autophosphorylation, leading to the recruitment of downstream signalling molecules. Once the two VEGFR2 receptors are cross-linked to each other, via simultaneous interaction with VEGFA dimer, their membrane-proximal Ig-like domain 7s are held in close proximity so that low-affinity homotypic interactions between these domains further stabilise the receptor dimers. This allows for the exact positioning of the intracellular kinase domains resulting in VEGFR2 autophosphorylation (Ruch et al. 2007, Holmes at al. 2007). The major tyrosine residues known to be autophosphorylated are Y801 and Y951 in the kinase-insert domain, Y1054 and Y1059 within the kinase domain, and Y1175 and Y1214 in the C-terminal tail of VEGFR (Dougher-Vermazen et al. 1994, Cunningham et al. 2007, Kendall et al. 1999, Matsumoto et al. 2005). The Y1175 (mice Y1173) is crucial for endothelial and haemopoietic cell development. Mice with mutation Y1173F die between E8.5 and E9.5 from lack of endothelial and haemopoietic development (Sakurai et al. 2005).

Followed by: p-6Y-VEGFR2 binds SHC-transforming protein 2, p-6Y-VEGFR2 binds NCK, p-6Y-VEGFR2 binds PI3K, p-6Y-VEGFR2 binds SH2D2A, p-6Y-VEGFR2 binds SHB, Integrin alphaVbeta3 binds p-6Y-VEGFR2

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Reviewer</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p-6Y-VEGFR2 binds SHB

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-4420099

**Type:** binding

**Compartments:** plasma membrane, cytosol

The adaptor protein SHB (Src homology 2 domain-containing adapter protein B) binds to phosphorylated tyrosine Y1175 in VEGFR2 and regulates the PTK2/FAK activity and endothelial cell migration. The SH2 domain located in the C-terminus of SHB interacts with the phosphotyrosine residue in VEGFR2 (Holmqvist et al. 2004). SHB is not required for vascular development, but SHB-deficient mice shows defects in vessel functionality (Christoffersson et al. 2012) and impaired tumor growth (Funa et al. 2009).

**Preceded by:** VEGFR2 autophosphorylates

**Followed by:** SRC-1 phosphorylates SHB

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Date</th>
<th>Authors/Editors</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
</tr>
</tbody>
</table>
**SRC-1 phosphorylates SHB**

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-4420128

**Type:** transition

**Compartments:** plasma membrane, cytosol

Association of SHB with VEGFR2 leads to its Src-dependent tyrosine phosphorylation and activation (Holmqvist et al. 2003, Holmqvist et al. 2004).

**Preceded by:** p-6Y-VEGFR2 binds SHB

**Followed by:** PTK2 binds p-S-SHB and is recruited to p-6Y-VEGFR2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
PTK2 binds p-S-SHB and is recruited to p-6Y-VEGFR2

Location: VEGFA-VEGFR2 Pathway
Stable identifier: R-HSA-4420083
Type: binding
Compartments: plasma membrane, cytosol

SHB binds focal adhesion kinase 1 (FAK1; also known as PTK2) via its PTB domain in a phosphotyrosine-dependent manner. This regulates FAK1 phosphorylation, leading to Src dependent enhanced cell spreading (Holmqvist et al. 2003). During vascular development, FAK1 is involved in the control of endothelial cell migration (Holmquist et al. 2004), vascular permeability (Chen et al. 2012) and tube formation (Bohsack & Hirsh, 2003).

Preceded by: SRC-1 phosphorylates SHB
Followed by: PTK2 autophosphorylates

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Review/Editing</th>
<th>Authors/Editors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
PTK2 autophosphorylates

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218642

**Type:** transition

**Compartments:** cytosol, plasma membrane

Six tyrosine phosphorylation sites in focal adhesion kinase 1 (FAK1) serve to modulate FAK1 kinase activity or mediate FAK1 interaction with SH2-domain containing proteins. These are Y397, Y407, Y576, Y577, Y861 and Y925 (Mitra et al. 2005). They are differentially phosphorylated by diverse agonists and implicated in transmitting different signals and effects (Ciccimaro et al. 2006, Le Boeuf et al. 2004, 2006). Y397 is the major autophosphorylation site present upstream of the FAK kinase domain (Schaller et al. 1994). In response to VEGF stimulation FAK1 is recruited and autophosphorylated at Y397. This phosphorylated tyrosine then creates a binding site for other signaling proteins that link FAK1 to downstream signaling pathways and the actin cytoskeleton (Toutant et al. 2002).

**Preceded by:** PTK2 binds p-S-SHB and is recruited to p-6Y-VEGFR2

**Followed by:** SRC-1 binds p-Y397-PTK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored, Edited</th>
<th>Reviewed</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Garapati, P V.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://reactome.org
SRC-1 binds p-Y397-PTK2

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218645

**Type:** binding

**Compartments:** plasma membrane, cytosol

Autophosphorylation of Y397 on FAK1 provides a high affinity binding site for the Src homology 2 (SH2) domain of Src family kinases (SFKs) allowing their recruitment, activation and subsequent transphosphorylation of FAK1 at additional sites (Calalb et al. 1995).

**Preceded by:** PTK2 autophosphorylates

**Followed by:** SRC-1 phosphorylates p-Y397-PTK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
**SRC-1 phosphorylates p-Y397-PTK2**

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218640

**Type:** transition

**Compartments:** plasma membrane, cytosol


**Preceded by:** SRC-1 binds p-Y397-PTK2

**Followed by:** HSP90AA1 binds p-6Y-VEGFR2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored, Edited</th>
<th>Reviewed</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Garapati, P.V.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Several receptor tyrosine kinases (RTKs) are known to associate with integrins, and it has been suggested that focal adhesion kinase (FAK) is at the crossroads of these signaling pathways. On endothelial cells integrin alphaVbeta3 acts as a regulator of VEGFR2 signaling and shown to be necessary for angiogenic response (Hood et al. 2003). In mouse endothelial cells VEGF stimulated complex formation between VEGFR2 and beta3 integrin. This association between alphaVbeta3 with VEGFR2 appears to be synergistic, because VEGFR2 activation induces beta3 integrin tyrosine phosphorylation, which, in turn, enhances the phosphorylation of VEGFR2 and mediates the activation of mitogenic pathways involving focal adhesion kinase (FAK) and stress-activated protein kinase-2/p38 (SAPK2/p38) (Masson-Gadais et al. 2003, Mahabeleshwar et al. 2006, Somanath et al. 2009). This promotes activation of alphaVbeta3 and results in the increase of ligand binding ability (integrin activation), integrin ligation, and phosphorylation of beta3 integrin by cSrc.

Preceded by: VEGFR2 autophosphorylates

Followed by: PTK2beta binds alphaVbeta3

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
HSP90AA1 binds p-6Y-VEGFR2

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218643

Type: binding

Compartments: plasma membrane, cytosol

Heat-shock protein of 90 kDa (HSP90) a molecular chaperone, associates with VEGFR2 in response to VEGF. The last 130 amino acids of VEGFR2 C-terminal portion are involved in the association of VEGFR2 with HSP90. HSP90 associated with VEGFR2 is involved in regulating the activity of a Rho-associated protein kinase (ROCK) that is required to phosphorylate FAK on residue S732 (Le Bouef et al. 2004, 2006).

Preceded by: SRC-1 phosphorylates p-Y397-PTK2

Followed by: Active ROCK1,ROCK2 phosphorylates p-5Y-PTK2 on S732, RHOA:GTP:Mg2+ binds ROCK1,ROCK2

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author Information</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited Garapati, P V.</td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
</tr>
</tbody>
</table>
RHOA:GTP:Mg²⁺ binds ROCK1,ROCK2

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-3928647

Type: binding

Compartments: plasma membrane, cytosol

RHOA propagates downstream signals by binding to effector proteins such as Rho-associated, coiled-coil containing protein kinases (ROCKs). ROCKs consist of an amino-terminal kinase domain, followed by a Rho-binding domain (RBD) and a carboxy terminal cysteine-rich domain (CRD) located within the pleckstrin homology (PH) motif. RHOA:GTP interacts with the RBD domain and activates the phosphotransferase activity (Ishizaki et al. 1996, Amano et al. 2000).

Preceded by: HSP90AA1 binds p-6Y-VEGFR2

Followed by: ROCK1,ROCK2 are activated

Literature references


**ROCK1,ROCK2 are activated**

**Location:** VEGFA-VEGFR2 Pathway  

**Stable identifier:** R-HSA-5228992  

**Type:** transition  

**Compartments:** cytosol

RHOA propagates downstream signals by binding to effector proteins such as Rho-associated, coiled-coil containing protein kinases (ROCKs). ROCKs consist of an amino-terminal kinase domain, followed by a Rho-binding domain (RBD) and a carboxy terminal cysteine-rich domain (CRD) located within the pleckstrin homology (PH) motif. RHOA:GTP interacts with the RBD domain and activates the phosphotransferase activity (Ishizaki et al. 1996, Amano et al. 2000).

**Preceded by:** RHOA:GTP:Mg2+ binds ROCK1,ROCK2  

**Followed by:** Active ROCK1,ROCK2 phosphorylates p-5Y-PTK2 on S732

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Active ROCK1, ROCK2 phosphorylates p-5Y-PTK2 on S732

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218826

**Type:** transition

**Compartments:** cytosol, plasma membrane

Activated ROCK directly phosphorylates FAK1 on S732. This phosphorylation induces a conformational change that is necessary to trigger the phosphorylation of FAK on Y407 (Le Bouef et al. 2006).

**Preceded by:** ROCK1, ROCK2 are activated, HSP90AA1 binds p-6Y-VEGFR2

**Followed by:** p-Y402-PTK2B phosphorylates p-5Y,S732-PTK2 on Y407

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
PTK2beta binds alphaVbeta3

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218836

Type: binding

Compartments: plasma membrane, cytosol

Proline tyrosine kinase 2-beta (PTK2B), also known as cell adhesion kinase-beta or related adhesion focal tyrosine kinase, is a nonreceptor protein-tyrosine kinase closely related to focal adhesion kinase (FAK1) that couples receptors, including integrins, with a variety of downstream effectors such as small G proteins belonging to the Ras and Rho families, mitogen-activated protein kinases, protein kinase C, and inositol phosphate metabolism (Avraham et al. 2000). PYK2B has been shown to play a critical role in the adhesion and migration of many cell types. PYK2B has been shown to localise to integrin and has been demonstrated to associate directly with integrin beta3 cytoplasmic tail (Butler & Blystone 2005, Duong & Rodan 2000, Le Boeuf et al. 2006).

Preceded by: Integrin alphaVbeta3 binds p-6Y-VEGFR2

Followed by: SRC-1 phosphorylates PTK2-beta

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
SRC-1 phosphorylates PTK2-beta

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218830

Type: transition

Compartments: plasma membrane, cytosol

Proline tyrosine kinase 2-beta (PTK2B/PYK2) is rapidly tyrosine phosphorylated on Y402 through Src-kinases in response to ligation of integrin beta3.

Preceded by: PTK2beta binds alphaVbeta3


Literature references


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
</tr>
</tbody>
</table>
Phosphorylation of S732 in FAK1 changes its conformation making Y407 accessible to Proline tyrosine kinase 2-beta (PTK2B). pY402-PTK2B then triggers the phosphorylation of FAK1 on Y407 (Le Boeuf et al. 2006). Phosphorylation of Y407 is required to recruit paxillin and vinculin to FAK1 and to ensure formation of focal adhesions and cell migration (Le Boeuf et al. 2004).

**Preceded by:** Active ROCK1,ROCK2 phosphorylates p-5Y-PTK2 on S732, SRC-1 phosphorylates PTK2-beta

**Followed by:** BCAR1 binds p-7Y-PTK2, PXN binds p-6Y,S732-PTK2

**Literature references**

PXN binds p-6Y,S732-PTK2

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218838

Type: binding

Compartments: cytosol, plasma membrane

Paxillin (PXN) is a multidomain scaffolding protein localized primarily in focal adhesions. It binds with focal adhesion kinase (FAK1, also known as PTK2) and is recruited to the focal adhesions. VEGF induced a quick and marked increase in the recruitment of both paxillin and vinculin to FAK (Abedi & Zachary 1997).


Followed by: PTK2 and SRC-1 phosphorylate PXN on Y31 and Y118

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored, Edited</th>
<th>Reviewed</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Garapati, P V.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PTK2 and SRC-1 phosphorylate PXN on Y31 and Y118

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218809

Type: transition

Compartments: plasma membrane, cytosol

Upon stimulation FAK1 (also known as PTK2), in association with Src family kinases (SFKs) phosphorylates paxillin (PXN) at two main sites- tyrosine 31 and tyrosine 118. These phosphorylated sites provides the functional SH2-binding sites for members of the Crk family of SH2-SH3 adaptor proteins (Bellis et al. 1995, Shaller & Schaefer 2001).

Preceded by: PXN binds p-6Y,S732-PTK2

Followed by: CRK binds BCAR1 and or PXN

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
BCAR1 binds p-7Y-PTK2

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218855

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: p130Cas binds Fak (Mus musculus)

P130CAS (Crk-associated substrate/BCAR1) is an adaptor protein which upon phosphorylation recruits additional signaling proteins that link the scaffold to the actin cytoskeleton of the cell (Klemke at al. 1998). The C-terminal proline-rich region of Focal adhesion kinase (FAK1) spanning amino acids 712-718 binds the SH3 domain-containing region of p130CAS (Polte & Hanks 1995). P130CAS also interacts with Src-family kinases (SFKs) via its C-terminal Src-binding domain (SBD). Though FAK1 has no tyrosine kinase activity towards p130CAS, it contributes to p130CAS phosphorylation by interacting with SFKs (Ruest et al. 2001).


Followed by: PTK2/SRC-1 phosphorylates BCAR1

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
PTK2/SRC-1 phosphorylates BCAR1

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218828

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Fak/Src phosphorylate p130Cas (Mus musculus)

P130CAS (CRK-associated substrate/BCAR1) contains multiple protein-protein interaction domains including an N-terminal SH3 domain, an interior substrate domain (SD), a Src-binding domain (SBD) near the C-terminus and a conserved C-terminal Cas-family homology (CCH) domain. The SH3 and CCH domains mediate localization to focal adhesions (FAs) while SD and SBD are involved in initiating signaling events (Meenderink et al. 2010, Shin et al. 2004). The BCAR1 SD undergoes tyrosine phosphorylation and mediates signals by recruiting downstream effectors. The SD is characterised by fifteen YxxP motifs, of which ten can be efficiently phosphorylated by Src family kinases (SFKs) (Shin et al. 2004). PTK2/FAK kinase phosphorylates the nearby SBD tyrosines 664 and 666 (mouse 668/670). These SBD tyrosines provide the additional binding sites for Src-SH2 domains, stabilizing the SRC-BCAR1 association (Ruest et al. 2001). Note: Phosphorylated tyrosine numbering in human BCAR1 is based on similarity with the mouse p130Cas.

Preceded by: BCAR1 binds p-7Y-PTK2

Followed by: CRK binds BCAR1 and or PXN

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P. V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
CRK binds BCAR1 and or PXN

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218822

Type: binding

Compartments: plasma membrane, cytosol, extracellular region

CRK (CT10 Regulator of Kinase) is composed of one SH2 and one or two SH3 domains. This adaptor protein binds with phosphorylated tyrosine motifs found in proteins involved in cell spreading, actin reorganisation, and cell migration. Paxillin (PAX) and p130CAS are the two major focal adhesion components that binds with CRK to form multiprotein signaling complexes and regulate cell migration (Klemke et al. 1998, Valles et al. 2004, Lamorte et al. 2003).

Preceded by: PTK2/SRC-1 phosphorylates BCAR1, PTK2 and SRC-1 phosphorylate PXN on Y31 and Y118

Followed by: DOCK180:ELMO binds CRK

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>

https://reactome.org
DOCK180:ELMO binds CRK

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218811

Type: binding

Compartments: plasma membrane, cytosol

The SH3 domain of CRK interacts constitutively with proline rich motifs present in Dedicator of cytokinesis (DOCK180), an exchange factor for RAC1. Unlike many GEFs, DOCK180 does not contain a conserved Dbl homology (DH) domain. Instead, it has a DHR2 or DOCKER domain capable of loading RAC1 with GTP (Brugnera et al 2002). Binding of DOCK180 to RAC1 alone is insufficient for GTP loading, a DOCK180-ELMO interaction is required. Engulfment and cell motility protein 1 (ELMO1) or ELMO2 form a complex with DOCK180 which functions as a bipartite GEF to optimally activate RAC1 (Gumienny et al 2001, Brugnera et al 2002, Birge et al. 2009).

Preceded by: CRK binds BCAR1 and or PXN

Followed by: DOCK180:ELMO exchanges GTP for GDP, activating RAC1

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
DOCK180:ELMO exchanges GTP for GDP, activating RAC1

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218839

**Type:** transition

**Compartments:** plasma membrane, cytosol

RAC1 is activated from inactive GDP-bound state to active GTP-bound form by the GEF activity of DOCK180:ELMO complex. RAC1 signaling facilitates VEGF-stimulated angiogenesis by regulating endothelial cell migration and vascular permeability. RAC1 promotes migration by stimulating actin reorganisation to form membrane ruffles and lamellipodia. RAC1 is also a critical component of endothelial NADPH oxidase promoting reactive oxygen species (ROS) production. Specifically, VEGF acts through RAC1 to stimulate lamellipodia formation at the leading edge of polarized cells for directional migration, or chemotaxis. RAC1 induces vascular permeability in part by disrupting endothelial cell-cell junctions (Soga et al. 2001a, Soga et al. 2001b, Claesson-Welsh & Welsh, 2013).

**Preceded by:** DOCK180:ELMO binds CRK

**Followed by:** WAVE Regulatory Complex (WRC) interacts with RAC1 and PIP3 and gets activated

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
WAVE Regulatory Complex (WRC) interacts with RAC1 and PIP3 and gets activated

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-2029465

**Type:** binding

**Compartments:** plasma membrane, cytosol

WASP family verprolin-homologous proteins (WAVEs) function downstream of RAC1 and are involved in activation of the ARP2/3 complex. The resulting actin polymerization mediates the projection of the plasma membrane in lamellipodia and membrane ruffles. WAVEs exist as a pentameric hetero-complex called WAVE Regulatory Complex (WRC). The WRC consists of a WAVE family protein (WASF1, WASF2 or WASF3 - commonly known as WAVE1, WAVE2 or WAVE3), ABI (Abelson-interacting protein), NCKAP1 (NAP1, p125NAP1), CYFIP1 (SRA1) or the closely related CYFIP2 (PIR121), and BRK1 (HSPC300, BRICK). Of the three structurally conserved WAVEs in mammals, the importance of WAVE2 in activation of the ARP2/3 complex and the consequent formation of branched actin filaments is best established. WAVEs in the WRC are intrinsically inactive and are stimulated by RAC1 GTPase and phosphatidylinositols (PIP3). The C-terminal VCA domain of WAVE2 (and likely WAVE1 and WAVE3) which can bind both the ARP2/3 complex and actin monomers (G-actin) is masked in the inactive state. After PIP3 binds to the polybasic region of WAVE2 (and likely WAVE1 and WAVE3) and RAC1:GTP binds to the CYFIP1 (or CYFIP2) subunit of the WRC, allosteric changes most likely occur which allow WAVEs to interact with the ARP2/3 complex. The interactions between WAVEs and RAC1 are indirect. BAIAP2/IRSp53, an insulin receptor substrate, acts as a linker, binding both activated RAC1 and the proline-rich region of WAVE2 (and likely WAVE1 and WAVE3) and forming a trimolecular complex. CYFIP1 (or CYFIP2) in the WAVE regulatory complex binds directly to RAC1:GTP and links it to WAVE2 (and likely WAVE1 and WAVE3) (Derivery et al. 2009, Yamazaki et al. 2006, Takenawa & Suetsugu 2007, Chen et al. 2010, Pollard 2007, Lebensohn & Kirschner 2009).

**Preceded by:** DOCK180:ELMO exchanges GTP for GDP, activating RAC1, VAV exchanges GTP for GDP on RAC1, activating it

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Rosales, C.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Reviewed</td>
<td>Rivero Crespo, F.</td>
</tr>
<tr>
<td>2015-02-02</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
p-6Y-VEGFR2 binds SHC-transforming protein 2

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-4420107

**Type:** binding

**Compartments:** plasma membrane, cytosol

Phosphorylated tyrosine Y1175 of VEGFR2 provides the binding site for the adaptor protein SHC-transforming protein 2 (SHC2) also referred as Shc-like protein (SCK). SCK is plausibly involved in coupling VEGFR2 to ERK (Warner et al. 2000, Ratcliffe et al. 2002).

**Preceded by:** VEGFR2 autophosphorylates

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Two-hybrid mapping showed that tyrosine 951 (Y951) serves as the binding site for T-cell specific adapter molecule (TSAD/SH2 domain-containing protein 2A (SH2D2A)), also referred as VEGF-receptor-associated protein (VRAP) (Wu et al. 2000). SH2D2A mediates vascular permeability downstream of VEGFR2 by forming a complex with c-SRC (Sun et al. 2012). Site-directed mutation of Y951 to phenylalanine (Y951F) in the VEGFR2, or siRNA mediated silencing of SH2D2A expression, prevented VEGFA mediated cytoskeletal reorganisation and migration but not mitogenicity (Matsumoto et al. 2005).

**Preceded by:** VEGFR2 autophosphorylates

**Followed by:** SRC1-1 binds SH2D2A and is recruited to VEGFR2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
SRC1-1 binds SH2D2A and is recruited to VEGFR2

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-4420140

Type: binding

Compartments: plasma membrane, cytosol

SH2D2A (also known as TSAD) bound to VEGFR2 forms a complex with Src to regulate stress fiber formation and endothelial cell (EC) migration. This contributes to EC migration during pathological angiogenesis and thus the recruitment of SH2D2A is associated with cancer angiogenesis (Matsumoto et al. 2005).

Preceded by: p-6Y-VEGFR2 binds SH2D2A

Followed by: Phosphorylation of SRC-1

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship</th>
<th>Editors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Phosphorylation of SRC-1

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-4420206

Type: transition

Compartments: plasma membrane, cytosol

SRC is activated in vivo and in vitro in a VEGF/SH2D2A-dependent manner. VEGF induces phosphorylation of the activating Y418 residue, located on the c-SRC kinase activation loop, but also decreases phosphorylation of the negative regulatory Y527 (Sun et al. 2012).

Preceded by: SRC1-1 binds SH2D2A and is recruited to VEGFR2

Followed by: AXL binds SRC-1

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
AXL binds SRC-1

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5357432

**Type:** binding

**Compartments:** plasma membrane

AXL/UFO (Tyrosine-protein kinase receptor UFO) is a member of the TAM (Tyro3/Axl/Mer) family of receptor tyrosine kinases (RTKs). AXL has been implicated in angiogenesis because of its ability to promote angiogenically related cellular responses in endothelial cells (Holland et al, 2005). AXL is required for VEGFA-dependent activation of PI3K. Activated Src family kinases recruit AXL via its juxtamembrane domain and thereby trigger ligand-independent autophosphorylation of AXL that promotes association with PI3K and activation (Ruan & Kazlauskas 2012).

**Preceded by:** Phosphorylation of SRC-1

**Followed by:** AXL autophosphorylates on Y772 and Y814

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
AXL autophosphorylates on Y772 and Y814

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5357429

Type: transition

Compartments: plasma membrane, cytosol

VEGFA-dependent activation of VEGFR2 causes autophosphorylation and activation of the Axl receptor tyrosine kinase via Src-1:SH2D2A-dependent reaction. Phosphorylation of Axl tyrosine residues 772 and 814 (773 and 815 in mouse) is required for VEGFA-dependent binding of the p85-subunit of PI3K and activation of PI3K (Ruan & Kazlauskas, 2012).

Preceded by: AXL binds SRC-1

Followed by: p-AXL binds PI3K

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Revised By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p-AXL binds PI3K

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5357479

**Type:** binding

**Compartments:** plasma membrane, cytosol

Axil with its two phosphorylated YxxM motifs associates with the p85 subunit of PI3K and mediates VEGFA mediated activation of PI3K/AKT pathway (Ruan & Kazlauskas, 2012).

**Preceded by:** AXL autophosphorylates on Y772 and Y814

**Followed by:** VEGFA dimer:p-6Y-VEGFR2 dimer:PI3K phosphorylates PIP2 to PIP3

**Literature references**

**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Activation of VEGFR2 results in the activation of phosphatidylinositol 3-kinase (PI3K) which plays an important role in regulating endothelial proliferation, migration and survival (Jiang et al. 2000). Activation of PI3K is also essential for VEGF-stimulated nitric oxide (NO) production from endothelial cells via protein kinase B (PKB/AKT) signaling to eNOS (Nitric oxide synthase, endothelial) (Blanes et al. 2007). Upon stimulation by VEGF the p85 regulatory subunit of PI3K is recruited to phosphorylated tyrosine-801 of VEGFR2 (Dayanir et al. 2001).

Preceded by: VEGFR2 autophosphorylates

Followed by: VEGFA dimer:p-6Y-VEGFR2 dimer:PI3K phosphorylates PIP2 to PIP3

Literature references

VEGFA dimer:p-6Y-VEGFR2 dimer:PI3K phosphorylates PIP2 to PIP3  

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218819

Type: transition

Compartments: plasma membrane, cytosol

PI3-kinase (PI3K) catalyzes the phosphorylation of inositol phospholipids at the 3 position to generate phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate. PIP2 and PIP3 generated serve as lipid substrates where they recruit guanine nucleotide exchange factors (GEFs) like VAV (Proto-oncogene vav) that catalyze the exchange of GDP for GTP on Rac, activating it (Han et al. 1998). VAV2 acts downstream of VEGF to activate Rac1 (Garretta et al. 2007).

Preceded by: p-6Y-VEGFR2 binds PI3K, p-AXL binds PI3K

Followed by: PIP3 binds stimulating VAV

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
**PIP3 binds stimulating VAV**

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-434637

**Type:** binding

**Compartments:** cytosol, plasma membrane

**Inferred from:** PIP3 stimulates Vav1 (Mus musculus)

Vav interacts directly with PIP2 and PIP3, with a fivefold selectivity for PIP3 over PIP2. PIP3 gives a two-fold stimulation of Vav1 GEF activity while PIP2 leads to 90% inhibition. Binding probably occurs through the PH domain, known to bind phosphoinositides.

**Preceded by:** VEGFA dimer:p-6Y-VEGFR2 dimer:PI3K phosphorylates PIP2 to PIP3

**Followed by:** Src kinases phosphorylate VAV

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-09-04</td>
<td>Authored</td>
<td>Akkerman, JW.</td>
</tr>
<tr>
<td>2009-11-02</td>
<td>Reviewed</td>
<td>Poole, AW., Jones, ML., Harper, MT.</td>
</tr>
<tr>
<td>2009-11-03</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
</tbody>
</table>
Src kinases phosphorylate VAV

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218820

Type: transition

Compartments: plasma membrane, cytosol

Following VEGF treatment, VAV2 phosphorylation on tyrosine 172 stimulates its GEF activity for RAC1 (Garrett et al. 2007) and thus plays an important role in linking VEGFR2 to endothelial migration. VAV exists in an auto-inhibitory state, folded in such a way as to inhibit the GEF activity of its DH domain. This folding is mediated through binding of tyrosines in the acidic domain to the DH domain and through binding of the calponin homology (CH) domain to the C1 region. Activation of VAV is thought to involve three events which relieve this auto-inhibition: phosphorylation of tyrosines in the acidic domain causes them to be displaced from the DH domain; binding of a ligand to the CH domain may cause it to release the C1 domain; binding of the PI3K product PIP3 to the PH domain may alter its conformation (Aghazadeh et al. 2000). VAV is phosphorylated on a tyrosine residue (Y174 in VAV1, 172 in VAV2, 173 in VAV3) in the acidic domain. This is mediated by Src and related family tyrosine kinases (Deckert et al. 1996, Schuebel et al. 1998).

Preceded by: PIP3 binds stimulating VAV

Followed by: p-VAV family:PIP3 binds RAC1:GDP

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p-VAV family: PIP3 binds RAC1:GDP

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-8951586

Type: binding

Compartments: plasma membrane, cytosol

Tyrosine-phosphorylated VAVs bind RAC1:GDP as RAC1 guanine nucleotide exchange factors (GEFs), catalysing the exchange of bound GDP for GTP. RAC1 is a key regulator for actin cytoskeleton and cell migration and is also a critical component of endothelial NADPH oxidase (Wittmann et al. 2003, Tan et al. 2008, Ushio–Fukai 2007, Ushio–Fukai et al. 2002).

Preceded by: Src kinases phosphorylate VAV

Followed by: VAV exchanges GTP for GDP on RAC1, activating it

Literature references

Tyrosine-phosphorylated VAVs act as guanine nucleotide exchange factors (GEFs) for RAC1, catalysing the exchange of bound GDP for GTP. RAC1 is a key regulator for actin cytoskeleton and cell migration and is also a critical component of endothelial NADPH oxidase (Wittmann et al. 2003, Tan et al. 2008, Ushio–Fukai 2007, Ushio–Fukai et al. 2002). Activated RAC1 then stimulates actin polymerisation to form lamellipodia through a number of proteins such as WASP-family veroprilin homologous protein (WAV). WAVE proteins stimulate the formation of a branched actin network by binding to the p21 subunit of the ARP2/3 nucleating complex, which is located on the sides of the pre-existing filaments.

**Preceded by:** p-VAV family: PIP3 binds RAC1:GDP

**Followed by:** NADPH oxidase 2 (NOX2) complex binds RAC1, WAVE Regulatory Complex (WRC) interacts with RAC1 and PIP3 and gets activated

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
VEGFR2 mediated vascular permeability

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218920

Compartments: cytosol, extracellular region, plasma membrane

The free radical nitric oxide (NO), produced by endothelial NO synthase (eNOS), is an important vasoactive substance in normal vascular biology and pathophysiology. It plays an important role in vascular functions such as vascular dilation and angiogenesis (Murohara et al. 1998, Ziche et al. 1997). NO has been reported to be a downstream mediator in the angiogenic response mediated by VEGF, but the mechanism by which NO promotes neovessel formation is not clear (Babaei & Stewart 2002). Persistent vasodilation and increase in vascular permeability in the existing vasculature is observed during the early steps of angiogenesis, suggesting that these hemodynamic changes are indispensable during an angiogenic processes. NO production by VEGF can occur either through the activation of PI3K or through a PLC-gamma dependent manner. Once activated both pathways converge on AKT phosphorylation of eNOS, releasing NO (Lin & Sessa 2006). VEGF also regulates vascular permeability by promoting VE-cadherin endocytosis at the cell surface through a VEGFR-2-Src-Vav2-Rac-PAK signalling axis.

Literature references

NADPH oxidase 2 (NOX2) complex binds RAC1

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218827

Type: binding

Compartments: plasma membrane

NADPH oxidase (NOX) proteins are membrane-associated, multiunit enzymes that catalyze the reduction of oxygen using NADPH as an electron donor. NOX proteins produce superoxide (O2.-) via a single electron reduction (Brown & Griendling 2009). Superoxide molecules function as second messengers to stimulate diverse redox signaling pathways linked to various functions including angiogenesis. VEGF specifically stimulates superoxide production via RAC1 dependent activation of NOX2 complex. VEGF rapidly activates RAC1 and promotes translocation of RAC1 from cytosol to the membrane. At the membrane RAC1 interacts with the NOX enzyme complex via a direct interaction with NOX2 (gp91phox or CYBB) followed by subsequent interaction with the NCF2 (Neutrophil cytosol factor 2) or p67phox subunit and this makes the complex active (Bedard & Krause 2007). O2.- derived from Rac1-dependent NOX2 are involved in oxidation and inactivation of protein tyrosine phosphatases (PTPs) which negatively regulate VEGFR2, thereby enhancing VEGFR2 autophosphorylation, and subsequent redox signaling linked to angiogenic responses such as endothelial cell proliferation and migration (Ushio-Fukai 2006, 2007).

Preceded by: VAV exchanges GTP for GDP on RAC1, activating it

Followed by: NADPH oxidase 2 generates superoxide from oxygen

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Reviewed</td>
<td>Rivero Crespo, F.</td>
</tr>
<tr>
<td>2015-02-02</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
NADPH oxidase 2 generates superoxide from oxygen

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218841

**Type:** transition

**Compartments:** cytosol, plasma membrane, extracellular region

The activated NOX2 complex generates superoxide (O2⁻) by transferring an electron from NADPH in the cytosol to oxygen on the luminal or extracellular space (Bedard & Krause 2007).

**Preceded by:** NADPH oxidase 2 (NOX2) complex binds RAC1

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Role</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Reviewed</td>
<td>Rivero Crespo, F.</td>
</tr>
<tr>
<td>2015-02-02</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-10-29</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
</tbody>
</table>
p-6Y-VEGFR2 binds NCK

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218815

**Type:** binding

**Compartments:** plasma membrane, cytosol

In response to VEGF, the increased actin polymerization required to trigger actin based motility involves the recruitment of adapter protein NCK to VEGFR2 (Lamalice et al. 2007). Phosphorylated tyrosine 1214 in VEGFR2 is the binding site for NCK. NCK later recruits FYN and PAK2, which are required for the activation of SAPK2/p38 activation, formation of stress fibers, and endothelial cell migration (Lamalice et al. 2006, Stoletov et al. 2004, Lu et al. 1997). NCK also participates in a signaling pathway leading to actin nucleation and polymerization through its interactions with N WASP and WAVE1 (Stoletov et al. 2004, Rhoatgi et al. 2001).

**Preceded by:** VEGFR2 autophosphorylates

**Followed by:** p-6Y-VEGFR2 binds FYN

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p-6Y-VEGFR2 binds FYN

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218824

**Type:** binding

**Compartments:** cytosol, extracellular region, plasma membrane

Tyrosine-1214 phosphorylation allows recruitment of cytoplasmic tyrosine kinase FYN along with NCK to VEGFR2. FYN and NCK associate with each other. This complex mediates phosphorylation of p21-activated protein kinase 2 (PAK2) and subsequent activation of p38MAPK mediating actin reorganization and cell migration (Lamalice et al. 2006).

**Preceded by:** p-6Y-VEGFR2 binds NCK

**Followed by:** FYN autophosphorylates

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
**FYN autophosphorylates**

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218806

**Type:** transition

**Compartments:** plasma membrane, cytosol

FYN recruited to VEGFR2 is activated; this is required for VEGF-induced actin remodelling and endothelial migration. Once Y531 in the negative regulatory site is dephosphorylated by a phosphatase, FYN undergoes autophosphorylation on Y420 (Yeo et al. 2011).

**Preceded by:** p-6Y-VEGFR2 binds FYN

**Followed by:** p-Y420-FYN is phosphorylated on S21

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p-Y420-FYN is phosphorylated on S21

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218854

Type: transition

Compartments: cytosol, extracellular region, plasma membrane

FYN has multiple phosphorylation sites which can affect its kinase activity. Among these phosphorylation sites, serine 21 (S21) has been identified as a target site for protein kinase A (PKA). The phosphorylation of FYN S21 is critical for both FYN's tyrosine kinase activity and its focal adhesion targeting (Yeo et al. 2007).

Preceded by: FYN autophosphorylates

Followed by: PAK2 binds NCK

Literature references


Editions

| 2013-08-30 | Authored, Edited | Garapati, P V. |
| 2014-05-12 | Reviewed | Welsh, M., Ballmer-Hofer, K., Berger, P. |
PAK2 binds NCK

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218847

**Type:** binding

**Compartments:** plasma membrane, cytosol

P21-activated kinase 2 (PAK2) is an effector of GTP-bound CDC42. It associates with NCK and possibly links activated CDC42 to the SAPK2/p38 module (Lamalice et al. 2006, Zhao et al. 2000).

**Preceded by:** p-Y420-FYN is phosphorylated on S21

**Followed by:** CDC42:GTP binds PAK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
VEGF induces CDC42 activation by unknown mechanism

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218829

**Type:** omitted

**Compartments:** cytosol

CDC42 is involved in the formation of filopodia with potential functions in guidance and migration in response to a VEGF gradient. CDC42 is activated downstream of VEGFR2 and involved in the formation of stress fibres by contributing to the activation of the p38 pathway. The activation of CDC42 may rely on FYN activity but the precise mechanism that leads to activation is not known (Lamalice et al. 2004, 2006).

**Followed by:** CDC42:GTP binds PAK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
**CDC42:GTP binds PAK2**

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218832

**Type:** binding

**Compartments:** plasma membrane

The PAK family of serine/threonine kinases are known to be activated by binding to the GTP-bound form of CDC42 or RAC1, small GTPases of the Rho family that are involved in regulating the organization of the actin cytoskeleton. PAK exists as homodimer in a trans-inhibited conformation. The kinase inhibitory (KI) domain of one PAK molecule binds to the C-terminal catalytic domain of the other and inhibits catalytic activity. Association of GTP-bound forms of CDC42 or RAC1 with the PAK PBD/CRIB domain induces conformational changes in the N-terminal domain that no longer support its autoinhibitory function. CDC42-mediated activation primes PAK2 for superactivation by tyrosine phosphorylation (Renkema et al. 2002).

**Preceded by:** VEGF induces CDC42 activation by unknown mechanism, PAK2 binds NCK

**Followed by:** PAK2 autophorylates

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Reviewer</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
PAK2 autophorylates

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218814

Type: transition

Compartments: plasma membrane, cytosol

PAK2 undergoes autophosphorylation on serine and threonine residues, which maintains PAK2 in a catalytically active state. PAK is autophosphorylated at several sites but S141 flanking the kinase inhibitor region and T402 within the catalytic domain are the two conserved sites that regulate the catalytic activity (Chong et al. 2001, Gatti et al. 1999).

Preceded by: CDC42:GTP binds PAK2

Followed by: FYN phosphorylates PAK2

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
FYN phosphorylates PAK2

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218812

**Type:** transition

**Compartments:** plasma membrane, cytosol

PAK2 activity via GTPases can be strongly potentiated by concurrent stimulation of cellular tyrosine kinase activity. FYN may be involved in this potentiation by phosphorylating Y130 in the N-terminal regulatory domain leading to a robust enhancement of the catalytic activity of PAK2 (Renkema et al. 2002).

**Preceded by:** PAK2 autophorylates

**Followed by:** p38 MAPK activation by VEGFR

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Edition Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
p38 MAPK activation by VEGFR

**Location:** VEGFA-VEGFR2 Pathway

**Stable identifier:** R-HSA-5218804

**Type:** omitted

**Compartments:** cytosol, extracellular region, plasma membrane

In primary cultured human umbilical vein endothelial cells (HUVECs) VEGF-induced activation of SAPK2/p38MAPK, and pharmacological inhibition of p38MAPK attenuated VEGF-induced cell migration (Rouseseau et al. 1997, 2000). The p38MAPK pathway conveys the VEGF signal to microfilaments inducing rearrangements of the actin cytoskeleton. These actin structures are thought to generate the contractile force within cells that is required for endothelial cell migration. Activation of p38 requires the activity of FYN and PAK2 (Lamalice et al. 2004). However, little is known of the exact molecular events that follow activation of PAK2 and lead to p38 activation. Like all MAP kinases, p38 MAP kinases are activated by dual kinases termed the MAP kinase kinases (MKKs). There are two main MAPKKs that are known to activate p38, MKK3 and MKK6 (Zarubin & Han 2005). Along with FYN and PAK these MKKs might contribute to the activation of p38. Activation of p38 resulted in activation of MAP kinase activated protein kinase 2/3 (MAPK 2/3) and phosphorylation of the F-actin polymerization modulator, heat shock protein 27 (HSP27) (Rousseau et al. 1997).

**Preceded by:** FYN phosphorylates PAK2

**Followed by:** p38 MAPK phosphorylates MAPKAPK2, MAPKAPK3

**Literature references**


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Activated p38 MAPK is known to activate the Ser/Thr protein kinase MAP kinase-activated protein kinase 2 (MAPK2/MAPKAPK2) and a closely related kinase, MAPKAP kinase 3. MAPK2 is phosphorylated on T222, S272, and T334 (Ben-Levy et al. 1995). MAPK3 shows 75% sequence identity to MAPK2 and, like MAPK2, is phosphorylated by p38 but the exact phosphorylation sites are not determined. According to some authors, NGF does not induce any significant activation of MAPKAPK2 activity in PC12 cells. Potential p38 signaling effectors include transcription factors, such as cAMP-response element-binding protein and MEF2, cytoskeleton modulators, and a number of protein kinases. After activation, MAPKAP kinase 2 and 3 move to the nucleus.

Preceded by: p38 MAPK activation by VEGFR

Followed by: p-MAPK2/3 phosphorylates HSP27

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-10-10</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2006-10-10</td>
<td>Authored</td>
<td>Annibali, D., Nasi, S.</td>
</tr>
<tr>
<td>2007-11-08</td>
<td>Reviewed</td>
<td>Greene, LA.</td>
</tr>
</tbody>
</table>
Activated MAP kinase-activated protein kinase (MAPK/MAPKAPK) 2 and 3 in turn phosphorylate heat shock protein beta 1 (HSPB1, HSP27). HSP27 is an actin-capping protein. Its phosphorylation has been proposed to release it from actin filaments, thus allowing addition of actin monomers and elongation of filaments. Phosphorylation-induced conformational changes causes disaggregation of oligomeric complexes of HSP27 and subsequent disassociation from actin filaments, which may result in a higher rate of actin polymerization (Lamalice et al. 2007, Rousseau et al. 2000, Lavoie et al. 1995).

**Preceded by:** p38 MAPK phosphorylates MAPKAPK2, MAPKAPK3

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
VEGFR2 mediated cell proliferation

Location: VEGFA-VEGFR2 Pathway

Stable identifier: R-HSA-5218921

Compartments: cytosol, plasma membrane, extracellular region

VEGFR2 stimulates ERK not via GRB2-SOS-RAS, but via pY1175-dependent phosphorylation of PLC gamma and subsequent activation of PKCs. PKC plays an important mediatory role in the proliferative Ras/Raf/MEK/ERK pathway. PKC alpha can intersect the Ras/Raf/MEK/ERK cascade at the level of Ras (Clark et al. 2004) or downstream of Ras through direct phosphorylation of Raf (Kolch et al. 1993). VEGF stimulation leads to Ras activation in a Ras-guanine nucleotide exchange factor (GEF) independent mechanism. It rather relies on modulating the regulation of Ras-GTPase activating protein (GAP) than regulation of Ras-GEFS (Wu et al. 2003).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-30</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2014-05-12</td>
<td>Reviewed</td>
<td>Welsh, M., Ballmer-Hofer, K., Berger, P.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

VEGFA-VEGFR2 Pathway 2

VEGFR2 autophosphorylates 3

p-6Y-VEGFR2 binds SHB 4

SRC-1 phosphorylates SHB 5

PTK2 binds p-S-SHB and is recruited to p-6Y-VEGFR2 6

PTK2 autophosphorylates 7

SRC-1 binds p-Y397-PTK2 8

SRC-1 phosphorylates p-Y397-PTK2 9

Integrin alphaVbeta3 binds p-6Y-VEGFR2 10

HSP90AA1 binds p-6Y-VEGFR2 11

RHOA:GTP:Mg2+ binds ROCK1,ROCK2 12

ROCK1,ROCK2 are activated 13

Active ROCK1,ROCK2 phosphorylates p-5Y-PTK2 on S732 14

PTK2beta binds alphaVbeta3 15

SRC-1 phosphorylates PTK2-beta 16

p-Y402-PTK2B phosphorylates p-5Y,S732-PTK2 on Y407 17

PXN binds p-6Y,S732-PTK2 18

PTK2 and SRC-1 phosphorylate PXN on Y31 and Y118 19

BCAR1 binds p-7Y-PTK2 20

PTK2/SRC-1 phosphorylates BCAR1 21

CRK binds BCAR1 and or PXN 22

DOCK180:ELMO binds CRK 23

DOCK180:ELMO exchanges GTP for GDP, activating RAC1 24

WAVE Regulatory Complex (WRC) interacts with RAC1 and PIP3 and gets activated 25

p-6Y-VEGFR2 binds SHC-transforming protein 2 27

p-6Y-VEGFR2 binds SH2D2A 28

SRC1-1 binds SH2D2A and is recruited to VEGFR2 29

Phosphorylation of SRC-1 30

AXL binds SRC-1 31

AXL autophosphorylates on Y772 and Y814 32

p-AXL binds PI3K 33

p-6Y-VEGFR2 binds PI3K 34

VEGFA dimer:p-6Y-VEGFR2 dimer:PI3K phosphorylates PIP2 to PIP3 35
PIP3 binds stimulating VAV
Src kinases phosphorylate VAV
p-VAV family: PIP3 binds RAC1:GDP
VAV exchanges GTP for GDP on RAC1, activating it
VEGFR2 mediated vascular permeability
NADPH oxidase 2 (NOX2) complex binds RAC1
NADPH oxidase 2 generates superoxide from oxygen
p-6Y-VEGFR2 binds NCK
p-6Y-VEGFR2 binds FYN
FYN autophosphorylates
p-Y420-FYN is phosphorylated on S21
PAK2 binds NCK
VEGF induces CDC42 activation by unknown mechanism
CDC42:GTP binds PAK2
PAK2 autophosphorylates
FYN phosphorylates PAK2
p38 MAPK activation by VEGFR
p38 MAPK phosphorylates MAPKAPH2, MAPKAPH3
p-MAPK2/3 phosphorylates HSP27
VEGFR2 mediated cell proliferation

Table of Contents