RHO GTPase Effectors

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25/08/2020
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: 73

This document contains 12 pathways (see Table of Contents)
RHO GTPase Effectors

Stable identifier: R-HSA-195258

RHO GTPases regulate cell behaviour by activating a number of downstream effectors that regulate cytoskeletal organization, intracellular trafficking and transcription (reviewed by Sahai and Marshall 2002).

One of the best studied RHO GTPase effectors are protein kinases ROCK1 and ROCK2, which are activated by binding RHOA, RHOB or RHOC. ROCK1 and ROCK2 phosphorylate many proteins involved in the stabilization of actin filaments and generation of actin-myosin contractile force, such as LIM kinases and myosin regulatory light chains (MRLC) (Amano et al. 1996, Ishizaki et al. 1996, Leung et al. 1996, Ohashi et al. 2000, Sumi et al. 2001, Riento and Ridley 2003, Watanabe et al. 2007).

PAK1, PAK2 and PAK3, members of the p21-activated kinase family, are activated by binding to RHO GTPases RAC1 and CDC42 and subsequent autophosphorylation and are involved in cytoskeleton regulation (Manser et al. 1994, Manser et al. 1995, Zhang et al. 1998, Edwards et al. 1999, Lei et al. 2000, Parrini et al. 2002; reviewed by Daniels and Bokoch 1999, Szczepanowska 2009).

RHOA, RHOB, RHOC and RAC1 activate protein kinase C related kinases (PKNs) PKN1, PKN2 and PKN3 (Maesaki et al. 1999, Zong et al. 1999, Owen et al. 2003, Modha et al. 2008, Hutchinson et al. 2011, Hutchinson et al. 2013), bringing them in proximity to the PIP3-activated PDPK1 (PDK1) and thus enabling PDPK1-mediated phosphorylation of PKN1, PKN2 and PKN3 (Flynn et al. 2000, Torbett et al. 2003). PKNs play important roles in cytoskeleton organization (Hamaguchi et al. 2000), regulation of cell cycle (Misaki et al. 2001), receptor trafficking (Metzger et al. 2003) and apoptosis (Takahashi et al. 1998). PKN1 is also involved in the ligand-dependent transcriptional activation by the androgen receptor (Metzger et al. 2003, Metzger et al. 2005, Metzger et al. 2008).

Citron kinase (CIT) binds RHO GTPases RHOA, RHOB, RHOC and RAC1 (Madaule et al. 1995), but the mechanism of CIT activation by GTP-bound RHO GTPases has not been elucidated. CIT and RHOA are implicated to act together in Golgi apparatus organization through regulation of the actin cytoskeleton (Camera et al. 2003). CIT is also involved in the regulation of cytokinesis through its interaction with KIF14 (Gruneberg et al. 2006, Bassi et al. 2013, Watanabe et al. 2013).


RHOQ (TC10) regulates the trafficking of CFTR (cystic fibrosis transmembrane conductance regulator) by binding to the Golgi-associated protein GOPC (also known as PIST, FIG and CAL). In the absence of RHOQ, GOPC bound to CFTR directs CFTR for lysosomal degradation, while GTP-bound RHOQ directs GOPC:CFTR complex to the plasma membrane, thereby rescuing CFTR (Neudauer et al. 2001, Cheng et al. 2005).

RAC1 and CDC42 activate WASP and WAVE proteins, members of the Wiskott-Aldrich Syndrome protein family. WASPs and WAVEs simultaneously interact with G-actin and the actin-related ARP2/3 complex, acting as nucleation promoting factors in actin polymerization (reviewed by Lane et al. 2014).

RHOA, RHOB, RHOC, RAC1 and CDC42 activate a subset of formin family members. Once activated, formins bind G-actin and the actin-bound profilins and accelerate actin polymerization, while some formins also interact with microtubules. Formin-mediated cytoskeletal reorganization plays important roles in cell motility, organelle trafficking and mitosis (reviewed by Kuhn and Geyer 2014).

Rhotekin (RTKN) and rhophilins (RHPN1 and RHPN2) are effectors of RHOA, RHOB and RHOC and have not been studied in detail. They regulate the organization of the actin cytoskeleton and are implicated in the establishment of cell polarity, cell motility and possibly endosome trafficking (Sudo et al. 2006, Watanabe et al. 1996, Fujita et al. 2000, Peck et al. 2002, Mircescu et al. 2002). Similar to formins (Miralles et al. 2003), cytoskeletal changes triggered by RTKN activation may lead to stimulation of SRF-mediated transcription (Reynaud et al. 2000).

RHO GTPases RAC1 and RAC2 are needed for activation of NADPH oxidase complexes 1, 2 and 3 (NOX1, NOX2 and NOX3), membrane associated enzymatic complexes that use NADPH as an electron donor to reduce oxygen and produce superoxide (O2-). Superoxide serves as a secondary messenger and also directly contributes to the microbicidal activity of neutrophils (Knaus et al. 1991, Roberts et al. 1999, Kim and Dinauer 2001, Jyoti et al. 2014, Cheng et al. 2006, Miyano et al. 2006, Ueyama et al. 2006).

**Literature references**


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RHO associated, coiled-coil containing protein kinases ROCK1 and ROCK2 consist of a serine/threonine kinase domain, a coiled-coil region, a RHO-binding domain and a plekstrin homology (PH) domain interspersed with a cysteine-rich region. The PH domain inhibits the kinase activity of ROCKs by an intramolecular fold. ROCKs are activated by binding of the GTP-bound RHO GTPases RHOA, RHOB and RHOC to the RHO binding domain of ROCKs (Ishizaki et al. 1996, Leung et al. 1996), which disrupts the autoinhibitory fold. Once activated, ROCK1 and ROCK2 phosphorylate target proteins, many of which are involved in the stabilization of actin filaments and generation of actin-myosin contractile force. ROCKs phosphorylate LIM kinases LIMK1 and LIMK2, enabling LIMKs to phosphorylate cofilin, an actin depolymerizing factor, and thereby regulate the reorganization of the actin cytoskeleton (Ohashi et al. 2000, Sumi et al. 2001). ROCKs phosphorylate MRLC (myosin regulatory light chain), which stimulates the activity of non-muscle myosin II (NMM2), an actin-based motor protein involved in cell migration, polarity formation and cytokinesis (Amano et al. 1996, Riento and Ridley 2003, Watanabe et al. 2007, Amano et al. 2010). ROCKs also phosphorylate the myosin phosphatase targeting subunit (MYPT1) of MLC phosphatase, inhibiting the phosphatase activity and preventing dephosphorylation of MRLC. This pathway acts synergistically with phosphorylation of MRLC by ROCKs towards stimulation of non-muscle myosin II activity (Kimura et al. 1996, Amano et al. 2010).

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The PAKs (p21-activated kinases) are a family of serine/threonine kinases mainly implicated in cytoskeletal rearrangements. All PAKs share a conserved catalytic domain located at the carboxyl terminus and a highly conserved motif in the amino terminus known as p21-binding domain (PBD) or Cdc42/Rac interactive binding (CRIB) domain. There are six mammalian PAKs that can be divided into two classes: class I (or conventional) PAKs (PAK1-3) and class II PAKs (PAK4-6). Conventional PAKs are important regulators of cytoskeletal dynamics and cell motility and are additionally implicated in transcription through MAPK (mitogen-activated protein kinase) cascades, death and survival signaling and cell cycle progression (Chan and Manser 2012).

PAK1, PAK2 and PAK3 are direct effectors of RAC1 and CDC42 GTPases. RAC1 and CDC42 bind to the CRIB domain. This binding induces a conformational change that disrupts inactive PAK homodimers and relieves autoinhibition of the catalytic carboxyl terminal domain (Manser et al. 1994, Manser et al. 1995, Zhang et al. 1998, Lei et al. 2000, Parrini et al. 2002; reviewed by Daniels and Bokoch 1999, Szczepanowska 2009). Autophosphorylation of a conserved threonine residue in the catalytic domain of PAKs (T423 in PAK1, T402 in PAK2 and T436 in PAK3) is necessary for the kinase activity of PAK1, PAK2 and PAK3. Autophosphorylation of PAK1 serine residue S144, PAK2 serine residue S141, and PAK3 serine residue S154 disrupts association of PAKs with RAC1 or CDC42 and enhances kinase activity (Lei et al. 2000, Chong et al. 2001, Parrini et al. 2002, Jung and Traugh 2005, Wang et al. 2011). LIMK1 is one of the downstream targets of PAK1 and is activated through PAK1-mediated phosphorylation of the threonine residue T508 within its activation loop (Edwards et al. 1999). Further targets are the myosin regulatory light chain (MRLC), myosin light chain kinase (MLCK), filamin, cortactin, p41Arc (a subunit of the Arp2/3 complex), caldesmon, paxillin and RhoGDI, to mention a few (Szczepanowska 2009).
Class II PAKs also have a CRIB domain, but lack a defined autoinhibitory domain and proline-rich regions. They do not require GTPases for their kinase activity, but their interaction with RAC or CDC42 affects their subcellular localization. Only conventional PAKs will be annotated here.

Literature references


Parrini, MC., Lei, M., Harrison, SC., Mayer, BJ. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. Mol Cell, 9, 73-83.

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**RHO GTPases activate PKNs**

**Location:** RHO GTPase Effectors

**Stable identifier:** R-HSA-5625740

Protein kinases N (PKN), also known as protein kinase C-related kinases (PKR) feature a C-terminal serine/threonine kinase domain and three RHO-binding motifs at the N-terminus. RHO GTPases RHOA, RHOB, RHOC and RAC1 bind PKN1, PKN2 and PKN3 (Maesaki et al. 1999, Zhong et al. 1999, Owen et al. 2003, Modha et al. 2008, Hutchinson et al. 2011, Hutchinson et al. 2013), bringing them in proximity to the PIP3-activated co-activator PDPK1 (PDK1) (Flynn et al. 2000, Torbett et al. 2003). PDPK1 phosphorylates PKNs on a highly conserved threonine residue in the kinase activation loop, which is a prerequisite for PKN activation. Phosphorylation of other residues might also be involved in activation (Flynn et al. 2000, Torbett et al. 2003, Dettori et al. 2009). PKNs are activated by fatty acids like arachidonic acid and phospholipids in vitro, but the in vivo significance of this activation remains unclear (Palmer et al. 1995, Yoshinaga et al. 1999).

PKNs play important roles in diverse functions, including regulation of cell cycle, receptor trafficking, vesicle transport and apoptosis. PKN is also involved in the ligand-dependent transcriptional activation by the androgen receptor. More than 20 proteins and several peptides have been shown to be phosphorylated by PKN1 and PKN2, including CPI-17 (Hamaguchi et al. 2000), alpha-actinin (Mukai et al. 1997), adducin (Collazos et al. 2011), CDC25C (Misaki et al. 2001), vimentin (Matsuzawa et al. 1997), TRAF1 (Kato et al. 2008), CLIP170 (Collazos et al. 2011) and EGFR (Collazos et al. 2011). There are no known substrates for PKN3 (Collazos et al. 2011).

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Citron kinase (CIT) or citron RHO-interacting kinase (CRIK) shares similarities with ROCK kinases. Like ROCK, it consists of a serine/threonine kinase domain, a coiled-coil region, a RHO-binding domain, a cysteine rich region and a plekstrin homology (PH) domain, but additionally features a proline-rich region and a PDZ-binding domain. A shorter splicing isoform of CIT, citron-N, is specifically expressed in the nervous system and lacks the kinase domain. Citron-N is a component of the post-synaptic density, where it binds to the PDZ domains of the scaffolding protein PDS-95/SAP90 (Zhang et al. 2006).

While the binding of CIT to RHO GTPases RHOA, RHOB, RHOC and RAC1 is well established (Madaule et al. 1995), the mechanism of CIT activation by GTP-bound RHO GTPases has not been elucidated. There are indications that CIT may be activated through autophosphorylation in the presence of active forms of RHO GTPases (Di Cunto et al. 1998). CIT appears to phosphorylate the myosin regulatory light chain (MRLC), the only substrate identified to date, on the same residues that are phosphorylated by ROCKs, but it has not been established yet how this relates to activation by RHO GTPases (Yamashiro et al. 2003). CIT and RHOA are implicated to act together in Golgi apparatus organization through regulation of the actin cytoskeleton (Camera et al. 2003). CIT is also involved in the regulation of cytokinesis through its interaction with KIF14 (Gruneberg et al. 2006, Bassi et al. 2013, Watanabe et al. 2013) and p27(Kip1) (Serres et al. 2012).

**Literature references**


RHO GTPases activate KTN1

**Location:** RHO GTPase Effectors

**Stable identifier:** R-HSA-5625970

**Compartments:** endoplasmic reticulum membrane, cytosol

GTP-bound active forms of RHO GTPases RHOA, RHOG, RAC1 and CDC42 bind kinectin (KTN1), a protein inserted in endoplasmic reticulum membranes that interacts with the cargo-binding site of kinesin and activates its microtubule-stimulated ATPase activity required for vesicle motility (Vignal et al. 2001, Hotta et al. 1996). The effect of RHOG activity on cellular morphology, exhibited in the formation of microtubule-dependent cellular protrusions, depends both on RHOG interaction with KTN1, as well as on the kinesin activity (Vignal et al. 2001). RHOG and KTN1 also cooperate in microtubule-dependent lysosomal transport (Vignal et al. 2001). The precise mechanism of kinectin-mediated Rho GTPase signaling cascade needs further elucidation, and only the first two steps, KTN1-activated RHO GTPase binding, and KTN1-kinesin-1 binding are annotated here.

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IQGAPs constitute a family of scaffolding proteins characterized by a calponin homology (CH) domain, a polyproline binding region (WW domain), a tandem of four IQ (isoleucine and glutamine-rich) repeats and a RAS GTPase-activating protein-related domain (GRD). Three IQGAPs have been identified in human, IQGAP1, IQGAP2 and IQGAP3. The best characterized is IQGAP1 and over 90 proteins have been reported to bind to it. IQGAPs integrate multiple signaling pathways and coordinate a large variety of cellular activities (White et al. 2012). IQGAP proteins IQGAP1, IQGAP2 and IQGAP3, bind activated RHO GTPases RAC1 and CDC42 via their GRD and stabilize them in their GTP-bound state (Kuroda et al. 1996, Swart-Mataraza et al. 2002, Wang et al. 2007). IQGAPs bind F-actin filaments via the CH domain and modulate cell shape and motility through regulation of G-actin/F-actin equilibrium (Brill et al. 1996, Fukata et al. 1997, Bashour et al. 1997, Wang et al. 2007, Pelikan-Conchaudron et al. 2011). Binding of IQGAPs to F-actin is inhibited by calmodulin binding to the IQ repeats (Bashour et al. 1997, Pelikan-Conchaudron et al. 2011). Based on IQGAP1 studies, IQGAPs presumably function as homodimers (Bashour et al. 1997).

IQGAP1 is involved in the regulation of adherens junctions through its interaction with E-cadherin (CDH1) and catenins (CTTN1 and CTTNA1) (Kuroda et al. 1998, Hage et al. 2009). IQGAP1 contributes to cell polarity and lamellipodia formation through its interaction with microtubules (Fukata et al. 2002, Suzuki and Takahashi 2008).

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Activated RHO GTPase RHOQ (TC10) regulates the trafficking of CFTR (cystic fibrosis transmembrane conductance regulator) by binding to GOPC (Golgi-associated and PDZ and coiled-coil motif-containing protein) also known as PIST, FIG or CAL. GOPC is a Golgi resident protein that binds several membrane proteins, thereby modulating their expression. In the absence of RHOQ, GOPC bound to CFTR directs CFTR for lysosomal degradation, while GTP-bound RHOQ directs GOPC:CFTR complex to the plasma membrane, thereby rescuing CFTR (Neudauer et al. 2001, Cheng et al. 2005).

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RHO GTPases Activate WASPs and WAVEs

**Location:** RHO GTPase Effectors

**Stable identifier:** R-HSA-5663213

WASP and WAVE proteins belong to the Wiskott-Aldrich Syndrome protein family, with recessive mutations in the founding member WASP being responsible for the X-linked recessive immunodeficiency known as the Wiskott-Aldrich Syndrome. WASP proteins include WASP and WASL (N-WASP). WAVE proteins include WASF1 (WAVE1), WASF2 (WAVE2) and WASF3 (WAVE3). WASPs and WAVEs contain a VCA domain (consisting of WH2 and CA subdomains) at the C-terminus, responsible for binding to G-actin (WH2 subdomain) and the actin-associated ARP2/3 complex (CA subdomain). WASPs contain a WH1 (WASP homology 1) domain at the N-terminus, responsible for binding to WIPs (WASP-interacting proteins). A RHO GTPase binding domain (GBD) is located in the N-terminal half of WASPs and C-terminally located in WAVEs. RHO GTPases activate WASPs by disrupting the autoinhibitory interaction between the GBD and VCA domains, which allows WASPs to bind actin and the ARP2/3 complex and act as nucleation promoting factors in actin polymerization. WAVEs have the WAVE/SCAR homology domain (WHD/SHD) at the N-terminus, which binds ABI, NCKAP1, CYFIP2 and BRK1 to form the WAVE regulatory complex (WRC). Binding of the RAC1:GTP to the GBD of WAVEs most likely induces a conformational change in the WRC that allows activating phosphorylation of WAVEs by ABL1, thus enabling them to function as nucleation promoting factors in actin polymerization through binding G-actin and the ARP2/3 complex (Reviewed by Lane et al. 2014).

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RHO GTPases Activate Formins

**Location:** RHO GTPase Effectors

**Stable identifier:** R-HSA-5663220

**Compartments:** cytosol, endosome membrane, nucleoplasm, plasma membrane

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Formins are a family of proteins with 15 members in mammals, organized into 8 subfamilies. Formins are involved in the regulation of actin cytoskeleton. Many but not all formin family members are activated by RHO GTPases. Formins that serve as effectors of RHO GTPases belong to different formin subfamilies but they all share a structural similarity to Drosophila protein diaphanous and are hence named diaphanous-related formins (DRFs).

DRFs activated by RHO GTPases contain a GTPase binding domain (GBD) at their N-terminus, followed by formin homology domains 3, 1, and 2 (FH3, FH1, FH2) and a diaphanous autoregulatory domain (DAD) at the C-terminus. Most DRFs contain a dimerization domain (DD) and a coiled-coil region (CC) in between FH3 and FH1 domains (reviewed by Kuhn and Geyer 2014). RHO GTPase-activated DRFs are autoinhibited through the interaction between FH3 and DAD which is disrupted upon binding to an active RHO GTPase (Li and Higgs 2003, Lammers et al. 2005, Nezami et al. 2006). Since formins dimerize, it is not clear whether the FH3-DAD interaction is intra- or intermolecular. FH2 domain is responsible for binding to the F-actin and contributes to the formation of head-to-tail formin dimers (Xu et al. 2004). The proline-rich FH1 domain interacts with the actin-binding proteins profilins, thereby facilitating actin recruitment to formins and accelerating actin polymerization (Romero et al. 2004, Kovar et al. 2006).

Different formins are activated by different RHO GTPases in different cell contexts. FMNL1 (formin-like protein 1) is activated by binding to the RAC1:GTP and is involved in the formation of lamellipodia in macrophages (Yayoshi-Yamamoto et al. 2000) and is involved in the regulation of the Golgi complex structure (Colon-Franco et al. 2011). Activation of FMNL1 by CDC42:GTP contributes to the formation of the phagocytic cup (Seth et al. 2006). Activation of FMNL2 (formin-like protein 2) and FMNL3 (formin-
like protein 3) by RHOC:GTP is involved in cancer cell motility and invasiveness (Kitzing et al. 2010, Vega et al. 2011). DIAPH1, activated by RHOA:GTP, promotes elongation of actin filaments and activation of SRF-mediated transcription which is inhibited by unpolymerized actin (Miralles et al. 2003). RHOF-mediated activation of DIAPH1 is implicated in formation of stress fibers (Fan et al. 2010). Activation of DIAPH1 and DIAPH3 by RHOB:GTP leads to actin coat formation around endosomes and regulates endosome motility and trafficking (Fernandez-Borja et al. 2005, Wallar et al. 2007). Endosome trafficking is also regulated by DIAPH2 transcription isoform 3 (DIAPH2-3) which, upon activation by RHOD:GTP, recruits SRC kinase to endosomes (Tominaga et al. 2000, Gasman et al. 2003). DIAPH2 transcription isoform 2 (DIAPH2-2) is involved in mitosis where, upon being activated by CDC42:GTP, it facilitates the capture of astral microtubules by kinetochores (Yasuda et al. 2004, Cheng et al. 2011). DIAPH2 is implicated in ovarian maintenance and premature ovarian failure (Bione et al. 1998). DAAM1, activated by RHOA:GTP, is involved in linking WNT signaling to cytoskeleton reorganization (Habas et al. 2001).

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Rhotekin (RTKN) is a protein with an N-terminally located RHO GTPase binding domain, that shares a limited sequence homology with PKNs and rhophilins. RTKN binds to GTP-bound RHOA, RHOB and RHOC and can inhibit their GTPase activity (Reid et al. 1996, Fu et al. 2000), which can be corroborated by protein kinase D-mediated phosphorylation of RTKN (Pusapati et al. 2012). RTKN is implicated in the establishment of cell polarity (Sudo et al. 2006), septin organization (Ito et al. 2005, Sudo et al. 2007) and stimulation of SRF-mediated transcription (Reynaud et al. 2000). RTKN can have an anti-apoptotic effect that depends on the activation of NFKB (NF-kappaB) (Liu et al. 2004). RTKN2 (rhotekin-2) is another rhotekin exclusively expressed in lymphocytes (Collier et al. 2004). The function and the mechanism of action of RTKN2 are unknown.

Rhophilins include two family members - rhophilin-1 (RHNPI) and rhophilin-2 (RHPN2) with ~75% sequence identity. A RHO GTPase binding domain is located at the N-terminus of rhophilins, followed by a BRO1 domain (characteristic of proteins involved in protein kinase C signaling) and a C-terminal PDZ domain. RHOA:GTP binds both RHPN1 and RHPN2 and these interactions may be involved in organization of the actin cytoskeleton and/or cell motility (Watanabe et al. 1996, Fujita et al. 2000, Peck et al. 2002). RHOB:GTP recruits RHPN2 to endosomes which may be involved in the function of thyroid cells (Mircescu et al. 2002). RHOB:GTP recruits RHPN2 to endosomes which may be involved in the function of thyroid cells (Mircescu et al. 2002).

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https://reactome.org
NADPH oxidases (NOX) are membrane-associated enzymatic complexes that use NADPH as an electron donor to reduce oxygen and produce superoxide (O2-) that serves as a secondary messenger (Brown and Griendling 2009).

NOX2 complex consists of CYBB (NOX2), CYBA (p22phox), NCF1 (p47phox), NCF2 (p67phox) and NCF4 (p40ohox). RAC1:GTP binds NOX2 complex in response to VEGF signaling by directly interacting with CYBB and NCF2, leading to enhancement of VEGF-signaling through VEGF receptor VEGFR2, which plays a role in angiogenesis (Ushio-Fukai et al. 2002, Bedard and Krause 2007). RAC2:GTP can also activate the NOX2 complex by binding to CYBB and NCF2, leading to production of superoxide in phagosomes of neutrophils which is necessary for the microbicidal activity of neutrophils (Knaus et al. 1991, Roberts et al. 1999, Kim and Dinauer 2001, Jyoti et al. 2014).

NOX1 complex (composed of NOX1, NOXA1, NOXO1 and CYBA) and NOX3 complex (composed of NOX3, CYBA, NCF1 and NCF2 or NOXA1) can also be activated by binding to RAC1:GTP to produce superoxide (Cheng et al. 2006, Miyano et al. 2006, Ueyama et al. 2006).

Literature references


Roberts, AW., Kim, C., Zhen, L., Lowe, JB., Kapur, R., Petryniak, B. et al. (1999). Deficiency of the hematopoietic cell-specific Rho family GTPase Rac2 is characterized by abnormalities in neutrophil function and host defense. *Immunology, 10*, 183-96.

**Editions**

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</table>
# Table of Contents

- Introduction  
- RHO GTPase Effectors
  - RHO GTPases Activate ROCKs  
  - RHO GTPases activate PAKs  
  - RHO GTPases activate PKNs  
  - RHO GTPases activate CIT  
  - RHO GTPases activate KTN1  
  - RHO GTPases activate IQGAPs  
  - RHO GTPases regulate CFTR trafficking  
  - RHO GTPases Activate WASPs and WAVEs  
  - RHO GTPases Activate Formins  
  - RHO GTPases Activate Rhotekin and Rhophilins  
  - RHO GTPases Activate NADPH Oxidases

Table of Contents