Signaling by Rho GTPases, Miro GTPases and RHOBTB3


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21/09/2022
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: 82

This document contains 4 pathways (see Table of Contents)
RAS-like proteins are small GTP binding proteins characterized structurally by 5 G boxes that are involved in nucleotide binding and hydrolysis. RAS-like proteins are typically active when bound to GTP and inactive when bound to GDP. Conversion between the two states is mediated by effector proteins: among others, GTPase activating proteins (GAPs) enable hydrolysis of bound GTP to form GDP, which remains bound, and guanine nucleotide exchange factors (GEFs) enable exchange of bound GDP for free GTP (intracellular GTP concentrations are typically an order of magnitude higher than GDP concentrations) (reviewed in Tetlow and Tamanoi, 2013).

The human genome includes over 150 members of the RAS superfamily grouped into five main subfamilies: RAS, RHO, ARF, RAB and RAN. These small GTPases affect a wide range of critical processes including gene expression, signal transduction, cell morphology, vesicle and nuclear trafficking, cellular proliferation and motility, among others (reviewed in Tetlow and Tamanoi, 2013).

The RHO family of GTPases is large and diverse, with many of its members considered to be master regulators of actin cytoskeleton, involved in the regulation of cellular processes that depend on dynamic reorganization of the cytoskeleton, including cell migration, cell adhesion, cell division, establishment of cellular polarity and intracellular transport (reviewed in Hodge and Ridley 2016, and Olson 2018).

MIRO proteins and RHOBTB3 protein, sometimes called atypical RHO proteins, show a high degree of overall sequence similarity to members of the five RAS-like subfamilies but diverge in their functions enough to constitute two separate subfamilies (Boureux et al. 2007). MIRO proteins have intrinsically high GTPase activity and do not require GTPase activator proteins (Peters et al. 2018). They play an important role mitochondrial biogenesis, maintenance and organization (reviewed in Birsa et al. 2013). The GTPase domain of RHOBTB3 is divergent from other Ras like superfamily members and displays ATPase activity (Espinosa et al. 2009). RHOBTB3 is involved in CUL3 dependent protein ubiquitination (Berthold et al. 2008; Ji and Rivero 2016), retrograde transport from endosomes to the Golgi apparatus (Espinosa et al. 2009), regulation of the cell cycle and in modulating the adaptive response to hypoxia (Ji and Rivero 2016).
Literature references


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<td>2021-02-25</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
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The Rho family of small guanine nucleotide binding proteins is one of seven phylogenetic branches of the Ras superfamily (Bernards 2005), which, besides Rho, Miro and RHOBTB3 also includes Ran, Arf, Rab and Ras families (Boureux et al. 2007). Miro GTPases and RHOBTB3 ATPase are sometimes described as Rho family members, but they are phylogenetically distinct (Boureux et al. 2007). Phylogenetically, RHO GTPases can be grouped into four clusters. The first cluster consists of three subfamilies: Rho, RhoD/RhoF and Rnd. The second cluster consists of three subfamilies: Rac, Cdc42 and RhoU/RhoV. The third cluster consists of the RhoH subfamily. The fourth cluster consists of the RhoBTB subfamily. Based on their activation type, RHO GTPases can be divided into classical (typical) and atypical (reviewed by Haga and Ridley 2016, and Kalpachidou et al. 2019). Classical RHO GTPases include four subfamilies: Rho (includes RHOA, RHOB and RHOC), Rac (includes RAC1, RAC2, RAC3 and RHOG), Cdc42 (includes CDC42, RHOJ and RHOQ) and Rhod/RhoP (includes RHOD and RHOF) (reviewed in Haga and Ridley 2016). Atypical RHO GTPases do not possess GTPase activity. They therefore constitutively exist in the active GTP-bound state. Atypical RHO GTPases include three subfamilies: Rnd (includes RND1, RND2 and RND3), RhoBTB (includes RHOBTB1 and RHOBTB2), RhoH (RHOH is the only member) and RhoU/RhoV (includes RHOU and RHOV). Members of the Rho family have been identified in all euca-
ryotes. Among Rho GTPases, RHOA, RAC1 and CDC42 have been most extensively studied.

RHO GTPases regulate cell behavior by activating a number of downstream effectors that regulate cytoskeletal organization, intracellular trafficking and transcription (reviewed by Sahai and Marshall 2002). They are best known for their ability to induce dynamic rearrangements of the plasma membrane-associated actin cytoskeleton (Aspenstrom et al. 2004; Murphy et al. 1999; Govek et al. 2005). Beyond this function, Rho GTPases also regulate actomyosin contractility and microtubule dynamics. Rho mediated effects on transcription and membrane trafficking are believed to be secondary to these functions. At the more macroscopic level, Rho GTPases have been implicated in many important cell biological processes, including cell growth control, cytokinesis, cell motility, cell-cell and cell-extracellular matrix adhesion, cell transformation and invasion, and development (Govek et al., 2005). One of the best studied RHO GTPase effectors are protein kinases ROCK1 and ROCK2, which 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) (reviewed in Riento and Ridley 2003). The p21-activated kinase family, which includes PAK1, PAK2 and PAK3, is another well characterized family of RHO GTPase effectors involved in cytoskeleton regulation (reviewed in Daniels and Bokoch 1999, Szczepanowska 2009). Protein kinase C related kinases (PKNs), PKN1, PKN2 and PKN3 play important roles in cytoskeleton organization (Hamaguchi et al. 2000), regulation of cell cycle (Misaki et al. 2001), receptor trafficking (Metzger et al. 2003), apoptosis (Takahashi et al. 1998), and transcription (Metzger et al. 2003, Metzger et al. 2005, Metzger et al. 2008). Citron kinase (CIT) is involved in Golgi apparatus organization through regulation of the actin cytoskeleton (Camera et al. 2003) and in the regulation of cytokinesis (Gruneberg et al. 2006, Bassi et al. 2013, Watanabe et al. 2013). Kinectin (KTN1), a kinesin anchor protein, is a RHO GTPase effector involved in kinesin-mediated vesicle motility (Vignal et al. 2001, Hotta et al. 1996), including microtubule-dependent lysosomal transport (Vignal et al. 2001). IQGAP proteins, IQGAP1, IQGAP2 and IQGAP3, are RHO GTPase effectors that 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-Conchadron et al. 2011), regulate adherens junctions (Kuroda et al. 1998, Hage et al. 2009), and contribute to cell polarity and lamellipodia formation (Fukata et al. 2002, Suzuki and Takahashi 2008). WASP and WAVE proteins (reviewed by Lane et al. 2014), as well as formins (reviewed by Kuhn and Geyer 2014), are RHO GTPase effectors that regulate actin polymerization and play important roles in cell motility, organelle trafficking and mitosis. Rhotekin (RTKN) and rhophilins (RHPN1 and RHPN2) are RHO GTPase effectors that 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). Cytoskeletal changes triggered by the activation of formins (Miralles et al. 2003) and RTKN (Reynaud et al. 2000) may lead to stimulation of SRF-mediated transcription. 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-), are also regulated by RHO GTPases (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). Every RHO GTPase activates multiple downstream effectors and most effectors are regulated by multiple RHO GTPases, resulting in an elaborate cross-talk.

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RHOBTB3 is a member of the Ras-like superfamily of proteins that is phylogenetically distinct from other related Ras-like families, which include, besides RHOBTB3, Rho, Miro, Ras, Ran, Arf and Rab (Boureux et al. 2007). Due to its similarity with RHOBTB1 and RHOBTB2 Rho GTPases, RHOBTB3 is sometimes classified as an atypical member of the RHO GTPase family. However, the GTPase domain of RHOBTB3 is divergent from other Ras-like superfamily members and actually displays ATPase activity (Espinosa et al. 2009). All three RHOBTBs possess other conserved domains in addition to the GTPase domain. The GTPase domain at the N terminus is followed by a proline rich region, a tandem of two BTB (broad complex, tramtrack, bric à brac) domains, and a conserved C terminal BACK (BTB and C terminal Kelch). Unlike RHOBTB1 and RHOBTB2, RHOBTB3 has a CAAX box (prenylation motif) domain (Berthold et al. 2008, Ji and Rivero 2016). RHOBTB proteins can form homo and heterodimers, but the role of dimerization in RHOBTB function is not known (Berthold et al. 2008, Ji and Rivero 2016). RHOBTB3 is ubiquitously expressed, with high levels in placenta, testis, pancreas, adrenal and salivary glands and neural and cardiac tissues (Berthold et al. 2016). RHOBTB3 is involved in CUL3-dependent protein ubiquitination (Berthold et al. 2008; Ji and Rivero 2016). RHOBTB3 is involved in retrograde transport from endosomes to the Golgi apparatus (Espinosa et al. 2009). RHOBTB3 participates in regulation of the cell cycle and in modulating the adaptive response to hypoxia (Ji and Rivero 2016). RHOBTB3 level is decreased in many tumor types and it is proposed to act as a tumor suppressor, although no pathogenic mutations have been reported (Berthold et al. 2008; Ji and Rivero 2016).

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Miro GTPases are a separate family of Ras-related GTPases that are sometimes included in the atypical RHO GTPases group, but are phylogenetically distinct from the Rho family (Jaffe and Hall 2005; Boureux et al. 2007; Devine et al. 2016; Liu et al. 2017). Miro GTPases possess an additional GTPase domain more closely related to Rheb (Klosowiak et al. 2013). Miro family of RAS-like GTPases includes two members, RHOT1 and RHOT2. RHOT1 and RHOT2 regulate the movement of mitochondria (Schwarz 2013; Devine et al. 2016) and peroxisomes (Castro et al. 2018, Okumoto et al. 2018, Covill-Cooke et al. 2020).

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