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 1 pathway and 9 reactions (see Table of Contents)
This pathway catalogues RHOD GTPase activator proteins (GAPs) and RHOD effectors. RHOD possesses GTPase activity and is therefore grouped with classical RHO GTPases but it is atypical in the sense that no known guanine nucleotide exchange factors (GEFs) and no GDP dissociation inhibitors (GDIs) (Blom et al. 2017) are involved in the regulation of RHOD activity. RHOD possesses an elevated intrinsic guanine nucleotide exchange activity and auto-activates (Jaiswal, Fansa et al. 2013). RHOD regulates cytoskeletal dynamics and intracellular transport of vesicles (Gad and Aspenstrom 2010; Aspenstrom et al. 2014), especially actin-dependent movement of endosomes (Gasman et al. 2003, reviewed in Randazzo 2003).

**Literature references**


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**RHOD auto-activates**

**Location:** RHOD GTPase cycle

**Stable identifier:** R-HSA-9013435

**Type:** transition

**Compartments:** plasma membrane, cytosol

RHOD is a RHO GTPase that possesses an elevated intrinsic guanine nucleotide exchange activity (Jaiswal, Fansa et al. 2013) and has never been shown to interact with any guanine nucleotide exchange factor (GEF) except with ARHGEF2 in a high-throughput study by Paul et al. 2017, although no activation of RHOD by ARHGEF2 was demonstrated. The following GEFs were specifically shown to not interact nor activate RHOD: DOCK11 (Ruiz-Lafuente et al. 2015), ITSN1 (Jaiswal et al. 2013), MCF2 (Jaiswal et al. 2013), MCF2L (Jaiswal et al. 2013), PREX1 (Jaiswal et al. 2013), TIAM1 (Jaiswal et al. 2013), TRIO (Jaiswal et al. 2013) and VAV2 (Jaiswal et al. 2013). As GTP is more abundant in cells than GDP (Traut 1994), RHOD is thought to be present in a constitutively active state (Jaiswal, Fansa et al. et al. 2013).

RHOD localization depends on its activation state - inactive RHOD is mainly cytosolic, while GTP-bound RHOD is found at the plasma membrane and at vesicle membranes (Blom et al. 2018).

**Followed by:** RHOD binds effectors at the plasma membrane, RHOD:GTP translocates to the endosome membrane, RHOD translocates to the mitochondrial outer membrane, RHOD GAPs stimulate RHOD GTPase activity, RHOD translocates to the Golgi membrane

**Literature references**


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The following GTPase activating proteins (GAPs) were shown to bind RHOD and stimulate its GTPase activity, resulting in GTP to GDP hydrolysis and conversion of the active RHOD:GTP complex to the inactive RHOD:GDP complex (the study by Bagci et al. 2020 is cited as supporting evidence since it only examined binding of GAPs to active RHOD without testing for RHOD-directed GAP activity):

ARHGAP1 (Amin et al. 2016; supported by Bagci et al. 2020)

ARHGAP26 (Amin et al. 2016)

ARHGAP32 (Paul et al. 2017; supported by Bagci et al. 2020)

ARHGAP35 (Amin et al. 2016; supported by Bagci et al. 2020)

The following GAPs were shown to bind RHOD and stimulate its GTPase activity in some but not all studies or were shown by Bagci et al. 2020 to bind to active RHOD without testing for RHOD-directed GAP activity and are annotated as candidate RHOD GAPs:

ARHGAP5 (Bagci et al. 2020)

ARHGAP12 (Bagci et al. 2020)

ARHGAP17 (Amin et al. 2016: RHOD directed GAP activity; Bagci et al. 2020: no binding to active RHOD)

ARHGAP21 (Bagci et al. 2020)

ARHGAP39 (Bagci et al. 2020)

DEPDC1B (Bagci et al. 2020)

PIK3R1 (Bagci et al. 2020)
PIK3R2 (Bagci et al. 2020)
RACGAP1 (Amin et al. 2016: RHOD directed GAP activity; Bagci et al. 2020: no binding to active RHOD)
The following GAPs do not act on RHOD or were shown by Bagci et al. 2020 to not bind to active RHOD:
ABR (Amin et al. 2016; Bagci et al. 2020)
ARAP2 (Bagci et al. 2020)
ARAP3 (Bagci et al. 2020)
ARHGAP29 (Bagci et al. 2020)
ARHGAP31 (Bagci et al. 2020)
ARHGAP42 (Bagci et al. 2020)
BCR (Bagci et al. 2020)
DLC1 (Amin et al. 2016)
MYO9A (Bagci et al. 2020)
MYO9B (Bagci et al. 2020)
OPHN1 (Amin et al. 2016; Bagci et al. 2020)
SRGAP2 (Bagci et al. 2020)
STARD13 (Amin et al. 2016)
STARD8 (Amin et al. 2016)
SYDE1 (Bagci et al. 2020)

Preceded by: RHOD auto-activates

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https://reactome.org
RHOD binds effectors at the plasma membrane

Location: RHOD GTPase cycle

Stable identifier: R-HSA-9693198

Type: binding

Compartments: plasma membrane, cytosol

Active GTP bound RHOD binds to the following effectors at the plasma membrane:

- DIAPH1 (Kyrkou et al. 2013)
- PAK6 (Durkin et al. 2017)
- PLXNA1 (Zanata et al. 2002)
- PLXNB1 (Tong et al. 2007)

The following candidate RHOD effectors that can localize to plasma membrane and cytosol were reported in the high throughput screen by Bagci et al. 2020:

- ACTN1 (Bagci et al. 2020)
- ADD3 (Bagci et al. 2020)
- AKAP12 (Bagci et al. 2020)
- ARHGAP1 (Bagci et al. 2020)
- ARHGAP39 (Bagci et al. 2020)
- CAPZB (Bagci et al. 2020)
- CAV1 (Bagci et al. 2020)
- CPNE8 (Bagci et al. 2020)
- DBN1 (Bagci et al. 2020)
- DIAPH3 (Bagci et al. 2020)
- EFHD2 (Bagci et al. 2020)
- ESYT1 (Bagci et al. 2020)
- LMNB1 (Bagci et al. 2020)
- MCAM (Bagci et al. 2020)
- RAB7A (Bagci et al. 2020)

https://reactome.org
SLC4A7 (Bagci et al. 2020)
STBD1 (Bagci et al. 2020)
STEAP3 (Bagci et al. 2020)
TMPO (Bagci et al. 2020)
TOR1AIP1 (Bagci et al. 2020)
VAMP3 (Bagci et al. 2020)
VANGL1 (Bagci et al. 2020)
The following putative effectors do not bind to active RHOD:
ACTB (Bagci et al. 2020)
BASP1 (Bagci et al. 2020)
FAM169A (Bagci et al. 2020)
MTMR1 (Bagci et al. 2020)
POTEE (Bagci et al. 2020)
SENP1 (Bagci et al. 2020)
SNAP23 (Bagci et al. 2020)
SOWAHC (Bagci et al. 2020)

**Preceded by:** RHOD auto-activates

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[https://reactome.org](https://reactome.org)
RHOD: GTP translocates to the endosome membrane

Location: RHOD GTPase cycle

Stable identifier: R-HSA-9013452

Type: omitted

Compartment: endosome membrane, plasma membrane

RHOD localizes to both plasma membrane and endosome membranes (Murphy et al. 1996). The translocation mechanism is not known.

Preceded by: RHOD auto-activates

Followed by: RHOD binds effectors at the endosome membrane

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Active GTP-bound RHOD binds the following effectors at the endosome membrane:

ANKFY1 (Nehru et al. 2013)

DIAPH2-3 (DIAPH2 isoform C) (Gasman et al. 2003)

The following candidate effectors that can localize to endosomal membranes were reported to bind active RHOD by Bagci et al. 2020:

EMD (Bagci et al. 2020)

LBR (Bagci et al. 2020)

LEMD3 (Bagci et al. 2020)

MOSPD2 (Bagci et al. 2020)

PGRMC2 (Bagci et al. 2020)

**Preceded by:** RHOD:GTP translocates to the endosome membrane

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RHOD translocates to the mitochondrial outer membrane

**Location:** RHOD GTPase cycle

**Stable identifier:** R-HSA-9693207

**Type:** uncertain

**Compartments:** plasma membrane, mitochondrial outer membrane

Active GTP-bound RHOD can be detected at the mitochondrial outer membrane (Wu and Frost 2006). The translocation mechanism is not known.

**Preceded by:** RHOD auto-activates

**Followed by:** RHOD binds effectors at the mitochondrial outer membrane

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RHOD binds effectors at the mitochondrial outer membrane

**Location:** RHOD GTPase cycle

**Stable identifier:** R-HSA-9693214

**Type:** binding

**Compartments:** cytosol, mitochondrial outer membrane

Active GTP-bound RHOD binds PAK5 and recruits it to the mitochondrial outer membrane (Wu and Frost 2006).

GTP-bound RHOD also binds HINT2 at the mitochondrial outer membrane, which triggers mitochondrial Ca2+ influx (Chen et al. 2017, supported by Bagci et al. 2020).

VRK2, which can localize to the mitochondrial outer membrane was reported to bind active RHOD by Bagci et al. 2020 and is annotated as a candidate effector.

**Preceded by:** RHOD translocates to the mitochondrial outer membrane

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**RHOD translocates to the Golgi membrane**

**Location:** RHOD GTPase cycle

**Stable identifier:** R-HSA-9693243

**Type:** uncertain

**Compartments:** plasma membrane, Golgi membrane

Active GTP-bound RHOD localizes to the Golgi membrane (Gad et al. 2012, Blom et al. 2015). The mechanism of translocation is not known.

**Preceded by:** RHOD auto-activates

**Followed by:** RHOD binds effectors at the Golgi membrane

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**RHOD binds effectors at the Golgi membrane**

**Location:** RHOD GTPase cycle

**Stable identifier:** R-HSA-9693250

**Type:** binding

**Compartments:** Golgi membrane, cytosol

Active GTP bound RHOD binds the following effectors at the Golgi membrane:

- FILIP1 (Gad et al. 2012)
- WHAMM (Gad et al. 2012; Blom et al. 2015)

The following candidate effectors were reported to bind active RHOD by Bagci et al. 2020:

- GOLGA8R (Bagci et al. 2020)
- LMAN1 (Bagci et al. 2020)
- VAPB (Bagci et al. 2020)

**Preceded by:** RHOD translocates to the Golgi membrane

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