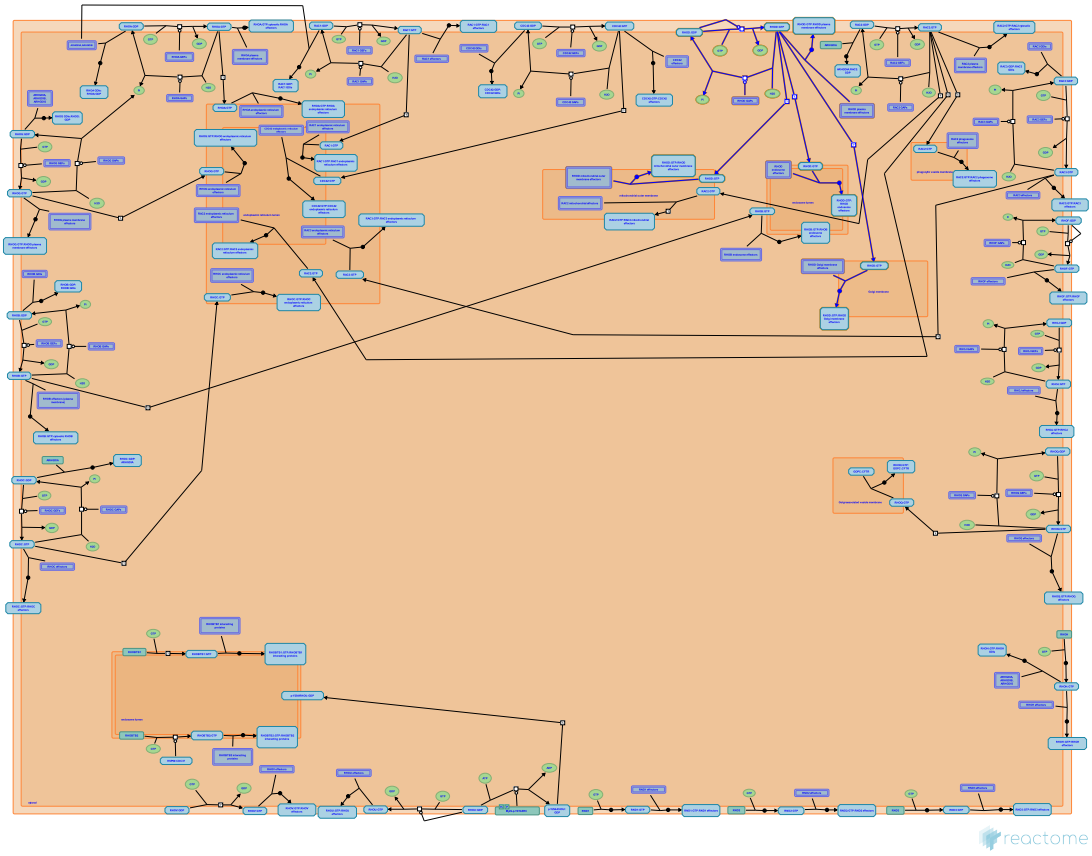
RHOD GTPase cycle



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27/04/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

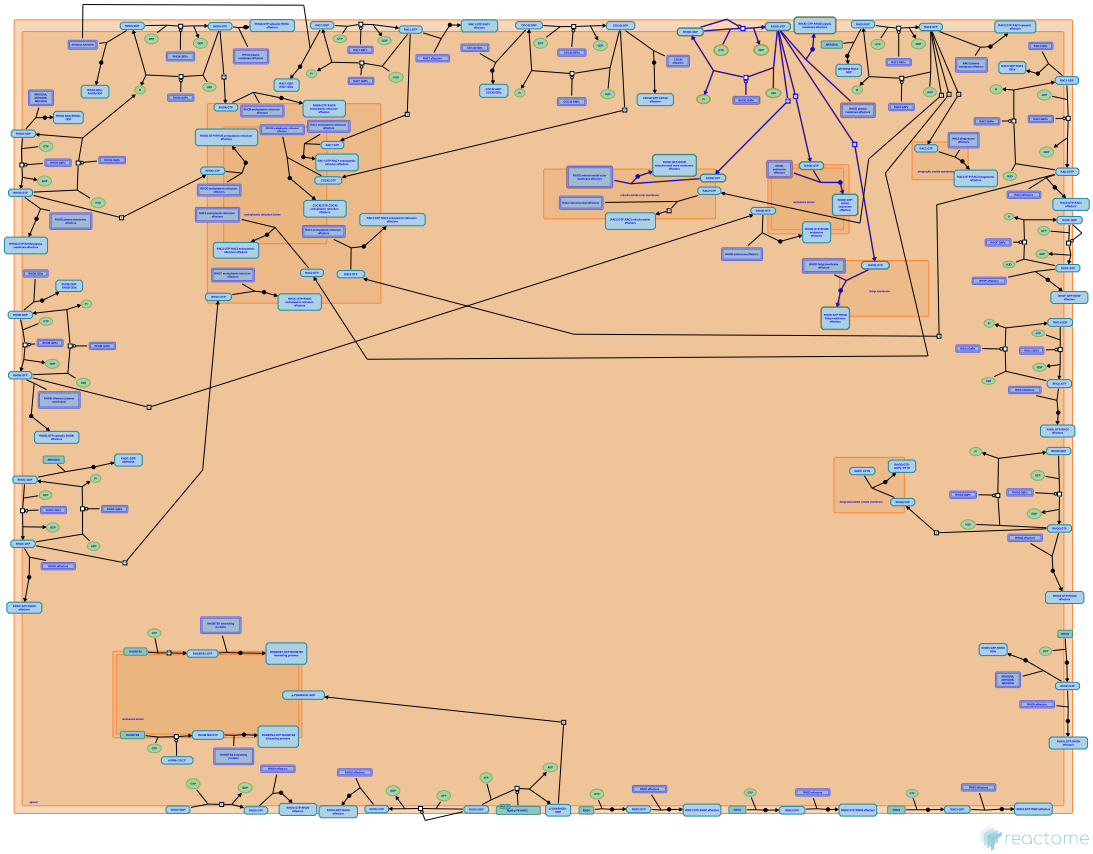
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

RHOD GTPase cycle ↗

Stable identifier: R-HSA-9013405



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

Aspenström, P. (2014). Atypical Rho GTPases RhoD and Rif integrate cytoskeletal dynamics and membrane trafficking. *Biol. Chem., 395*, 477-84. ↗

Randazzo, PA. (2003). RhoD, Src, and hDia2C in endosome motility. *Dev. Cell, 4*, 287-8. ↗

Gad, AK., Aspenström, P. (2010). Rif proteins take to the RhoD: Rho GTPases at the crossroads of actin dynamics and membrane trafficking. *Cell. Signal., 22*, 183-9. ↗

Blom, M., Reis, K., Kreuger, J., Heldin, J., Aspenström, P. (2017). The atypical Rho GTPase RhoD is a regulator of actin cytoskeleton dynamics and directed cell migration. *Exp. Cell Res., 352*, 255-264. ↗

Ahmadian, MR., Jaiswal, M., Fansa, EK., Dvorsky, R. (2013). New insight into the molecular switch mechanism of human Rho family proteins: shifting a paradigm. *Biol. Chem., 394*, 89-95. ↗

Editions

2020-07-14	Authored	Orlic-Milacic, M.
2021-02-05	Reviewed	Fort, P.
2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

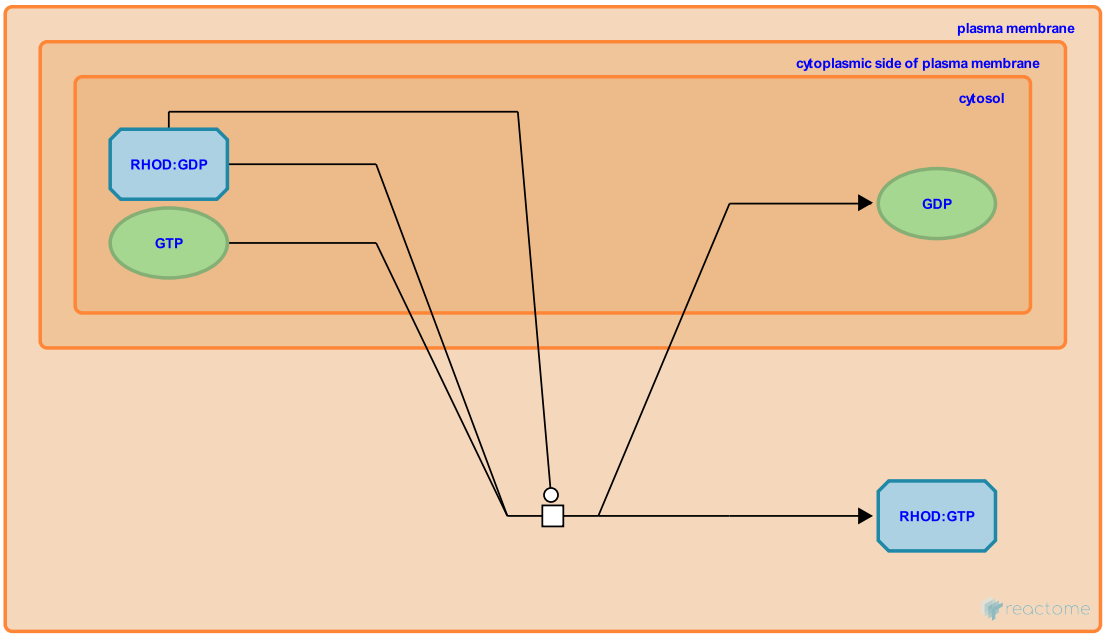
RHOD auto-activates ↗

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

Blom, M., Reis, K., Aspenström, P. (2018). RhoD localization and function is dependent on its GTP/GDP-bound state and unique N-terminal motif. *Eur. J. Cell Biol., 97*, 393-401. ↗

Ahmadian, MR., Jaiswal, M., Fansa, EK., Dvorsky, R. (2013). New insight into the molecular switch mechanism of human Rho family proteins: shifting a paradigm. *Biol. Chem., 394*, 89-95. ↗

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2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

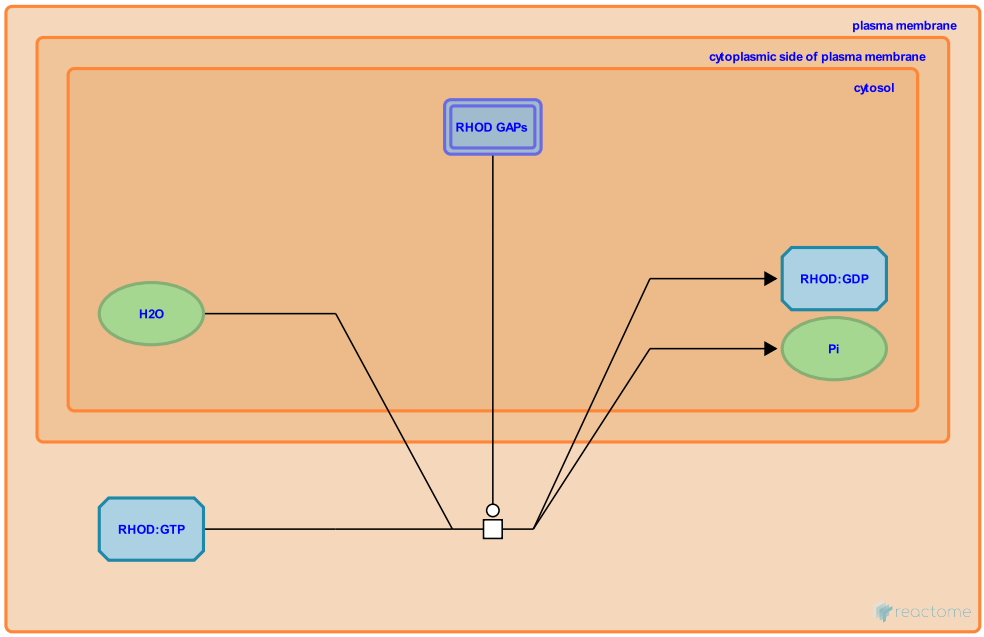
RHOD GAPs stimulate RHOD GTPase activity ↗

Location: RHOD GTPase cycle

Stable identifier: R-HSA-9013437

Type: transition

Compartments: plasma membrane, cytosol



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

Literature references

Ahmadian, MR., Somlyo, AV., Amin, E., Koessmeier, KT., Jaiswal, M., Dvorsky, R. et al. (2016). Deciphering the Molecular and Functional Basis of RHOGAP Family Proteins: A SYSTEMATIC APPROACH TOWARD SELECTIVE INACTIVATION OF RHO FAMILY PROTEINS. *J. Biol. Chem., 291*, 20353-71. ↗

Paul, F., von Berg, L., Selbach, M., Daumke, O., Zauber, H., Rocks, O. (2017). Quantitative GTPase Affinity Purification Identifies Rho Family Protein Interaction Partners. *Mol. Cell Proteomics, 16*, 73-85. ↗

Tran, V., Gingras, AC., Elkholi, IE., Robert, A., Boulais, J., Faubert, D. et al. (2020). Mapping the proximity interaction network of the Rho-family GTPases reveals signalling pathways and regulatory mechanisms. *Nat. Cell Biol., 22*, 120-134. ↗

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2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

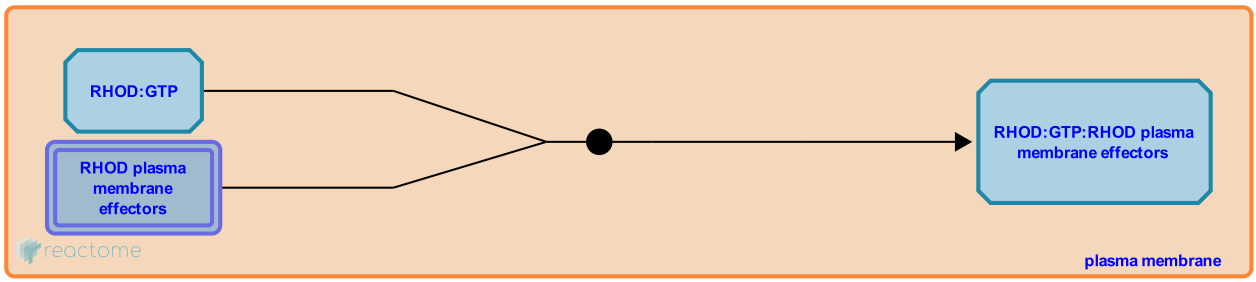
RHOD binds effectors at the plasma membrane ↗

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)
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

Literature references

Hota, PK., Park, HW., Tempel, W., Chugha, P., Alviani, RS., Shen, L. et al. (2007). Binding of Rac1, Rnd1, and RhoD to a novel Rho GTPase interaction motif destabilizes dimerization of the plexin-B1 effector domain. *J Biol Chem, 282*, 37215-24. ↗

Bai, M., Zerial, M., Ferguson, C., Hoffmann, I., Kyrkou, A., Soufi, M. et al. (2013). RhoD participates in the regulation of cell-cycle progression and centrosome duplication. *Oncogene, 32*, 1831-42. ↗

Rohm, B., Hovatta, I., Zanata, SM., Püschel, AW. (2002). Antagonistic effects of Rnd1 and RhoD GTPases regulate receptor activity in Semaphorin 3A-induced cytoskeletal collapse. *J Neurosci, 22*, 471-7. ↗

Leite, F., Valderrama, F., Arakawa, Y., Cordeiro, JV., Way, M., Handa, Y. et al. (2017). RhoD Inhibits RhoC-ROCK-Dependent Cell Contraction via PAK6. *Dev. Cell, 41*, 315-329.e7. ↗

Tran, V., Gingras, AC., Elkholi, IE., Robert, A., Boulais, J., Faubert, D. et al. (2020). Mapping the proximity interaction network of the Rho-family GTPases reveals signalling pathways and regulatory mechanisms. *Nat. Cell Biol., 22*, 120-134. ↗

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2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

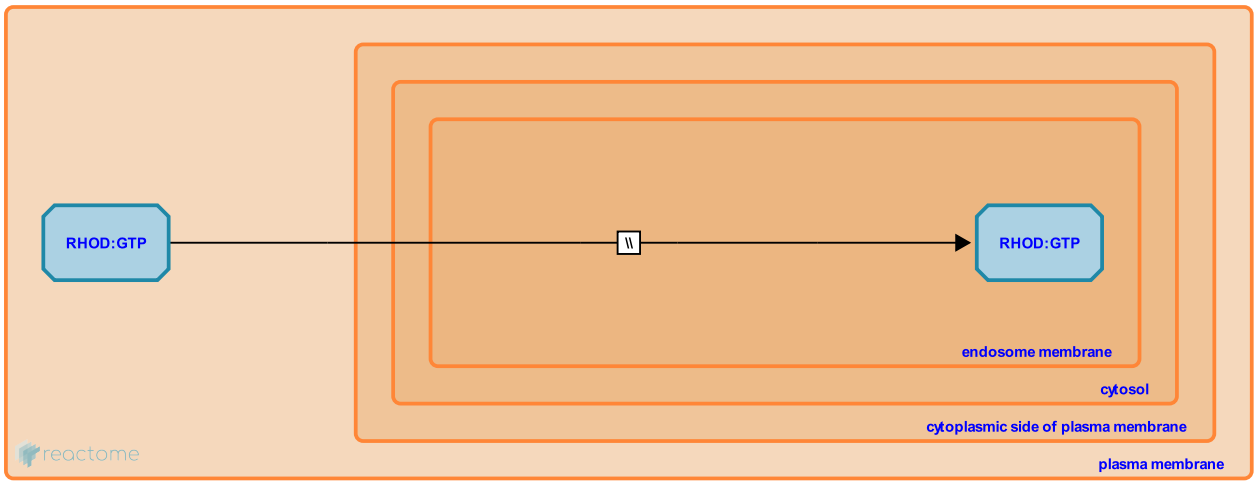
RHOD:GTP translocates to the endosome membrane ↗

Location: RHOD GTPase cycle

Stable identifier: R-HSA-9013452

Type: omitted

Compartments: 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

Literature references

Zerial, M., Rybin, V., Rubino, M., Saffrich, R., Gournier, H., Murphy, C. et al. (1996). Endosome dynamics regulated by a Rho protein. *Nature, 384*, 427-32. ↗

Editions

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2021-02-05	Reviewed	Fort, P.
2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

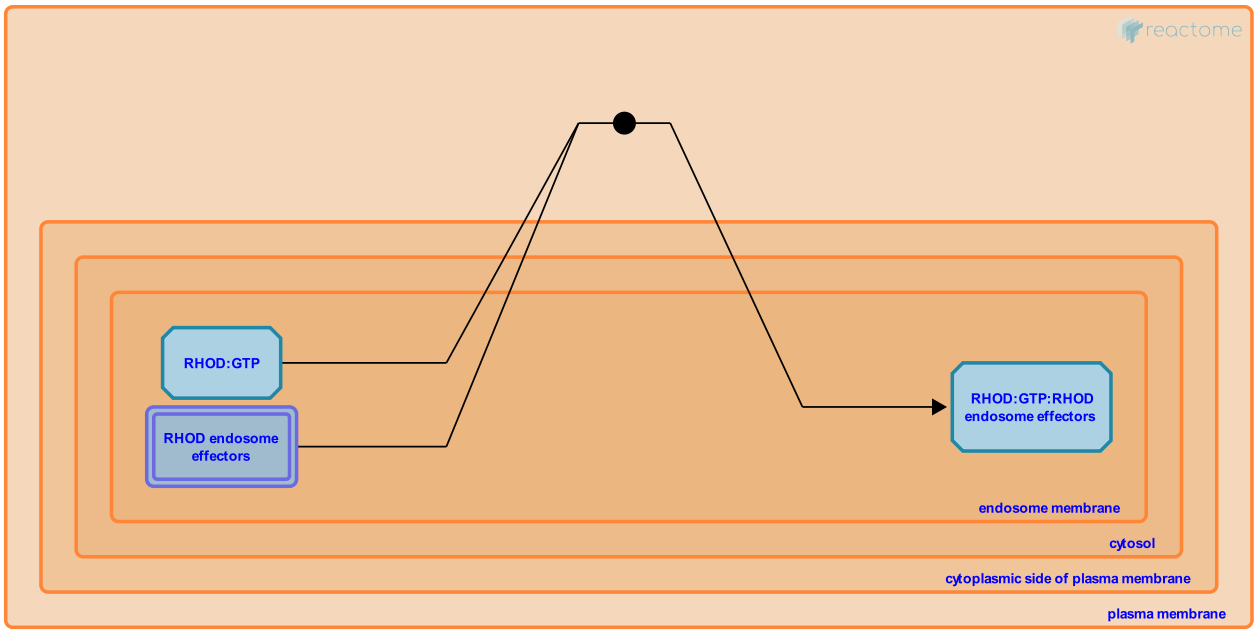
RHOD binds effectors at the endosome membrane ↗

Location: RHOD GTPase cycle

Stable identifier: R-HSA-9013438

Type: binding

Compartments: plasma membrane, cytosol



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

Literature references

Nehru, V., Voytyuk, O., Aspenström, P., Lennartsson, J. (2013). RhoD binds the Rab5 effector Rabankyrin-5 and has a role in trafficking of the platelet-derived growth factor receptor. *Traffic, 14*, 1242-54. ↗

Tran, V., Gingras, AC., Elkholi, IE., Robert, A., Boulais, J., Faubert, D. et al. (2020). Mapping the proximity interaction network of the Rho-family GTPases reveals signalling pathways and regulatory mechanisms. *Nat. Cell Biol., 22*, 120-134. ↗

Kalaidzidis, Y., Gasman, S., Zerial, M. (2003). RhoD regulates endosome dynamics through Diaphanous-related Formin and Src tyrosine kinase. *Nat. Cell Biol., 5*, 195-204. ↗

Editions

2020-07-14	Authored	Orlic-Milacic, M.
2021-02-05	Reviewed	Fort, P.
2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

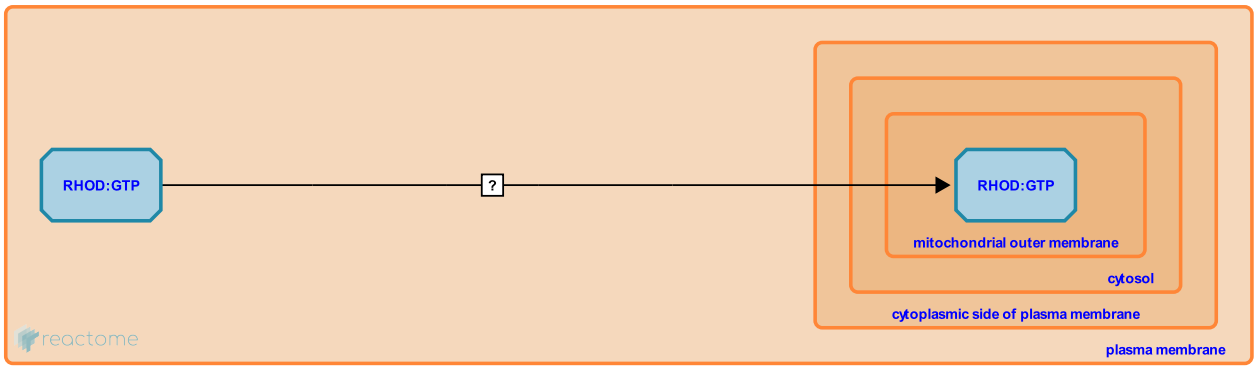
RHOD translocates to the mitochondrial outer membrane ↗

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

Literature references

Frost, JA., Wu, X. (2006). Multiple Rho proteins regulate the subcellular targeting of PAK5. *Biochem. Biophys. Res. Commun., 351*, 328-35. ↗

Editions

2020-07-14	Authored	Orlic-Milacic, M.
2021-02-05	Reviewed	Fort, P.
2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

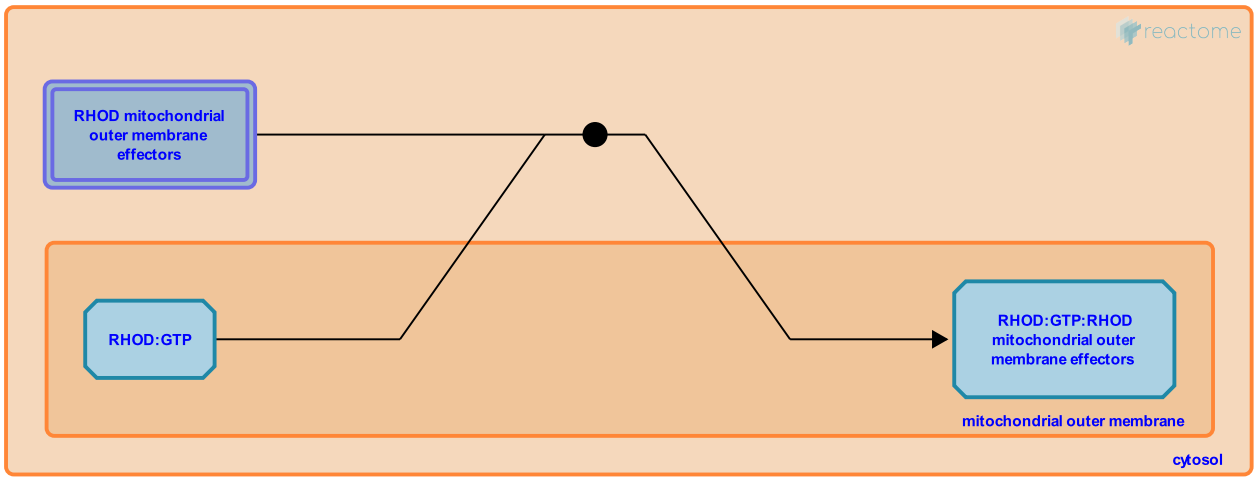
RHOD binds effectors at the mitochondrial outer membrane ↗

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

Literature references

Hu, Z., Chen, L., Wang, W., Yang, Q., Xie, H., Zhou, D. et al. (2017). HINT2 triggers mitochondrial Ca²⁺ influx by regulating the mitochondrial Ca²⁺ uniporter (MCU) complex and enhances gemcitabine apoptotic effect in pancreatic cancer. *Cancer Lett, 411*, 106-116. ↗

Tran, V., Gingras, AC., Elkholi, IE., Robert, A., Boulais, J., Faubert, D. et al. (2020). Mapping the proximity interaction network of the Rho-family GTPases reveals signalling pathways and regulatory mechanisms. *Nat. Cell Biol., 22*, 120-134. ↗

Frost, JA., Wu, X. (2006). Multiple Rho proteins regulate the subcellular targeting of PAK5. *Biochem. Biophys. Res. Commun., 351*, 328-35. ↗

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2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

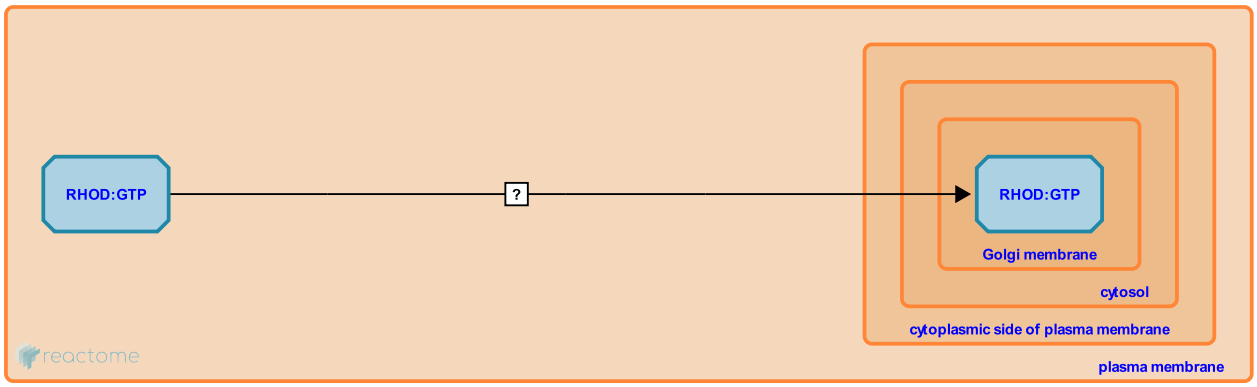
RHOD translocates to the Golgi membrane ↗

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

Literature references

Nehru, V., Ruusala, A., Gad, AK., Aspenström, P. (2012). RhoD regulates cytoskeletal dynamics via the actin nucleation-promoting factor WASp homologue associated with actin Golgi membranes and microtubules. *Mol. Biol. Cell, 23*, 4807-19. ↗

Nehru, V., Gad, AK., Blom, M., Reis, K., Blom, H., Aspenström, P. (2015). RhoD is a Golgi component with a role in anterograde protein transport from the ER to the plasma membrane. *Exp. Cell Res., 333*, 208-19. ↗

Editions

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2021-02-20	Reviewed	Bisbal, M.
2021-02-25	Edited	Orlic-Milacic, M.
2021-03-26	Edited, Revised	Orlic-Milacic, M.

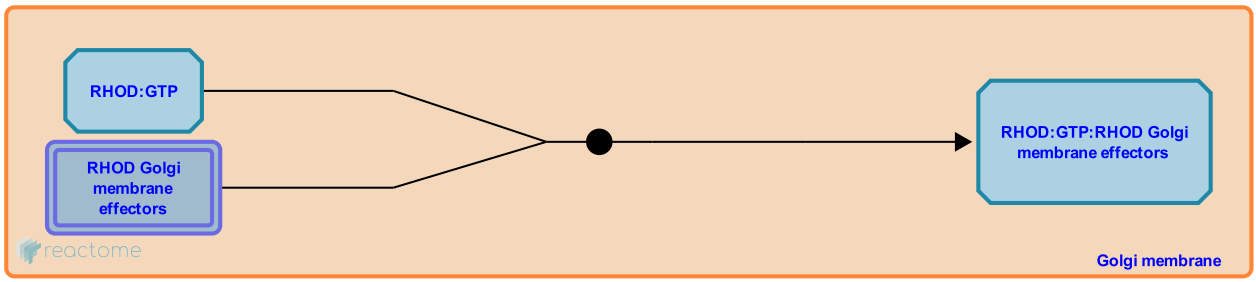
RHOD binds effectors at the Golgi membrane ↗

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

Literature references

Nehru, V., Ruusala, A., Gad, AK., Aspenström, P. (2012). RhoD regulates cytoskeletal dynamics via the actin nucleation-promoting factor WASp homologue associated with actin Golgi membranes and microtubules. *Mol. Biol. Cell, 23*, 4807-19. ↗

Tran, V., Gingras, AC., Elkholi, IE., Robert, A., Boulais, J., Faubert, D. et al. (2020). Mapping the proximity interaction network of the Rho-family GTPases reveals signalling pathways and regulatory mechanisms. *Nat. Cell Biol., 22*, 120-134. ↗

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