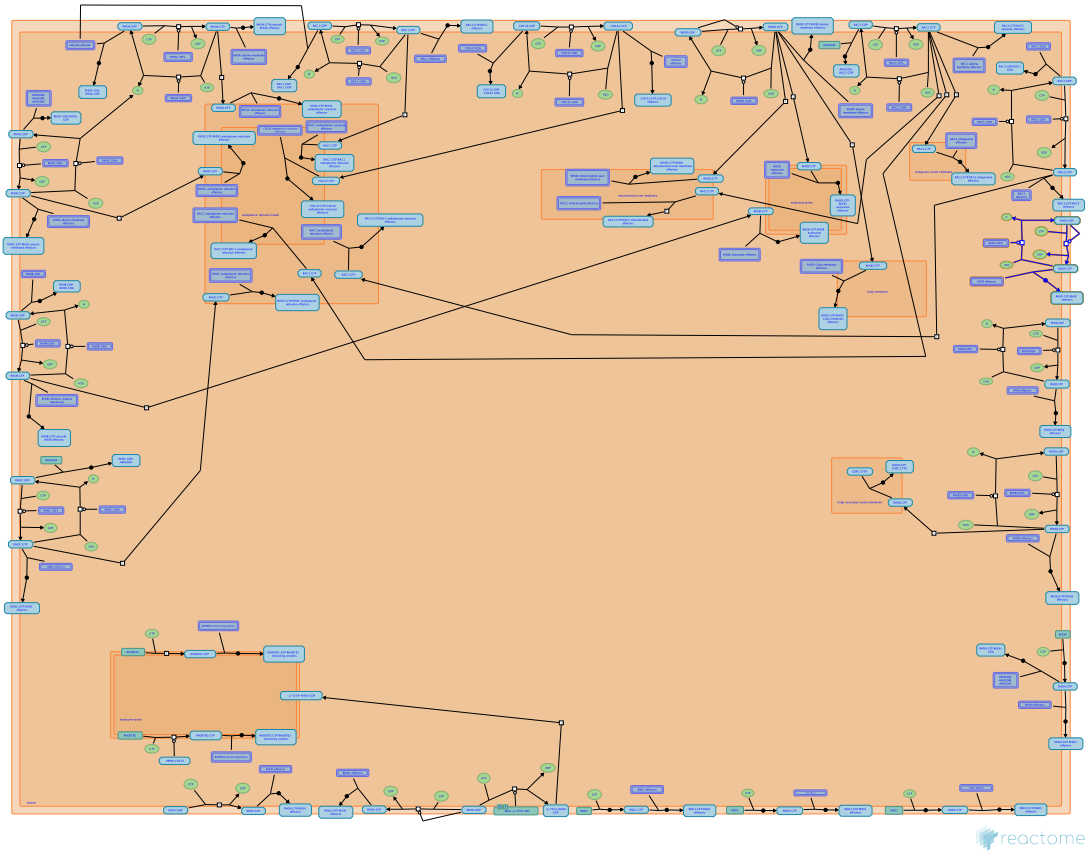
RHOF GTPase cycle



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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.

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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. ↗

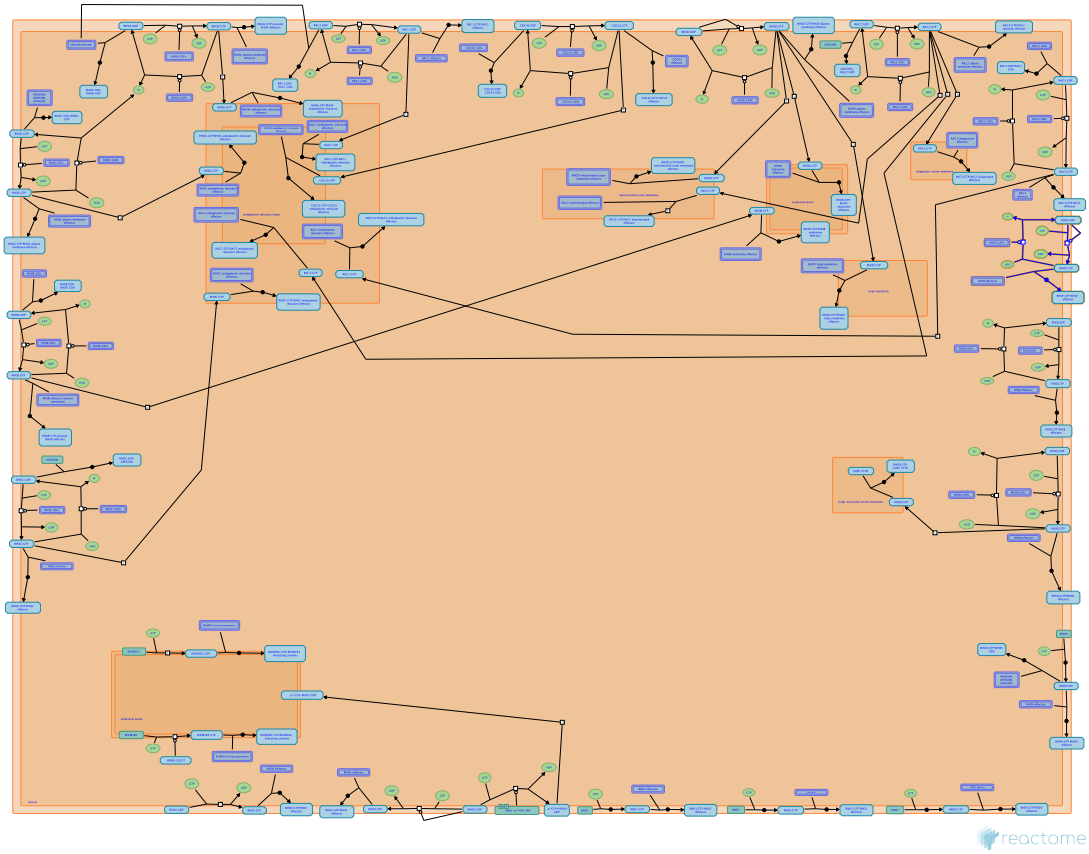
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RHOF GTPase cycle ↗

Stable identifier: R-HSA-9035034



This pathway catalogues RHOF (RIF) GTPase activator proteins (GAPs) and RHOF effectors. RHOF GTPase is thought to exist in the active GTP-bound state in the absence of any GEF activity (Tian et al. 2017). No GDP dissociation inhibitors (GDIs) have been shown to interact with RHOF. RHOF is only found in vertebrates (Gad and Aspenstrom 2010; Fan and Mellor 2012). RHOF regulates cytoskeletal dynamics (Gad and Aspenstrom 2010; Aspenstrom et al. 2014) and promotes the formation of filopodia and stress fibers (Fan and Mellor 2012). RHOF may be involved in actin remodelling in lymphocyte microvilli (Fan and Mellor 2012). In neurons, RHOF contributes to the formation of dendritic spines (Fan and Mellor 2012).

Literature references

Tian, X., Yan, H., Li, J., Wu, S., Wang, J., Fan, L. (2017). Neurotrophin Promotes Neurite Outgrowth by Inhibiting Rif GTPase Activation Downstream of MAPKs and PI3K Signaling. *Int J Mol Sci, 18*. ↗

Fan, L., Mellor, H. (2012). The small Rho GTPase Rif and actin cytoskeletal remodelling. *Biochem. Soc. Trans., 40*, 268-72. ↗

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. ↗

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

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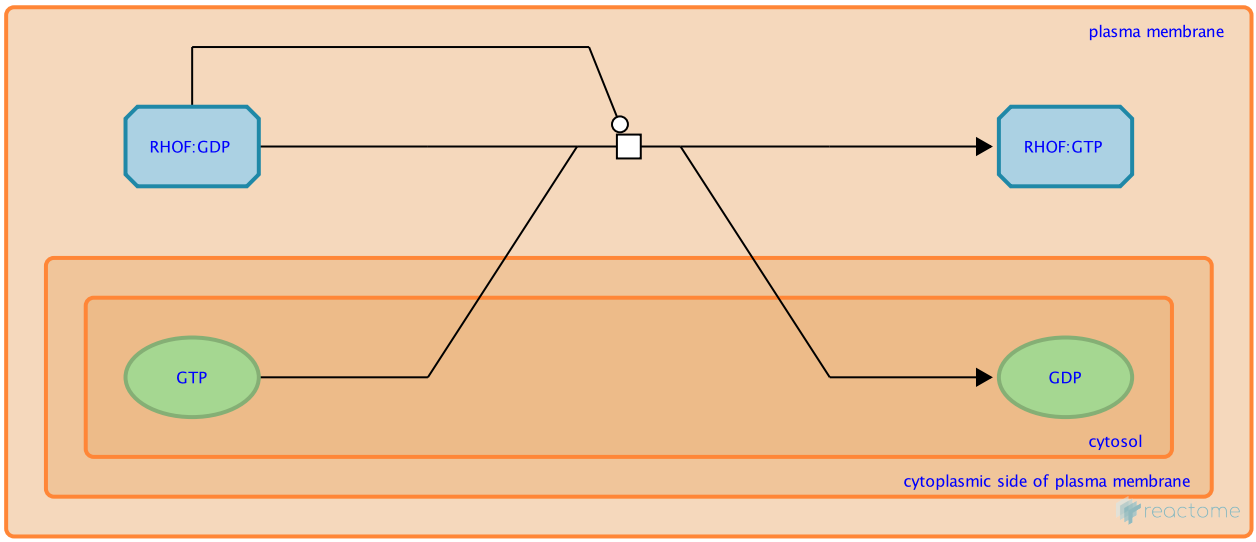
RHOF auto-activates ↗

Location: RHOF GTPase cycle

Stable identifier: R-HSA-9693111

Type: transition

Compartments: plasma membrane, cytosol



RHOF (Rif) possesses an elevated intrinsic guanine nucleotide exchange activity (Jaiswal, Fansa et al. 2013). As GTP is more abundant in cells than GDP (Traut 1994), the exchange of guanine nucleotide on RHOF is spontaneous and insensitive to the presence of EDTA. RHOF is thought to be present in a constitutively active state (Jaiswal, Fansa et al. et al. 2013).

Followed by: RHOF GAPs stimulate RHOF GTPase activity

Literature references

Jaiswal, M., Fansa, EK., Dvorsky, R., Ahmadian, MR. (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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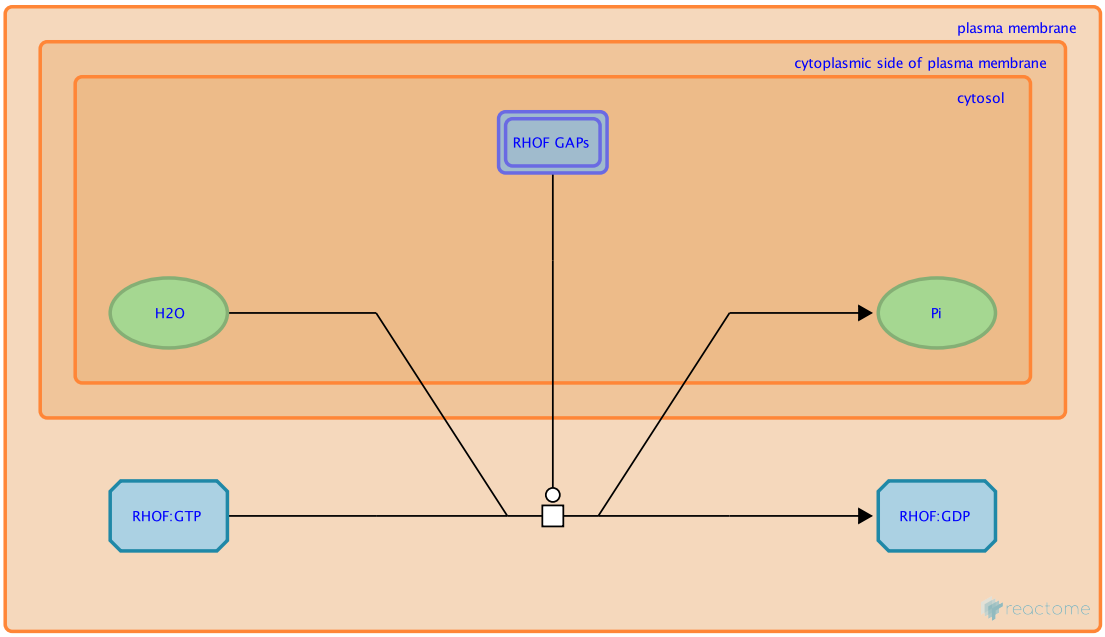
RHOF GAPs stimulate RHOF GTPase activity ↗

Location: RHOF GTPase cycle

Stable identifier: R-HSA-9693282

Type: transition

Compartments: plasma membrane, cytosol



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

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

The following candidate RHOF GAPs were reported by Bagci et al. 2020 to bind active RHOF, but their RHOF-directed GAP activity has not been tested:

ARHGAP5 (Bagci et al. 2020)

ARHGAP12 (Bagci et al. 2020)

ARHGAP21 (Bagci et al. 2020)

ARHGAP32 (Bagci et al. 2020)

ARHGAP39 (Bagci et al. 2020)

DEPDC1B (Bagci et al. 2020)

MYO9B (Bagci et al. 2020)

PIK3R1 (Bagci et al. 2020)

PIK3R2 (Bagci et al. 2020)

SRGAP2 (Bagci et al. 2020)

SYDE1 (Bagci et al. 2020)

The following GAPs were reported to not act on RHOF or were reported by Bagci et al. 2020 to not bind active RHOF without testing of their RHOF-directed GAP activity:

ABR (Amin et al. 2016; Bagci et al. 2020)

ARAP2 (Bagci et al. 2020)

ARAP3 (Bagci et al. 2020)

ARHGAP17 (Amin et al. 2016; Bagci et al. 2020)

ARHGAP26 (Amin et al. 2016)

ARHGAP29 (Bagci et al. 2020)

ARHGAP31 (Bagci et al. 2020)

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

ARHGAP42 (Bagci et al. 2020)

BCR (Bagci et al. 2020)

DLC1 (Amin et al. 2016)

MYO9A (Bagci et al. 2020)

OCRL (Lichter Konecki et al. 2006; Erdmann et al. 2007; Bagci et al. 2020)

OPHN1 (Amin et al. 2016; Bagci et al. 2020)

RACGAP1 (Amin et al. 2016; Bagci et al. 2020)

STARD13 (Amin et al. 2016)

STARD8 (Amin et al. 2016)

Preceded by: RHOF auto-activates

Literature references

Amin, E., Jaiswal, M., Derewenda, U., Reis, K., Nouri, K., Koessmeier, KT. 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. ↗

Bagci, H., Sriskandarajah, N., Robert, A., Boulais, J., Elkholi, IE., Tran, V. 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. ↗

Erdmann, KS., Mao, Y., McCrea, HJ., Zoncu, R., Lee, S., Paradise, S. et al. (2007). A role of the Lowe syndrome protein OCRL in early steps of the endocytic pathway. *Dev. Cell, 13*, 377-90. ↗

Lichter-Konecki, U., Farber, LW., Cronin, JS., Suchy, SF., Nussbaum, RL. (2006). The effect of missense mutations in the RhoGAP-homology domain on ocrl1 function. *Mol. Genet. Metab., 89*, 121-8. ↗

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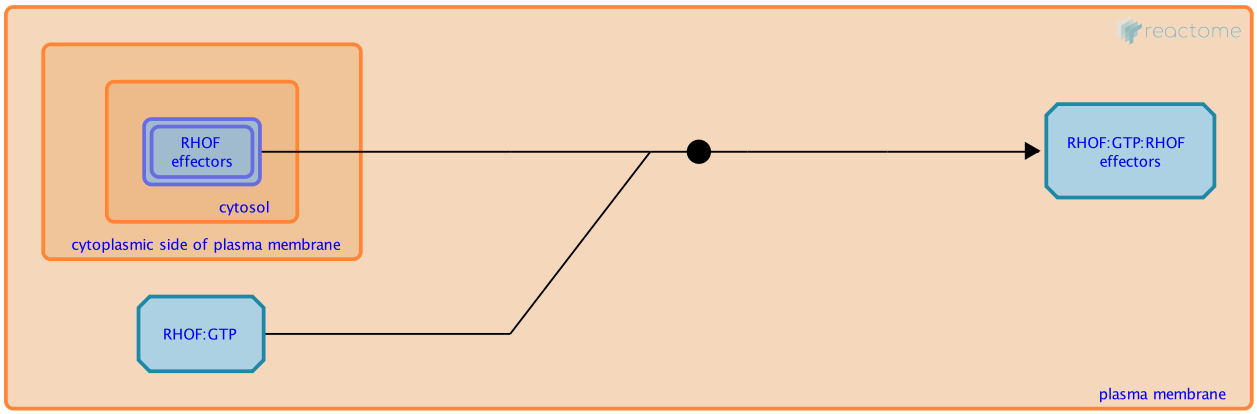
RHOF binds effectors at the plasma membrane ↗

Location: RHOF GTPase cycle

Stable identifier: R-HSA-9693125

Type: binding

Compartments: plasma membrane, cytosol



Active GTP-bound RHOF binds the following effectors:

BAIAP2L1 (Sudhaharan et al. 2016)

BAIAP2L2 (Sudhaharan et al. 2016)

DIAPH1 (Fan et al. 2010)

DIAPH2 (Gorelik et al. 2011)

FARP1 (Fan et al. 2015)

The following candidate RHOF effectors that can localize to cytosol or the plasma membrane were reported by Bagci et al. 2020 to bind active RHOF:

ACTB (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)

BASP1 (Bagci et al. 2020)

CAPZB (Bagci et al. 2020)

CAV1 (Bagci et al. 2020)

CPNE8 (Bagci et al. 2020)

DIAPH3 (Bagci et al. 2020)

ESYT1 (Bagci et al. 2020)

FAM169A (Bagci et al. 2020)

LMNB1 (Bagci et al. 2020)

MCAM (Bagci et al. 2020)

MTMR1 (Bagci et al. 2020)

POTEE (Bagci et al. 2020)

RAB7A (Bagci et al. 2020)

SENP1 (Bagci et al. 2020)

SLC4A7 (Bagci et al. 2020)

SNAP23 (Bagci et al. 2020)

SOWAHC (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)

Several putative effectors that localize to endoplasmic reticulum, endosomes or the mitochondrial outer membrane were reported to bind active RHOF by Bagci et al. 2020, but as the localization of RHOF to these cellular compartments has not been established, these effectors have not been annotated:

EMD

LBR

LEMD3

LMAN1

PGRMC2

VRK2

The following putative effectors were reported not to bind active RHOF:

DBN1 (Bagci et al. 2020)

EFHD2 (Bagci et al. 2020)

GOLGA8R (Bagci et al. 2020)

HINT2 (Bagci et al. 2020)

MOSPD2 (Bagci et al. 2020)

STBD1 (Bagci et al. 2020)

VAPB (Bagci et al. 2020)

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Sudhaharan, T., Sem, KP., Liew, HF., Yu, YH., Goh, WI., Chou, AM. et al. (2016). The Rho GTPase Rif signals through IRTKS, Eps8 and WAVE2 to generate dorsal membrane ruffles and filopodia. *J. Cell. Sci., 129*, 2829-40. ↗

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