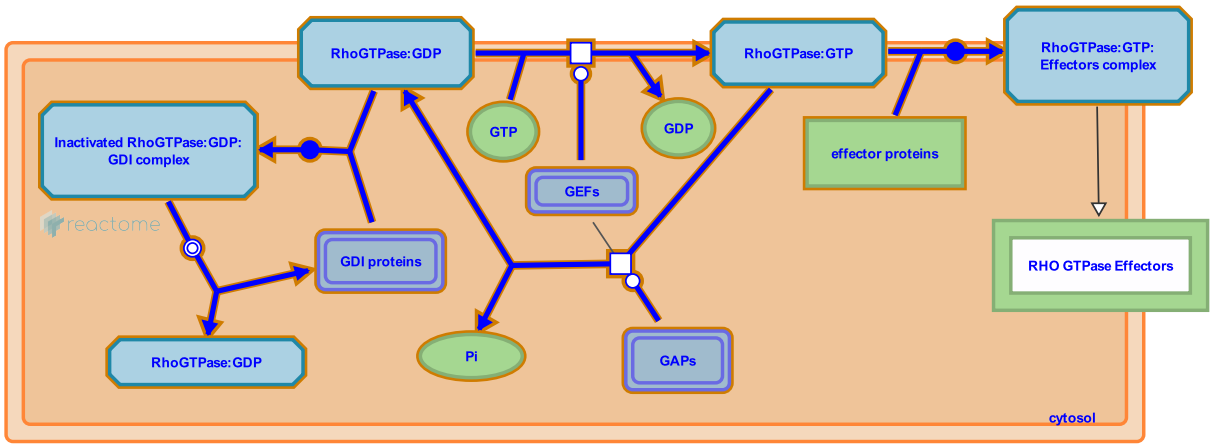
Rho GTPase cycle



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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. ↗

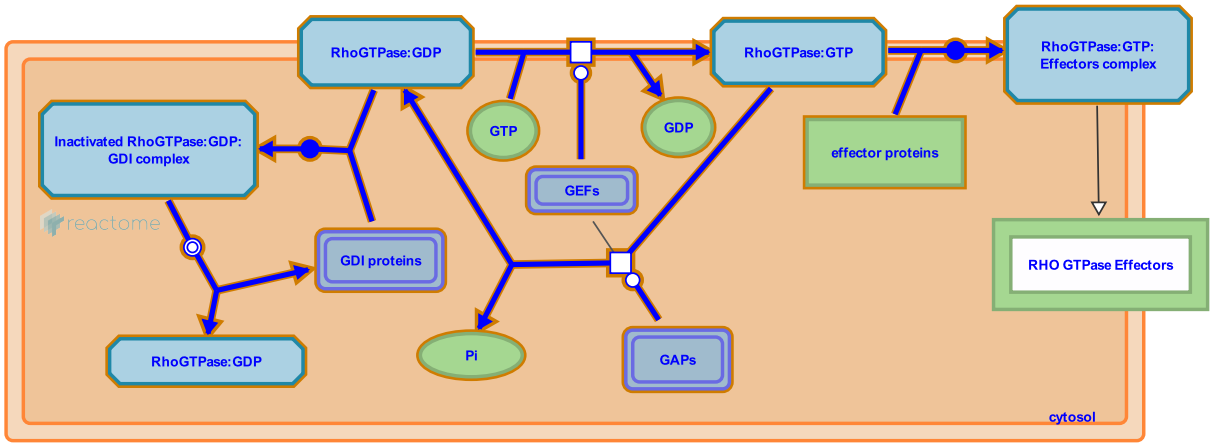
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Rho GTPase cycle ↗

Stable identifier: R-HSA-194840

Compartments: cytosol



The cycling of Rho GTPases is tightly controlled by three classes of protein. These are (1) guanine nucleotide dissociation inhibitors or GDIs, which maintain Rho proteins in an inactive state in the cytoplasm, (2) guanine nucleotide exchange factors or GEFs, which destabilize the interaction between Rho proteins and their bound nucleotide, the net result of which is the exchange of bound GDP for the more abundant GTP, and (3) GTPase Activating Proteins or GAPs, which stimulate the low intrinsic GTP hydrolysis activity of Rho family members, thus promoting their inactivation. GDIs, GEFs, and GAPs are themselves subject to tight regulation, and the overall level of Rho activity reflects the balance of their activities.

In their active GTP-bound state, Rho family members have the ability to interact with a large variety of so-called effector proteins. By changing the subcellular localization of effectors, by altering their enzymatic properties, or by directing the formation of specific effector complexes, members of the Rho family mediate their various effects.

This Rho GTPase cycle is diagrammed in the figure below. External or internal cues promote the release of Rho GTPases from the inhibitory complex (1) which allows them to associate with the plasma membrane (2) where they are activated by GEFs (3) and can signal to effector proteins. Then, GAPs inactivate the GTPases by accelerating the intrinsic GTPase activity, leading to the GDP bound form (4). Once again, the GDI molecules stabilize the inactive GDP bound form in the cytoplasm, waiting for further instructions (5). (Figure and text from Tcherkezian and Lamarche Vane, 2007).

Literature references

Tcherkezian, J., Lamarche-Vane, N. (2007). Current knowledge of the large RhoGAP family of proteins. *Biol Cell, 99,* 67-86. ↗

Van Aelst, L., D'Souza-Schorey, C. (1997). Rho GTPases and signaling networks. *Genes Dev, 11,* 2295-322. ↗

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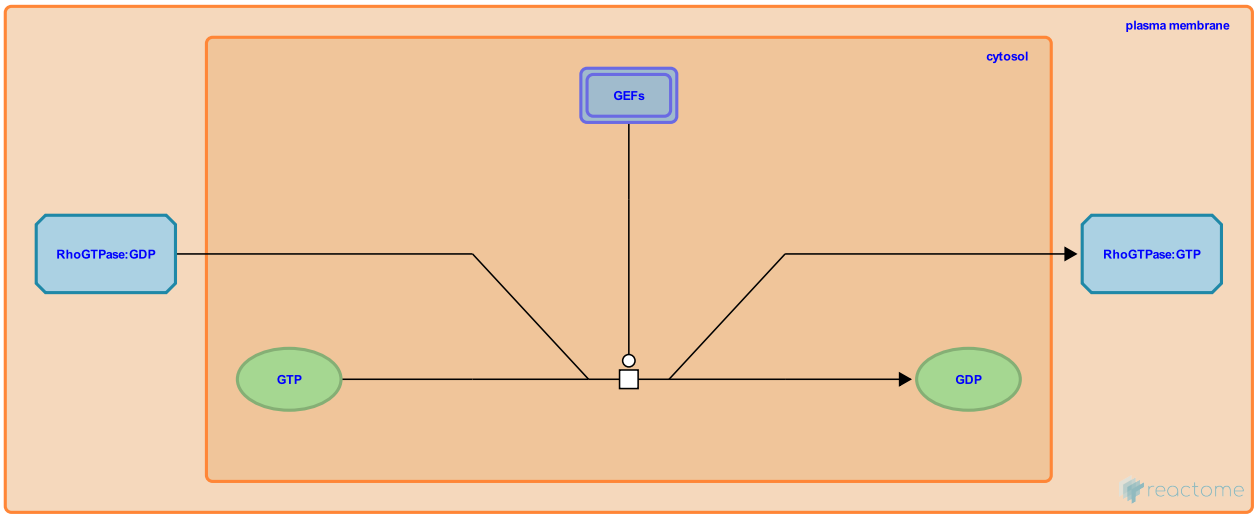
GEFs activate Rho GTPase:GDP ↗

Location: Rho GTPase cycle

Stable identifier: R-HSA-194913

Type: transition

Compartments: cytosol, plasma membrane



Guanine nucleotide exchange factors (GEFs) activate GTPases by enhancing the exchange of bound GDP for GTP. Much evidence points to GEFs being critical mediators of Rho GTPase activation (Schmidt and Hall, 2002). Many GEFs are known to be highly specific for a particular GTPase, e.g. Fgd1/Cdc42 and p115RhoGEF/Rho (Hart et al., 1996, Zheng et al., 1996). Others have a broader spectrum and activate several GTPases, e.g. Vav1 for Rac, Rho, and Cdc42 (Hart et al, 1994).

Followed by: Rho GTPase:GTP activates downstream effectors, GAPs inactivate Rho GTPase:GTP by hydrolysis

Literature references

Schmidt, A., Hall, A. (2002). Guanine nucleotide exchange factors for Rho GTPases: turning on the switch. *Genes Dev, 16*, 1587-609. ↗

Van Aelst, L., D'Souza-Schorey, C. (1997). Rho GTPases and signaling networks. *Genes Dev, 11*, 2295-322. ↗

Jaffe, AB., Hall, A. (2005). Rho GTPases: biochemistry and biology. *Annu Rev Cell Dev Biol, 21*, 247-69. ↗

Zheng, Y., Fischer, DJ., Santos, MF., Tigyi, G., Pasteris, NG., Gorski, JL. et al. (1996). The faciogenital dysplasia gene product FGD1 functions as a Cdc42Hs-specific guanine-nucleotide exchange factor. *J Biol Chem, 271*, 33169-72. ↗

Pasteris, NG., Cadle, A., Logie, LJ., Porteous, ME., Schwartz, CE., Stevenson, RE. et al. (1994). Isolation and characterization of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: a putative Rho/Rac guanine nucleotide exchange factor. *Cell, 79*, 669-78. ↗

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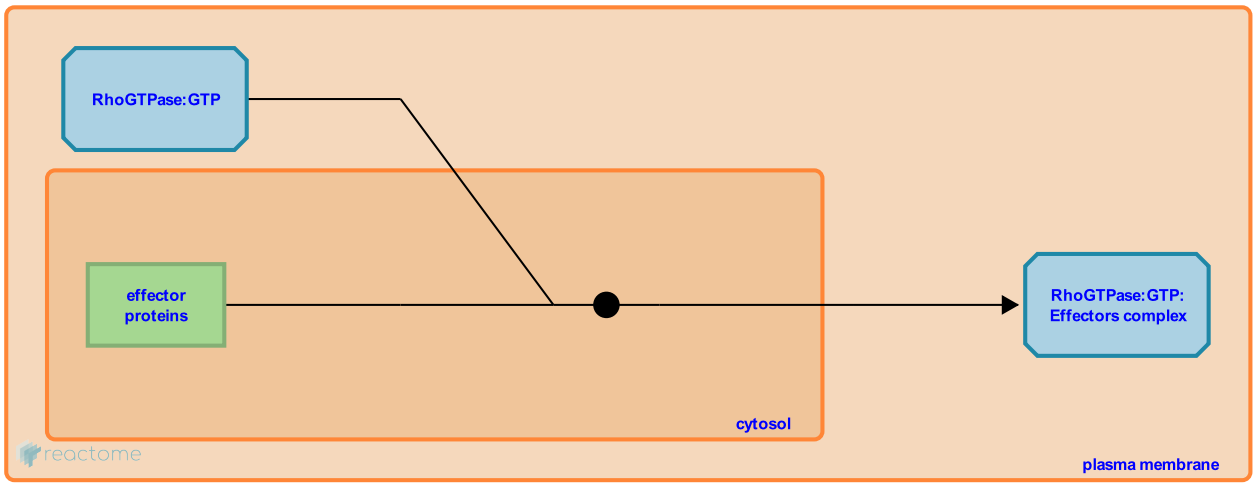
Rho GTPase:GTP activates downstream effectors ↗

Location: Rho GTPase cycle

Stable identifier: R-HSA-194894

Type: binding

Compartments: cytosol, plasma membrane



To transduce signals, the activated, GTP-bound Rho GTPases interact with specific effector molecules. It has been observed that GEFs contribute to the signaling specificity of their downstream target GTPase via association with scaffolding molecules that link them and the GTPase to specific GTPase effectors (Govek et al., 2005). Some of the effector molecules implicated in actin and microtubule dynamics include diaphanous-related formins, Toca 1, WIP, WASP, Pak, p35/Cdk5, Wave, Nap125, MLCK, MLC, IRSp53.

Preceded by: GEFs activate Rho GTPase:GDP

Literature references

Van Aelst, L., D'Souza-Schorey, C. (1997). Rho GTPases and signaling networks. *Genes Dev, 11*, 2295-322. ↗

Zheng, Y. (2001). Dbl family guanine nucleotide exchange factors. *Trends Biochem Sci, 26*, 724-32. ↗

Tan, YC., Wu, H., Wang, WN., Zheng, Y., Wang, ZX. (2002). Characterization of the interactions between the small GTPase RhoA and its guanine nucleotide exchange factors. *Anal Biochem, 310*, 156-62. ↗

Govind, S., Kozma, R., Monfries, C., Lim, L., Ahmed, S. (2001). Cdc42Hs facilitates cytoskeletal reorganization and neurite outgrowth by localizing the 58-kD insulin receptor substrate to filamentous actin. *J Cell Biol, 152*, 579-94. ↗

Soltau, M., Richter, D., Kreienkamp, HJ. (2002). The insulin receptor substrate IRSp53 links postsynaptic shank1 to the small G-protein cdc42. *Mol Cell Neurosci, 21*, 575-83. ↗

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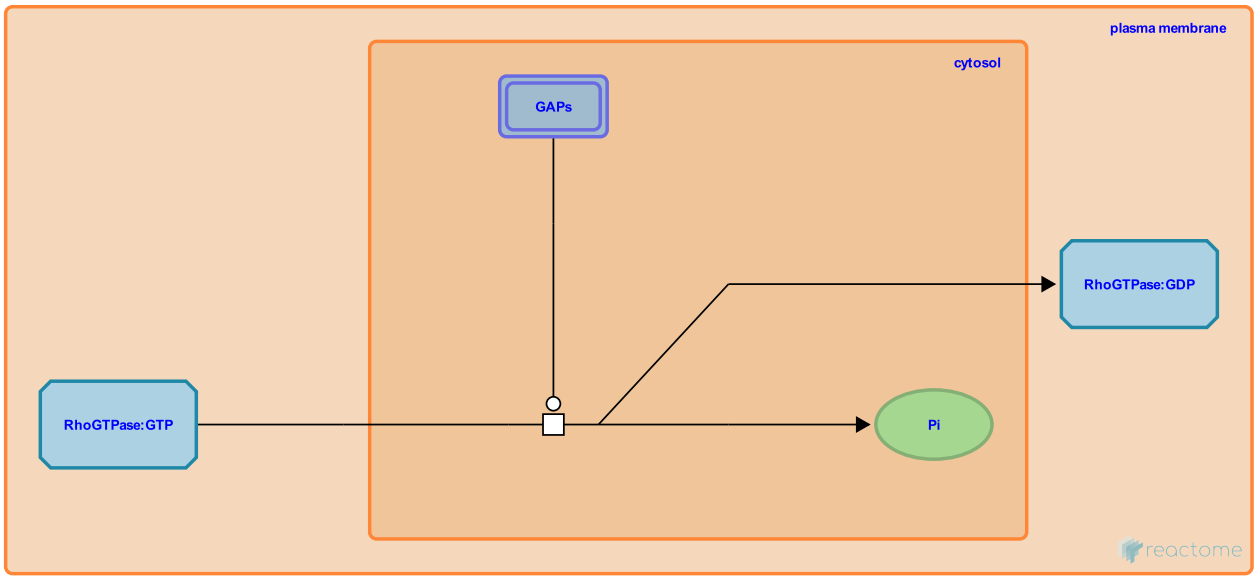
GAPs inactivate Rho GTPase:GTP by hydrolysis ↗

Location: Rho GTPase cycle

Stable identifier: R-HSA-194922

Type: transition

Compartments: cytosol, plasma membrane



The human genome includes approximately 70 genes that are predicted to encode Rho-specific GTPase Activating Proteins (RhoGAPs). As in the case of GEFs, some RhoGAPs are believed to be highly specific, whereas others are more promiscuous with respect to their target GTPases. Increasing evidence suggests that GAPs are also regulated by external cues in addition to being signal terminators leading to Rho GTPase inactivation. These proteins play important role in many Rho mediated signaling pathways.

Some known GAPs include p190 A, cdGAP, ARAP3, MgcRacGAP, Chimaerin, Nadrin, TCGAP, DLC 1, 2, ArhGAP6, Myosin IXA. These and other GAPs have been implicated in many processes, such as exocytosis, endocytosis, cytokinesis, cell differentiation, migration, neuronal morphogenesis, angiogenesis and tumor suppression.

Preceded by: GEFs activate Rho GTPase:GDP

Literature references

Tcherkezian, J., Lamarche-Vane, N. (2007). Current knowledge of the large RhoGAP family of proteins. *Biol Cell, 99*, 67-86. ↗

Lancaster, CA., Taylor-Harris, PM., Self, AJ., Brill, S., van Erp, HE., Hall, A. (1994). Characterization of rhoGAP. A GTPase-activating protein for rho-related small GTPases. *J Biol Chem, 269*, 1137-42. ↗

Fainstein, E., Marcelle, C., Rosner, A., Canaani, E., Gale, RP., Dreazen, O. et al. (1987). A new fused transcript in Philadelphia chromosome positive acute lymphocytic leukaemia. *Nature, 330*, 386-8. ↗

Krugmann, S., Anderson, KE., Ridley, SH., Risso, N., McGregor, A., Coadwell, J. et al. (2002). Identification of ARAP3, a novel PI3K effector regulating both Arf and Rho GTPases, by selective capture on phosphoinositide affinity matrices. *Mol Cell, 9*, 95-108. ↗

Yuan, BZ., Miller, MJ., Keck, CL., Zimonjic, DB., Thorgeirsson, SS., Popescu, NC. (1998). Cloning, characterization, and chromosomal localization of a gene frequently deleted in human liver cancer (DLC-1) homologous to rat RhoGAP. *Cancer Res, 58*, 2196-9. ↗

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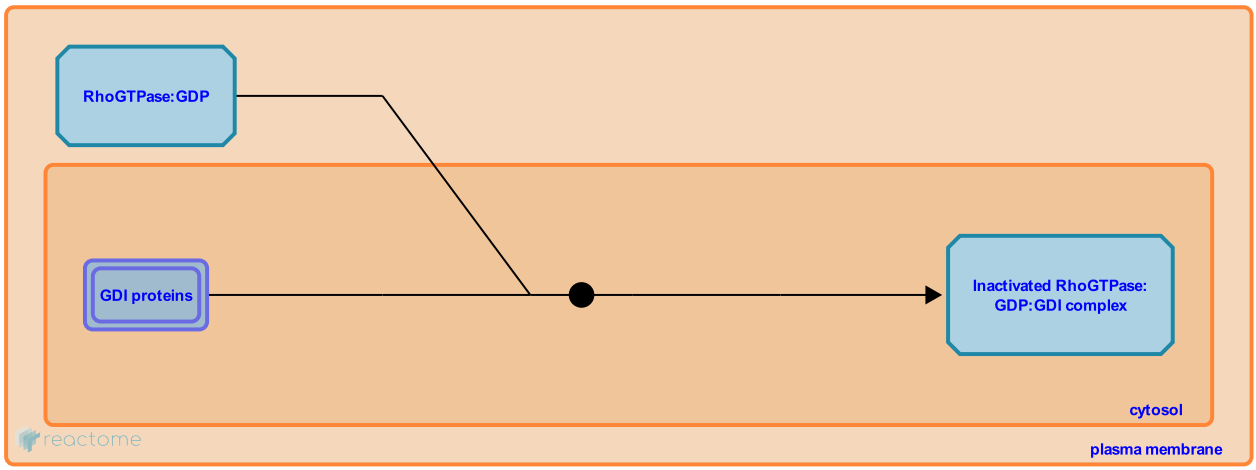
GDIs block activation of Rho GTPase:GDP ↗

Location: Rho GTPase cycle

Stable identifier: R-HSA-194854

Type: binding

Compartments: cytosol, plasma membrane



GDP dissociation inhibitors or GDIs confer an additional but important layer of Rho GTPase regulation along with GEFs and GAPs. GDIs mainly inhibit the dissociation of bound guanine nucleotide (usually GDP) from their partner GTPases. So far, three human GDIs with proven biological functions have been found: RhoGDI/GDIalpha/GDI1, hematopoietic cell selective Ly/D4GDI/GDIbeta/GDI2, and Rho GDI-gamma/GDI3 (DerMardirossian and Bokoch, 2005). Three specific biochemical functions of GDIs have been established: inhibiting the dissociation of GDP from Rho proteins, maintaining the GTPases in an inactive form, and preventing GTPase activation by GEFs (Olofsson, 1999).

Followed by: Dissociation of Rho GTP:GDP from GDI complex

Literature references

DerMardirossian, C., Bokoch, GM. (2005). GDIs: central regulatory molecules in Rho GTPase activation. *Trends Cell Biol, 15*, 356-63. ↗

Sun, J., Barbieri, JT. (2004). ExoS Rho GTPase-activating protein activity stimulates reorganization of the actin cytoskeleton through Rho GTPase guanine nucleotide disassociation inhibitor. *J Biol Chem, 279*, 42936-44. ↗

Bachner, D., Sedlacek, Z., Korn, B., Hameister, H., Poustka, A. (1995). Expression patterns of two human genes coding for different rab GDP-dissociation inhibitors (GDIs), extremely conserved proteins involved in cellular transport. *Hum Mol Genet, 4*, 701-8. ↗

Hart, MJ., Maru, Y., Leonard, D., Witte, ON., Evans, T., Cerione, RA. (1992). A GDP dissociation inhibitor that serves as a GTPase inhibitor for the Ras-like protein CDC42Hs. *Science, 258*, 812-5. ↗

Hoffman, GR., Nassar, N., Cerione, RA. (2000). Structure of the Rho family GTP-binding protein Cdc42 in complex with the multifunctional regulator RhoGDI. *Cell, 100*, 345-56. ↗

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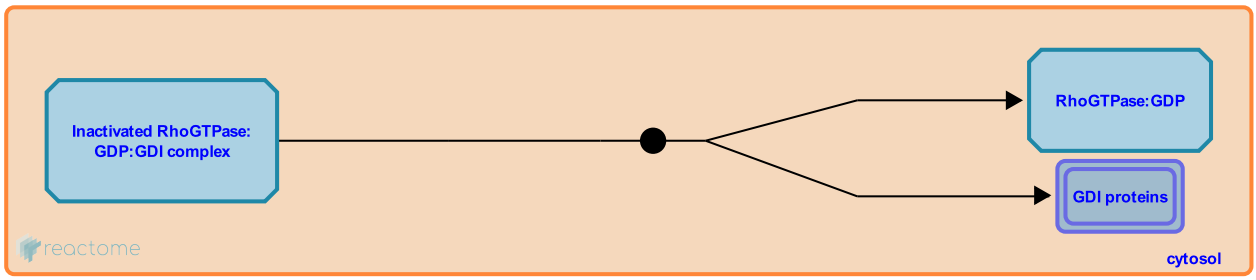
Dissociation of Rho GTP:GDP from GDI complex ↗

Location: Rho GTPase cycle

Stable identifier: R-HSA-195146

Type: dissociation

Compartments: cytosol



GDIs sequester the inactive GTPases, preventing the dissociation of GDP and interactions with regulatory and effector molecules. They maintain Rho GTPases as soluble cytosolic proteins by forming high affinity complexes. In these complexes, the geranylgeranyl membrane targeting moiety present at the C terminus of the Rho GTPases is shielded from the solvent by its insertion into the hydrophobic pocket formed by the immunoglobulin like beta sandwich of the GDI (DerMardirossian and Bokoch, 2005).

Rho proteins, when released from the sequestering cytosolic GDIs, insert into the lipid bilayer of the plasma membrane with their isoprenylated C termini. The membrane bound GEFs activate these free RhoGTPases and thereby trigger the downstream signaling events via respective effector proteins on the membrane (Robbe et al., 2003).

Preceded by: GDIs block activation of Rho GTPase:GDP

Literature references

Scheffzek, K., Stephan, I., Jensen, ON., Illenberger, D., Gierschik, P. (2000). The Rac-RhoGDI complex and the structural basis for the regulation of Rho proteins by RhoGDI. *Nat Struct Biol, 7*, 122-6. ↗

DerMardirossian, C., Bokoch, GM. (2005). GDIs: central regulatory molecules in Rho GTPase activation. *Trends Cell Biol, 15*, 356-63. ↗

Hoffman, GR., Nassar, N., Cerione, RA. (2000). Structure of the Rho family GTP-binding protein Cdc42 in complex with the multifunctional regulator RhoGDI. *Cell, 100*, 345-56. ↗

Gosser, YQ., Nomanbhoy, TK., Aghazadeh, B., Manor, D., Combs, C., Cerione, RA. et al. (1997). C-terminal binding domain of Rho GDP-dissociation inhibitor directs N-terminal inhibitory peptide to GTPases. *Nature, 387*, 814-9. ↗

Robbe, K., Otto-Bruc, A., Chardin, P., Antonny, B. (2003). Dissociation of GDP dissociation inhibitor and membrane translocation are required for efficient activation of Rac by the Dbl homology-pleckstrin homology region of Tiam. *J Biol Chem, 278*, 4756-62. ↗

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