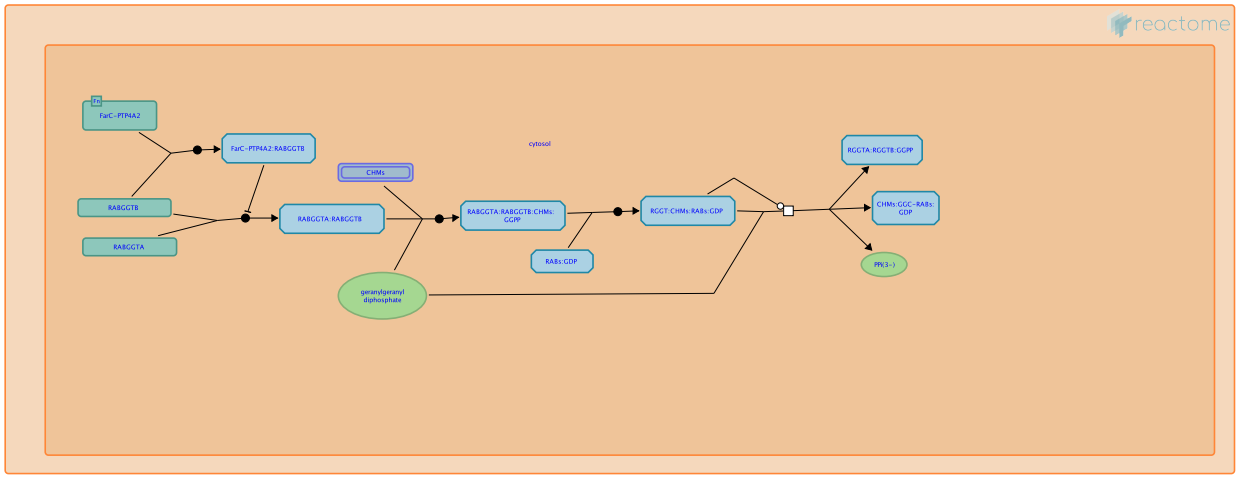
RAB geranylgeranylation



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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. ↗

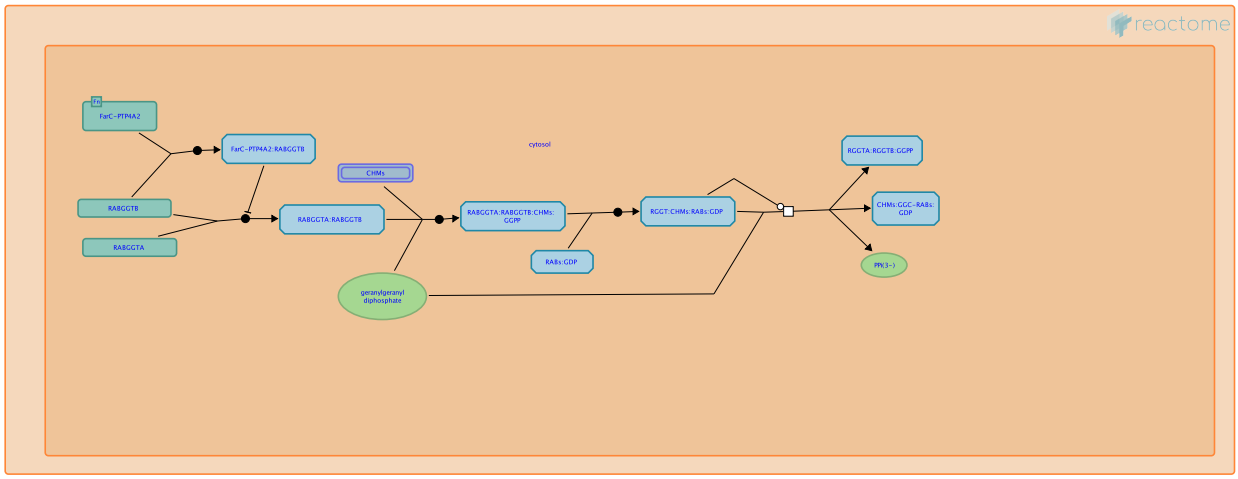
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RAB geranylgeranylation ↗

Stable identifier: R-HSA-8873719



Human cells have more than 60 RAB proteins that are involved in trafficking of proteins in the endolysosomal system. These small GTPases contribute to trafficking specificity by localizing to the membranes of different endocytic compartments and interacting with effectors such as sorting adaptors, tethering factors, kinases, phosphatases and tubular-vesicular cargo (reviewed in Stenmark et al, 2009; Wandinger-Ness and Zerial, 2014). RAB localization depends on a number of factors including C-terminal prenylation, the sequence of an upstream hypervariable regions and what nucleotide is bound (Chavrier et al, 1991; Ullrich et al, 1993; Soldati et al, 1994; Farnsworth et al, 1994; Seabra, 1996; Wu et al, 2010; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014). In the active, GTP-bound form, prenylated RAB proteins are membrane associated, while in the inactive GDP-bound form, RABs are extracted from the target membrane and exist in a soluble form in complex with GDP dissociation inhibitors (GDIs) (Ullrich et al, 1993; Soldati et al, 1994; Gavriljuk et al, 2103). Conversion between the inactive and active form relies on the activities of RAB guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs) (Yoshimura et al, 2010; Wu et al, 2011; Pan et al, 2006; Frasa et al, 2012; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Newly synthesized RABs are bound by a RAB escort protein, CHM (also known as REP1) or CHML (REP2) (Alexandrov et al, 1994; Shen and Seabra, 1996). CHM/REP proteins are the substrate-binding component of the trimeric RAB geranylgeranyltransferase enzyme (GGTaseII) along with the two catalytic subunits RABGGTA and RABGGTB (reviewed in Gutkowska and Swiezewska, 2012; Palsuledesai and Distefano, 2015). REP proteins recruit the unmodified RAB in its GDP-bound state to the GGTase for sequential geranylgeranylation at one or two C-terminal cysteine residues (Alexandrov et al, 1994; Seabra et al 1996; Shen and Seabra, 1996; Baron and Seabra, 2008). After geranylgeranylation, CHM/REP proteins remain in complex with the geranylgeranylated RAB and escort it to its target membrane, where its activity is regulated by GAPs, GEFs, GDIs and membrane-bound GDI displacement factors (GDFs) (Sivars et al, 2003; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Literature references

Sivars, U., Aivazian, D., Pfeffer, SR. (2003). Yip3 catalyses the dissociation of endosomal Rab-GDI complexes. *Nature, 425*, 856-9. ↗

Wandinger-Ness, A., Zerial, M. (2014). Rab proteins and the compartmentalization of the endosomal system. *Cold Spring Harb Perspect Biol, 6*, a022616. ↗

Ullrich, O., Stenmark, H., Alexandrov, K., Huber, LA., Kaibuchi, K., Sasaki, T. et al. (1993). Rab GDP dissociation inhibitor as a general regulator for the membrane association of rab proteins. *J. Biol. Chem., 268*, 18143-50. ↗

Baron, RA., Seabra, MC. (2008). Rab geranylgeranylation occurs preferentially via the pre-formed REP-RGGT complex and is regulated by geranylgeranyl pyrophosphate. *Biochem. J., 415*, 67-75. ↗

Wu, X., Bradley, MJ., Cai, Y., Kümmel, D., De La Cruz, EM., Barr, FA. et al. (2011). Insights regarding guanine nucleotide exchange from the structure of a DENN-domain protein complexed with its Rab GTPase substrate. *Proc. Natl. Acad. Sci. U.S.A., 108*, 18672-7. ↗

Editions

2016-06-03	Authored, Edited	Rothfels, K.
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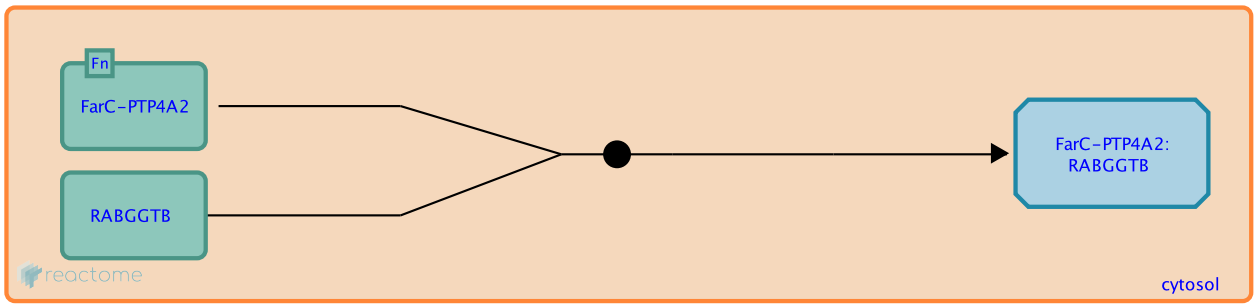
FarC-PTP4A2 binds RABGGTB ↗

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870457

Type: binding

Compartments: cytosol



PTP4A2, also known as PRL2, is a member of the protein tyrosine phosphatase family. Farnesylated PTP4A2 interacts with RABGGTB, one of the two catalytic subunits of the RAB geranylgeranyl transferase complex and prevents its association with the other catalytic subunit RABGBTA (Si et al, 2001). In this way, binding of PTP4A2 acts as a negative regulator of RAB geranylgeranylation (reviewed in Gutkowska and Swiezewska, 2012).

Literature references

Si, X., Zeng, Q., Ng, CH., Hong, W., Pallen, CJ. (2001). Interaction of farnesylated PRL-2, a protein-tyrosine phosphatase, with the beta-subunit of geranylgeranyltransferase II. *J. Biol. Chem., 276*, 32875-82. ↗

Gutkowska, M., Swiezewska, E. (2012). Structure, regulation and cellular functions of Rab geranylgeranyl transferase and its cellular partner Rab Escort Protein. *Mol. Membr. Biol., 29*, 243-56. ↗

Editions

2016-06-08	Authored, Edited	Rothfels, K.
2016-08-04	Reviewed	Palsuledesai, CC.

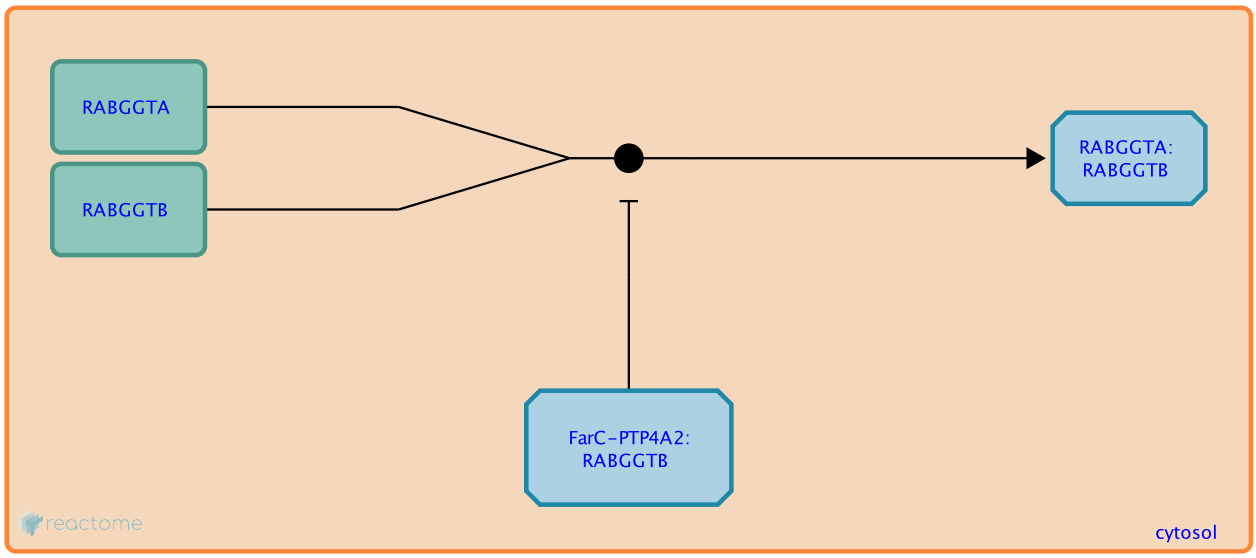
RABGGTA and RABGGTB bind ↗

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870461

Type: binding

Compartments: cytosol



RABGGTA and RABGGTB are the two catalytic subunits of a trimeric RAB geranylgeranyl transferase complex (GGTase); the third subunit is the RAB binding subunit CHM or CHML (reviewed in Leung et al, 2006; Gutkowska and Swiezewska, 2012). RABGGTB also interacts in a mutually exclusive way with PTP4A2, preventing formation of a functional gernanylgeranyl transferase complex (Si et al, 2001; Baron and Seabra, 2008). Newly synthesized RAB proteins are singly or more commonly doubly geranylgeranylated near their C-termini by the GGTase. Geranylgeranylation promotes association of active RAB proteins with membranes. Membrane association is additionally modulated by the nucleotide state of the GTPase through regulatory proteins such as guanine nucleotide exchange factors (GEFs), GTPase activating proteins (GAPs) and GDP Dissocation Inhibitors (GDIs), among others (reviewed in Stenmark et al, 2009; Wandinger-Ness and Zerial, 2014). An exception to this is RAB13, which has recently been shown to be membrane-associated even in the inactive state and to traffic on vesicles independently of geranylgeranylation (Ioannou et al, 2016).

Followed by: RGGT binds the RAB-binding subunit

Literature references

Si, X., Zeng, Q., Ng, CH., Hong, W., Pallen, CJ. (2001). Interaction of farnesylated PRL-2, a protein-tyrosine phosphatase, with the beta-subunit of geranylgeranyltransferase II. *J. Biol. Chem., 276*, 32875-82. ↗

Gutkowska, M., Swiezewska, E. (2012). Structure, regulation and cellular functions of Rab geranylgeranyl transferase and its cellular partner Rab Escort Protein. *Mol. Membr. Biol., 29*, 243-56. ↗

Baron, RA., Seabra, MC. (2008). Rab geranylgeranylation occurs preferentially via the pre-formed REP-RGGT complex and is regulated by geranylgeranyl pyrophosphate. *Biochem. J., 415*, 67-75. ↗

Leung, KF., Baron, R., Seabra, MC. (2006). Thematic review series: lipid posttranslational modifications. geranylgeranylation of Rab GTPases. *J. Lipid Res., 47*, 467-75. ↗

Stenmark, H. (2009). Rab GTPases as coordinators of vesicle traffic. *Nat. Rev. Mol. Cell Biol., 10*, 513-25. ↗

Editions

2016-06-08	Authored, Edited	Rothfels, K.
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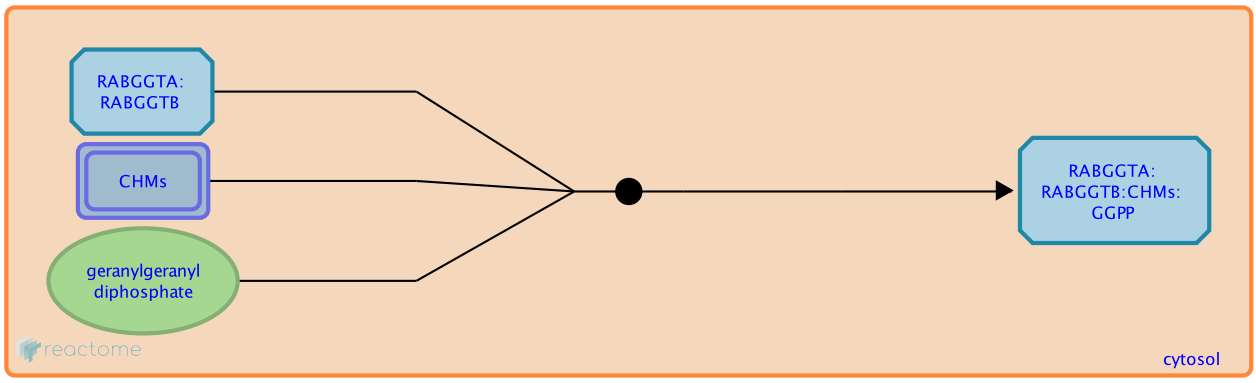
RGGT binds the RAB-binding subunit ↗

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870465

Type: binding

Compartments: cytosol



The catalytic dimer of RGGTA and B interacts with RAB-escorting proteins 1 or 2 (CHM and CHML, also known as REP-1 and REP-2) to form a functional trimeric RAB geranylgeranyl transferase complex that is capable of binding and geranylgeranylating newly synthesized RAB proteins (Baron and Seabra, 2008; reviewed in Leung et al, 2006; Gutkowska and Swiezewska, 2012). There are two models for the formation of a functional enzyme:substrate complex. In the classical model, unprenylated RAB first binds to REP and is subsequently presented to the catalytic subunits of the GGTase. Incorporation of geranylgeranyl pyrophosphate (GGPP) strengthens the interaction between enzyme and substrate (Andres et al, 1993; Thoma et al, 2001a). In the alternate route, which is depicted in this pathway, RGGTA and RGGTB first bind to REP in a GGPP-dependent manner in the absence of the RAB substrate. Unprenylated RABs then bind to the fully formed GGTase for geranylgeranylation (Thoma et al, 2001b; Baron and Seabra, 2008).

Preceded by: RABGGTA and RABGGTB bind

Followed by: RGGT:CHM binds RABs

Literature references

Baron, RA., Seabra, MC. (2008). Rab geranylgeranylation occurs preferentially via the pre-formed REP-RGGT complex and is regulated by geranylgeranyl pyrophosphate. *Biochem. J., 415*, 67-75. ↗

Gutkowska, M., Swiezewska, E. (2012). Structure, regulation and cellular functions of Rab geranylgeranyl transferase and its cellular partner Rab Escort Protein. *Mol. Membr. Biol., 29*, 243-56. ↗

Leung, KF., Baron, R., Seabra, MC. (2006). Thematic review series: lipid posttranslational modifications. geranylgeranylation of Rab GTPases. *J. Lipid Res., 47*, 467-75. ↗

Thomä, NH., Iakovenko, A., Kalinin, A., Waldmann, H., Goody, RS., Alexandrov, K. (2001). Allosteric regulation of substrate binding and product release in geranylgeranyltransferase type II. *Biochemistry, 40*, 268-74. ↗

Thomä, NH., Iakovenko, A., Goody, RS., Alexandrov, K. (2001). Phosphoisoprenoids modulate association of Rab geranylgeranyltransferase with REP-1. *J. Biol. Chem., 276*, 48637-43. ↗

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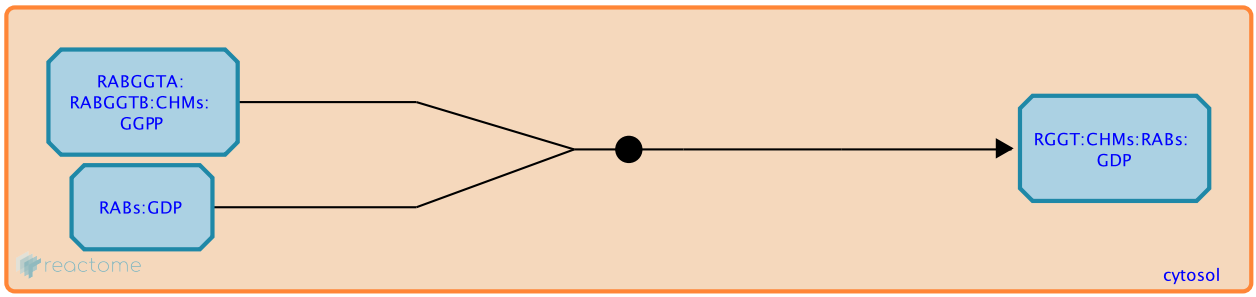
RGGT:CHM binds RABs ↗

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870466

Type: binding

Compartments: cytosol



CHM and CHML are the substrate-binding subunits of the RAB geranylgeranyltransferase (GGTase) complex. CHMs, also known as RAB escort proteins (REPs) bind to unprenylated RAB proteins in the GDP bound state (Seabra, 1996). In the classical model of RAB recruitment, CHM proteins first bind the unprenylated RAB alone and then present it to the catalytic dimer of the RAB GGTase, while in the alternative model, depicted here, RAB recruitment occurs after the GGPP-dependent formation of a highly stable trimeric GGTase complex (Andres et al, 1993; Thoma et al, 2001a; Thoma et al 2001b; Baron and Seabra, 2008). After geranylgeranylation, binding of additional GGPP to the GGTase promotes release of the CHM:RAB complex, possibly through an allosteric mechanism (Baron and Seabra, 2008). CHM proteins remain in complex with the RABs after geranylgeranylation, dissociating after the RAB has been transferred to the target membrane (Alexandrov et al, 1994; Shen and Seabra, 1996; Baron and Seabra, 2008).

Preceded by: RGGT binds the RAB-binding subunit

Followed by: RGGT geranylgeranylates RAB proteins

Literature references

Seabra, MC. (1996). Nucleotide dependence of Rab geranylgeranylation. Rab escort protein interacts preferentially with GDP-bound Rab. *J. Biol. Chem., 271*, 14398-404. ↗

Andres, DA., Seabra, MC., Brown, MS., Armstrong, SA., Smeland, TE., Cremers, FP. et al. (1993). cDNA cloning of component A of Rab geranylgeranyl transferase and demonstration of its role as a Rab escort protein. *Cell, 73*, 1091-9. ↗

Thomä, NH., Iakovenko, A., Kalinin, A., Waldmann, H., Goody, RS., Alexandrov, K. (2001). Allosteric regulation of substrate binding and product release in geranylgeranyltransferase type II. *Biochemistry, 40*, 268-74. ↗

Thomä, NH., Iakovenko, A., Goody, RS., Alexandrov, K. (2001). Phosphoisoprenoids modulate association of Rab geranylgeranyltransferase with REP-1. *J. Biol. Chem., 276*, 48637-43. ↗

Baron, RA., Seabra, MC. (2008). Rab geranylgeranylation occurs preferentially via the pre-formed REP-RGGT complex and is regulated by geranylgeranyl pyrophosphate. *Biochem. J., 415*, 67-75. ↗

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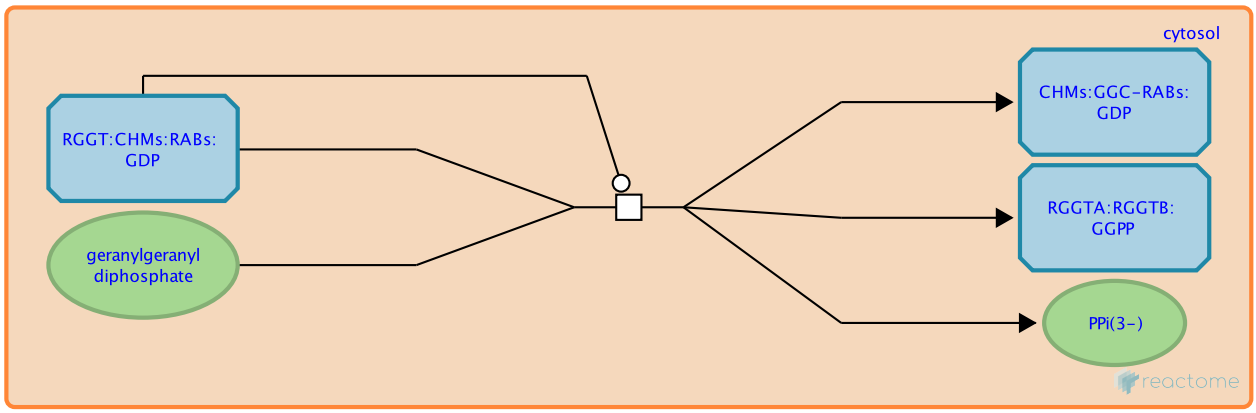
RGGT geranylgeranylates RAB proteins ↗

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870469

Type: transition

Compartments: cytosol



RAB geranylgeranyltransferase (GGTase) recognizes and geranylgeranylates cysteine residues in -CXCX, -CCXX or -XXCC motifs in the C-termini of RAB proteins. Most RAB proteins are doubly geranylgeranylated, most likely in a sequential fashion, but some are only singly modified (Baron and Seabra, 2008; Farnsworth et al 1994; Wilson et al, 1996; Overmeyer et al, 2000; Khosravi-Far et al, 1991; Joberty et al, 1993; Catherman et al, 2013; Leung et al, 2007; Maurer-Stroh et al, 2007). In most cases, geranylgeranylation is required for proper localization and function of the RAB proteins. After geranylgeranylation, RABs remain associated with the RAB escort protein CHM or CHML, which dissociates when the GTPase reaches its target membrane (Alexandrov et al, 1994; Seabra et al, 1996; Shen and Seabra, 1996). Release of the geranylgeranyl RAB:CHM complex from the catalytic subunits is promoted by the binding of additional GGPP to the enzyme (Baron and Seabra, 2008). Once prenylated, RABs cycle between active GTP bound forms that are membrane associated, and inactive GDP bound forms that are cytosolic and associated with RAB GDP dissociation inhibitor (GDI) proteins. Conversion between these states is governed by the activities of guanine nucleotide exchange factors (GEFs), which promote the exchange of GDP for GTP, and GTPase activating proteins (GAPs), which stimulate the intrinsic GTPase activity of RABs (Ullrich et al, 1993; Soldati et al, 1994; reviewed in Wandinger-Ness and Zerial, 2014; Stenmark, 2009).

Preceded by: RGGT:CHM binds RABs

Literature references

Farnsworth, CC., Seabra, MC., Ericsson, LH., Gelb, MH., Glomset, JA. (1994). Rab geranylgeranyl transferase catalyzes the geranylgeranylation of adjacent cysteines in the small GTPases Rab1A, Rab3A, and Rab5A. *Proc. Natl. Acad. Sci. U.S.A., 91*, 11963-7. ↗

Wilson, AL., Sheridan, KM., Erdman, RA., Maltese, WA. (1996). Prenylation of a Rab1B mutant with altered GTPase activity is impaired in cell-free systems but not in intact mammalian cells. *Biochem. J., 318*, 1007-14. ↗

Overmeyer, JH., Wilson, AL., Maltese, WA. (2001). Membrane targeting of a Rab GTPase that fails to associate with Rab escort protein (REP) or guanine nucleotide dissociation inhibitor (GDI). *J. Biol. Chem., 276*, 20379-86. ↗

Khosravi-Far, R., Lutz, RJ., Cox, AD., Conroy, L., Bourne, JR., Sinensky, M. et al. (1991). Isoprenoid modification of rab proteins terminating in CC or CXC motifs. *Proc. Natl. Acad. Sci. U.S.A., 88*, 6264-8. ↗

Joberty, G., Tavitian, A., Zahraoui, A. (1993). Isoprenylation of Rab proteins possessing a C-terminal CaaX motif. *FEBS Lett., 330*, 323-8. ↗

Editions

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Table of Contents