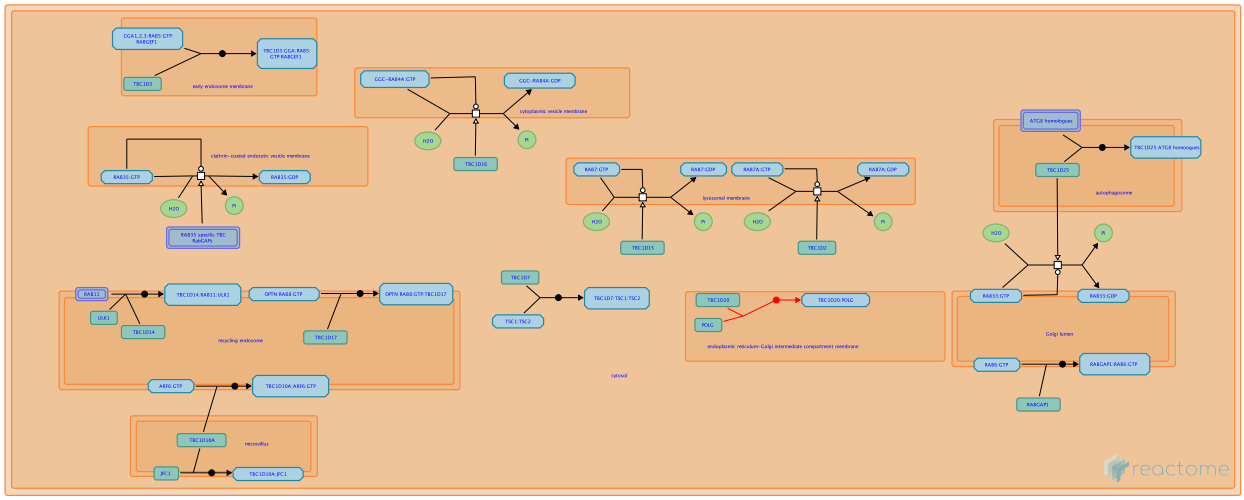
TBC/RABGAPs



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15/09/2021

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. ↗

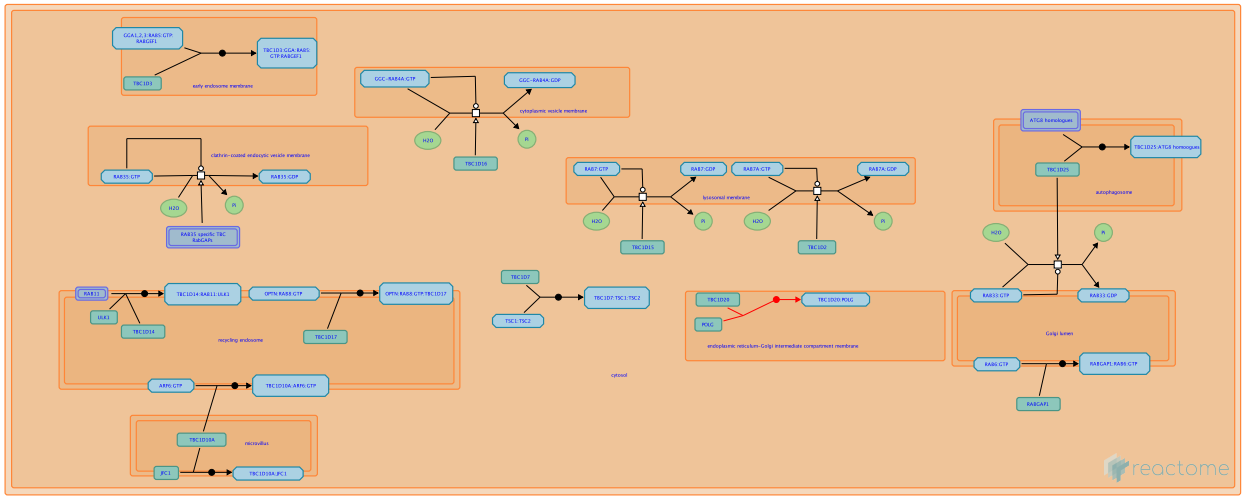
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

TBC/RABGAPs ↗

Stable identifier: R-HSA-8854214



Rab GTPases are peripheral membrane proteins involved in membrane trafficking. Often through their indirect interactions with coat components, motors, tethering factors and SNAREs, the Rab GTPases serve as multifaceted organizers of almost all membrane trafficking processes in eukaryotic cells. To perform these diverse processes, Rab GTPases interconvert between an active GTP-bound form and an inactive, GDP-bound form. The GTP-bound activated form mediates membrane transport through specific interaction with multiple effector molecules (Zerial & McBride 2001, Stenmark 2009, Zhen & Stenmark 2015, Cherfils & Zeghouf 2013). Conversion from the GTP- to the GDP-bound form occurs through GTP hydrolysis, which is not only driven by the intrinsic GTPase activity of the Rab protein but is also catalysed by GTPase-activating proteins (GAPs). GAPs not only increase the rate of GTP hydrolysis, but they are also involved in the inactivation of RABs, making sure they are inactivated at the correct membrane. Human cells contain as many as 70 Rabs and at least 51 putative Rab GAPs (Pfeffer 2005). Only a few of these GAPs have been matched to a specific Rab substrate. The Tre-2/Bub2/Cdc16 (TBC) domain-containing RAB-specific GAPs (TBC/RABGAPs) are a key family of RAB regulators, where the TBC domain facilitates the inactivation of RABs by facilitating activation of GTPase activity of the RAB (Pan et al. 2006, Frasa et al. 2012, Stenmark 2009). Studies suggest that TBC/RABGAPs are more than just negative regulators of RABs and can integrate signalling between RABs and other small GTPases, thereby regulating numerous cellular processes like intracellular trafficking (Frasa et al. 2012).

Literature references

Pan, X., Eathiraj, S., Munson, M., Lambright, DG. (2006). TBC-domain GAPs for Rab GTPases accelerate GTP hydrolysis by a dual-finger mechanism. *Nature, 442*, 303-6. ↗

Frasa, MA., Koessmeier, KT., Ahmadian, MR., Braga, VM. (2012). Illuminating the functional and structural repertoire of human TBC/RABGAPs. *Nat. Rev. Mol. Cell Biol., 13*, 67-73. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

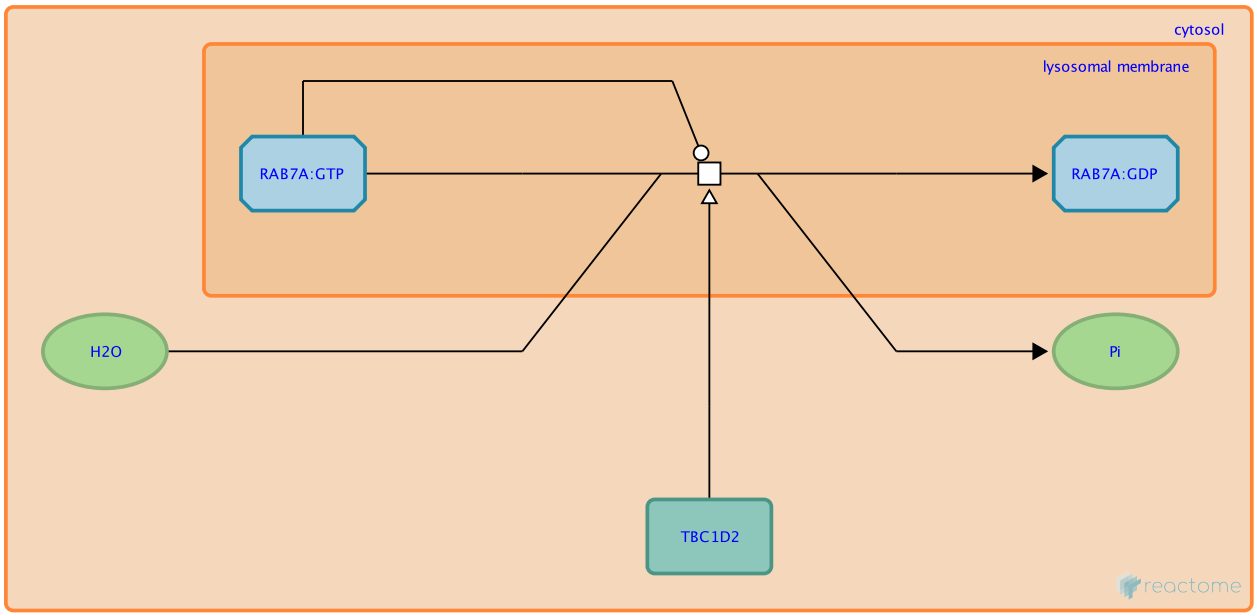
TBC1D2A accelerates GTP hydrolysis by RAB7 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854255

Type: transition

Compartments: lysosomal membrane, cytosol



RAB7, a small GTPase of the Rab family is associated with both endosomes and lysosomes. It facilitates endosomal maturation, transport from late endosomes to lysosomes, and the positioning of endosomes and lysosomes via regulating their movement along the cytoskeleton. RAB7 is inactivated through hydrolysis of bound GTP into GDP by its intrinsic GTPase activity, which is catalysed by the activity of a GAP (GTPase activating protein).

TBC1 domain family member 2A (TBC1D2A also referred as ARMUS for variant c; PARIS1 for variant a) is a member of the TBC/RabGAP family (Tre2/Bub2/Cdc16; TBC domain) that specifically inactivates RAB7 by accelerating its GTPase activity. TBC1D2A binds specifically to activated Rac1 and its C-terminal TBC/RabGAP domain inactivates RAB7 to promote ARF6-induced E-Cadherin degradation (Frasa et al. 2010). During the regulation of autophagy, TBC1D2A is recruited to autophagosomes by interacting with LC3, a core autophagy regulator, thereby inhibiting RAB7 (Carroll et al. 2013)

Literature references

Frasa, MA., Maximiano, FC., Smolarczyk, K., Francis, RE., Betson, ME., Lozano, E. et al. (2010). Armus is a Rac1 effector that inactivates Rab7 and regulates E-cadherin degradation. *Curr. Biol., 20,* 198-208. ↗

Carroll, B., Mohd-Naim, N., Maximiano, F., Frasa, MA., McCormack, J., Finelli, M. et al. (2013). The TBC/RabGAP Armus coordinates Rac1 and Rab7 functions during autophagy. *Dev. Cell, 25,* 15-28. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

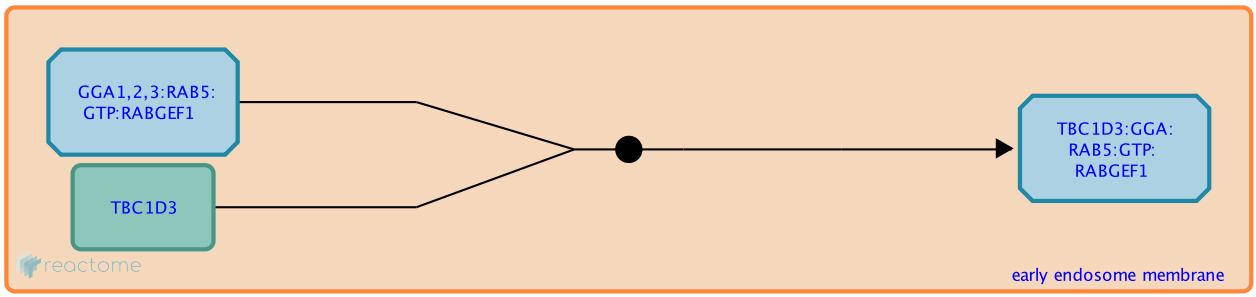
TBC1D3 associates with RAB5 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854222

Type: binding

Compartments: early endosome membrane



TBC1 domain family member 3 (TBC1D3) belongs to the TBC/RabGAPs family and contains a TBC (Tre-2/Bub2/Cdc16) domain but has no GAP activity. It regulates macropinocytosis in response to epidermal growth factor (EGF), and facilitates crosstalk between the GTPases ARF6 and RAB5 (Frittoli et al. 2008). TBC1D3 binds to the ARF6 effector protein GGA (Golgi-localized, gamma-ear-containing, ARF-binding protein), which binds to a complex consisting of the RAB5GEF, rabaptin 5-associated exchange factor for Rab5 (RABEX5), and the Rab5 effector Rabaptin-5, thereby providing an indirect interaction between TBC1D3 and RAB5. Although TBC1D3 associates with Rab5, it may operate as a Rab5 effector, and not as a Rab5 GAP (Huaiping et al. 2007, Wainszelbaum et al. 2008).

Literature references

Wainszelbaum, MJ., Charron, AJ., Kong, C., Kirkpatrick, DS., Srikanth, P., Barbieri, MA. et al. (2008). The hominoid-specific oncogene TBC1D3 activates Ras and modulates epidermal growth factor receptor signaling and trafficking. *J. Biol. Chem., 283*, 13233-42. ↗

Frittoli, E., Palamidessi, A., Pizzigoni, A., Lanzetti, L., Garrè, M., Troglio, F. et al. (2008). The primate-specific protein TBC1D3 is required for optimal macropinocytosis in a novel ARF6-dependent pathway. *Mol. Biol. Cell, 19*, 1304-16. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

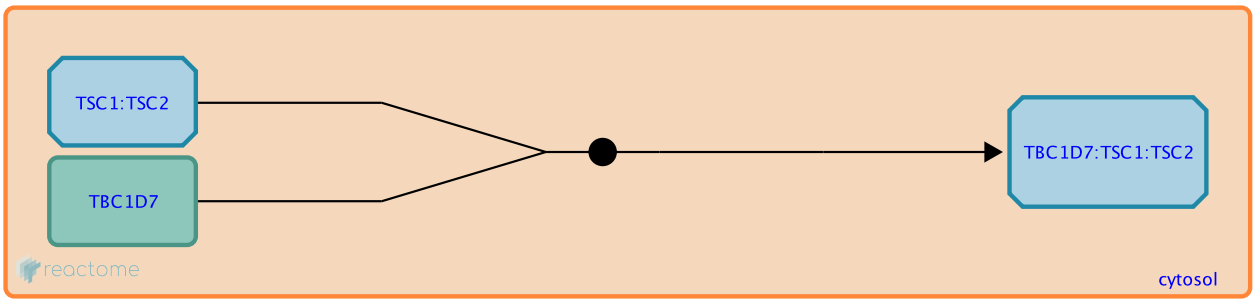
TBC1D7 binds the TSC1-TSC2 complex ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854302

Type: binding

Compartments: cytosol



TBC1D7 (TBC1 domain family, member 7) is a TBC (Tre-2/Bub2/Cdc16) 1 domain protein. Though TBC domain not only acts as a putative GTPase-activating protein (GAP) for small GTPases like Rab, it also have important role in cell cycle regulation and/or oncogenesis. The tuberous sclerosis complex (TSC) tumor suppressors form the TSC1-TSC2 complex that senses specific cellular conditions to control rapamycin (mTOR) complex 1 (mTORC1) signalling. TBC1D7 stably binds to TSC1 to form the third core subunit of TSC1-TSC2 complex. The TSC1-TSC2-TBC1D7 interaction helps stabilise these three proteins in the Rhebulator complex (Nakashima et al. 2007, Dibble et al. 2012). This TSC1-TSC2 complex acts as a GAP for the small G-protein RHEB, accelerating its conversion from its active GTP-bound state to its inactive GDP-form (Huang & Manning 2008). The active RHEB is required for activation of the mTORC1, a key promoter of cell growth. In poor growth conditions, the TSC1-TSC2 complex is activated to down-regulate TORC1 activity, whereas in response to growth factors, the TSC1-TSC2 complex is inactivated to allow RHEB-GTP-dependent stimulation of growth.

Literature references

Sato, N., Koinuma, J., Ito, T., Tsuchiya, E., Kondo, S., Nakamura, Y. et al. (2010). Activation of an oncogenic TBC1D7 (TBC1 domain family, member 7) protein in pulmonary carcinogenesis. *Genes Chromosomes Cancer, 49*, 353-67. ↗

Nakashima, A., Yoshino, K., Miyamoto, T., Eguchi, S., Oshiro, N., Kikkawa, U. et al. (2007). Identification of TBC7 having TBC domain as a novel binding protein to TSC1-TSC2 complex. *Biochem. Biophys. Res. Commun., 361*, 218-23. ↗

Huang, J., Manning, BD. (2008). The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. *Biochem J , 412*, 179-90. ↗

Dibble, CC., Elis, W., Menon, S., Qin, W., Klekota, J., Asara, JM. et al. (2012). TBC1D7 is a third subunit of the TSC1-TSC2 complex upstream of mTORC1. *Mol. Cell, 47*, 535-46. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

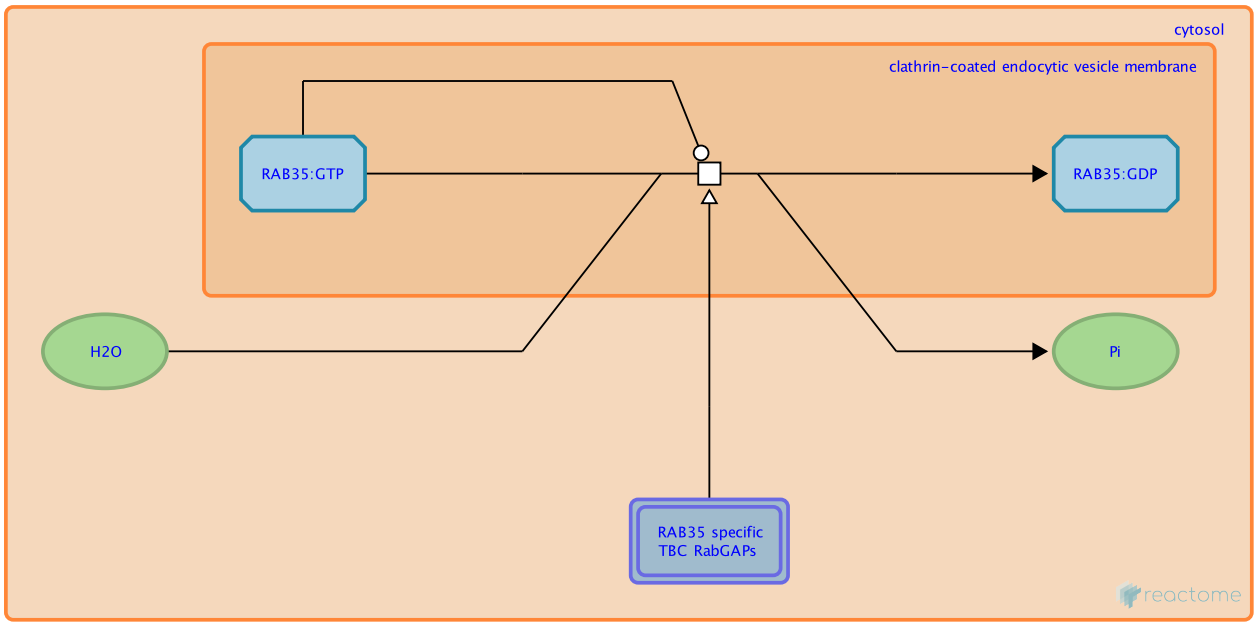
TBC RabGAPs accelerate GTP hydrolysis by RAB35 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854173

Type: transition

Compartments: clathrin-coated endocytic vesicle membrane, cytosol



RAB35 is a Rab protein with both plasma membrane and endosomal membrane localization, where it controls vesicular trafficking. RAB35 regulates the endocytic recycling of numerous protein cargoes, is involved in the recycling of synaptic vesicles (Uytterhoeven et al. 2011; Allaire et al. 2010, Sato et al. 2008, Sheehan et al. 2106, Klinkert & Echard 2016), controls the fusion of exosomes (Hsu et al. 2010), and regulates the actin cytoskeleton (Zhang et al. 2009). At least five different members of the TBC protein family are GAPs for Rab35. The three members of TBC1D10A-C family (also known as EPI64A-C) are identified to have Rab35-specific GAP activity and regulate exosome secretion (Hsu et al. 2010). TBC1D10 family members are also involved in the endocytic recycling and prevent cytokinesis (Kouranti et al. 2006, Chesneau et al. 2012).

TBC1D13 was identified as a specific GAP for Rab35 and observed to act as a potent inhibitor of insulin-stimulated GLUT4 translocation (Davey et al. 2012). TBC1D24 is a homolog of a Drosophila protein called skywalker, which has been shown to exhibit GAP activity towards Rab35 (Uytterhoeven et al. 2011).

Literature references

Hsu, C., Morohashi, Y., Yoshimura, S., Manrique-Hoyos, N., Jung, S., Lauterbach, MA. et al. (2010). Regulation of exosome secretion by Rab35 and its GTPase-activating proteins TBC1D10A-C. *J. Cell Biol., 189*, 223-32. ↗

Davey, JR., Humphrey, SJ., Junutula, JR., Mishra, AK., Lambright, DG., James, DE. et al. (2012). TBC1D13 is a RAB35 specific GAP that plays an important role in GLUT4 trafficking in adipocytes. *Traffic, 13*, 1429-41. ↗

Uytterhoeven, V., Kuenen, S., Kasprowicz, J., Miskiewicz, K., Verstreken, P. (2011). Loss of skywalker reveals synaptic endosomes as sorting stations for synaptic vesicle proteins. *Cell, 145*, 117-32. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

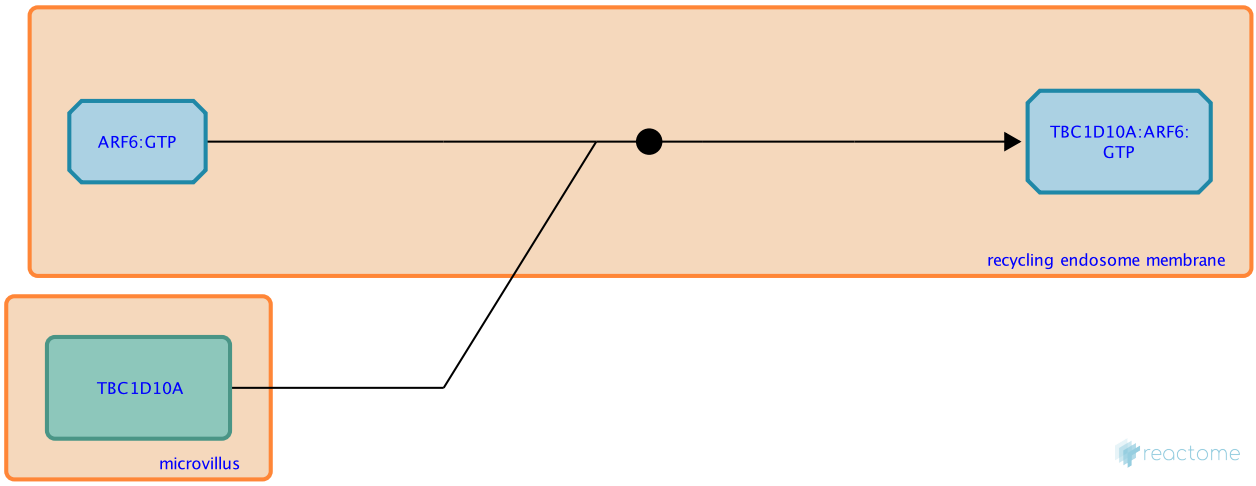
TBC1D10A (EPI64) binds ARF6:GTP ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854293

Type: binding

Compartments: recycling endosome membrane, microvillus



TBC1D10A (EPI64), a RabGAP protein with a Tre-2/Bub2/Cdc16 (TBC) domain, is an effector of ARF6 and regulates ARF6-dependent membrane trafficking (Hanono et al. 2006). The TBC domain of EPI64 binds to ARF6 and stabilizes ARF6:GTP levels in a manner that is independent of its GAP activity. This interaction keeps ARF6 in an active state either by locking ARF6:GTP in an active state or may sterically hinders ARF6 from associating with its GAP, delaying the hydrolysis of bound GTP to GDP (Hokanson & Bretscher 2011).

Literature references

Hokanson, DE., Bretscher, AP. (2012). EPI64 interacts with Slp1/JFC1 to coordinate Rab8a and Arf6 membrane trafficking. *Mol. Biol. Cell, 23,* 701-15. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

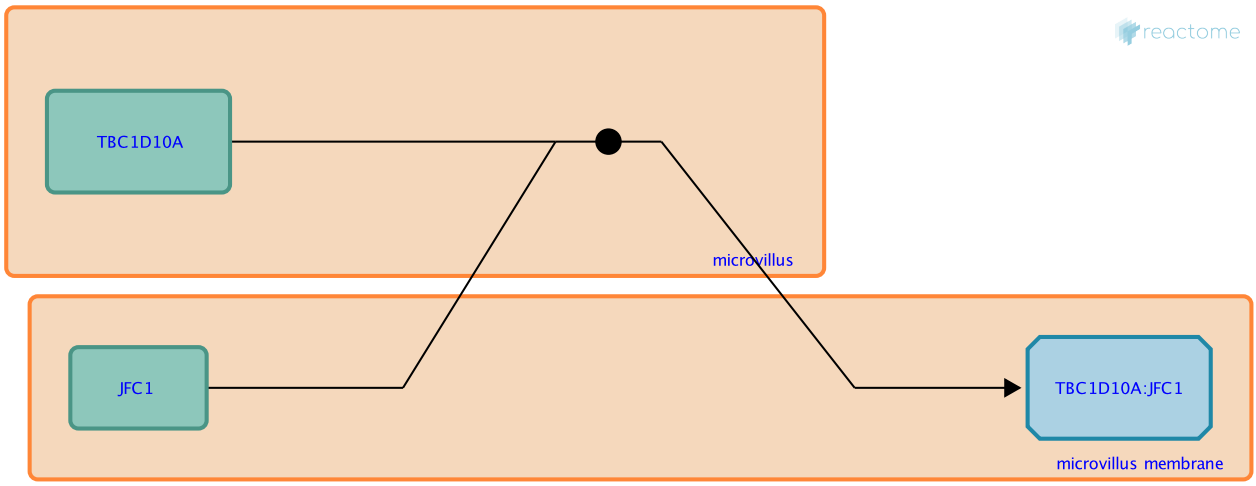
TBC1D10A binds JFC1 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854209

Type: binding

Compartments: microvillus, microvillus membrane



TBC1D10A (EPI64) stabilizes active ARF6 and also has an additional function in the ARF6-dependent pathway through regulating the levels of active RAB8A. RAB8A is involved in the recycling pathway from endosomes back to the plasma membrane. TBC1D10A binds the Rab8a effector JFC1 and reduces the level of Rab8a:GTP to regulate Rab8a/Arf6-dependent membrane trafficking. TBC1D10A binds JFC1 through its (Slp) homology domain (SHD), and JFC1 can simultaneously interact with active Rab8a (Hokanson & Bretscher 2011).

Literature references

Hokanson, DE., Bretscher, AP. (2012). EPI64 interacts with Slp1/JFC1 to coordinate Rab8a and Arf6 membrane trafficking. *Mol. Biol. Cell, 23,* 701-15. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

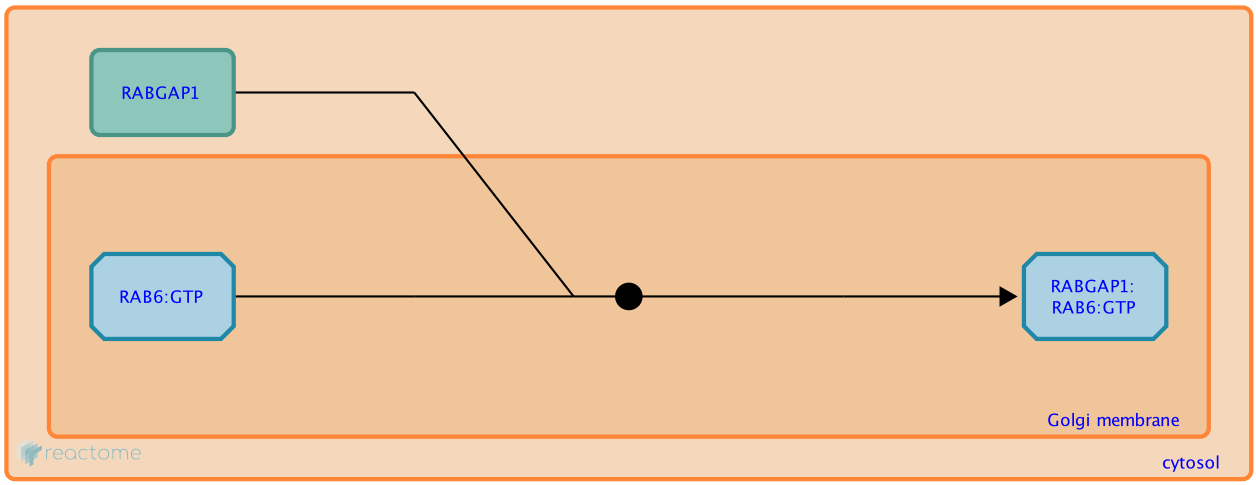
TBC1D11 binds RAB6 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854303

Type: binding

Compartments: Golgi membrane, cytosol



Rab6 is associated with Golgi and trans-Golgi (TGN) membranes in interphase and regulates a retrograde transport route connecting early endosomes to the endoplasmic reticulum (ER). TBC domain family, member 11 (TBC1D11 also referred as GAPCENA is a Rab GTPase and directly binds Rab6 via its N-terminal PTB domain (Cuif et al. 1999, Miserey-Lenkei et al. 2006).

Literature references

Miserey-Lenkei, S., Couëdel-Courteille, A., del Nery, E., Bardin, S., Piel, M., Racine, V. et al. (2006). A role for the Rab6A' GTPase in the inactivation of the Mad2-spindle checkpoint. *EMBO J., 25*, 278-89. ↗

Cuif, MH., Possmayer, F., Zander, H., Bordes, N., Jollivet, F., Couedel-Courteille, A. et al. (1999). Characterization of GAPCenA, a GTPase activating protein for Rab6, part of which associates with the centrosome. *EMBO J., 18*, 1772-82. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

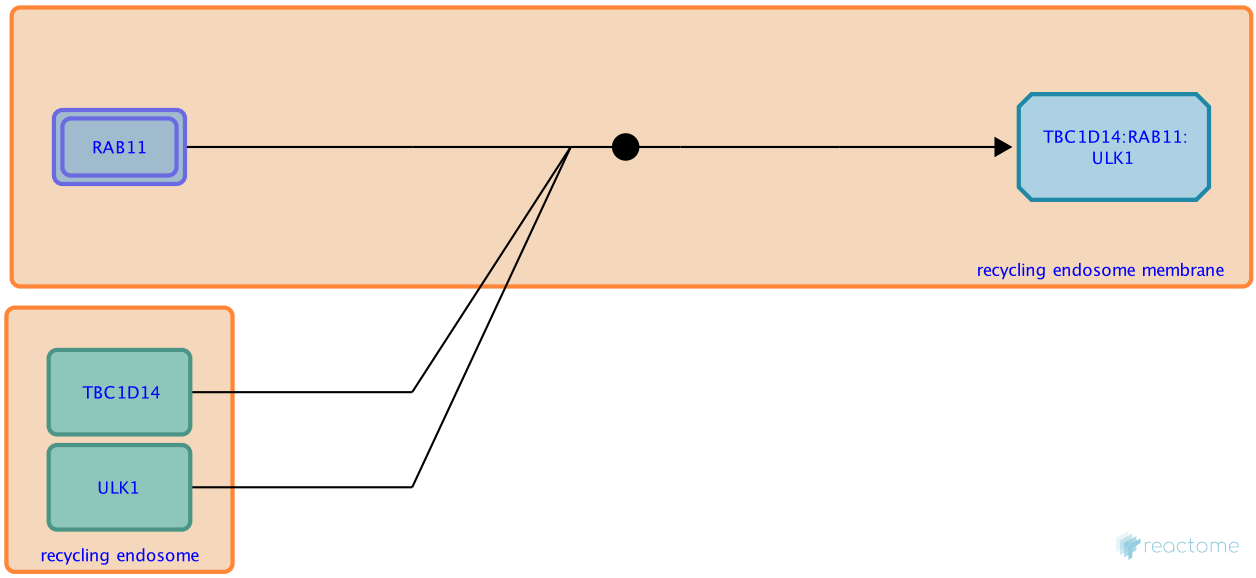
TBC1D14 binds RAB11 and ULK1 ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854759

Type: binding

Compartments: recycling endosome membrane



TBC (Tre2/Bub2/Cdc16) domain family, member 14 (TBC1D14) is a putative Rab GTPase activating protein (GAP) member that binds to activated Rab11 and regulates starvation-induced autophagy. TBC1D14 does not have the GAP activity and may function as Rab11 effector. TBC1D14 also colocalizes and interacts with the autophagy kinase ULK1. Overexpression of TBC1D14 causes tubulation of recycling endosomes (REs), accumulation of the ULK1 complex and Rab11 on REs, and inhibition of vesicular transport from the RE (Longatti et al. 2012).

Literature references

Longatti, A., Lamb, CA., Razi, M., Yoshimura, S., Barr, FA., Tooze, SA. (2012). TBC1D14 regulates autophagosome formation via Rab11- and ULK1-positive recycling endosomes. *J. Cell Biol., 197*, 659-75. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

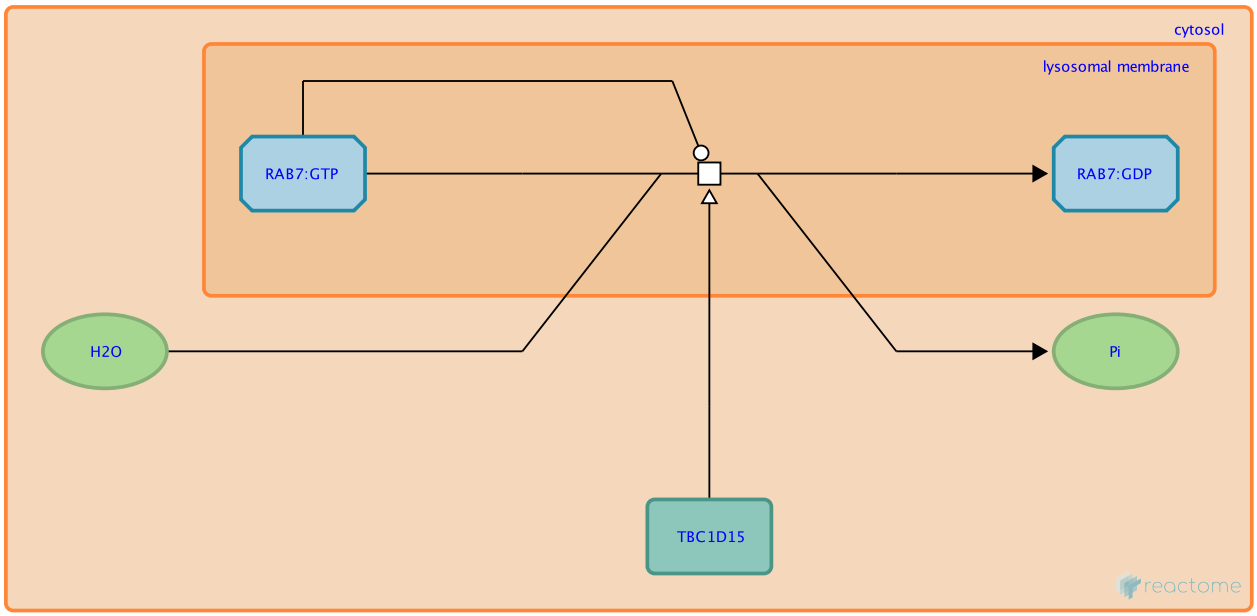
TBC1D15 accelerates GTP hydrolysis by RAB7

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854329

Type: transition

Compartments: lysosomal membrane, cytosol



The small GTPase Rab7 promotes fusion events between late endosomes and lysosomes. TBC domain family, member 15 (TAB1CD15) is ubiquitously expressed and localized predominantly to the cytosol. TBC1D15 stimulates the intrinsic GTPase activity of Rab7, reducing Rab7 binding to its effector protein RILP, fragmenting the lysosome, and conferring resistance to growth factor withdrawal-induced cell death (Zhang et al. 2005, Peralta et al. 2010).

Literature references

Peralta, ER., Martin, BC., Edinger, AL. (2010). Differential effects of TBC1D15 and mammalian Vps39 on Rab7 activation state, lysosomal morphology, and growth factor dependence. *J. Biol. Chem., 285*, 16814-21.

Zhang, XM., Walsh, B., Mitchell, CA., Rowe, T. (2005). TBC domain family, member 15 is a novel mammalian Rab GTPase-activating protein with substrate preference for Rab7. *Biochem. Biophys. Res. Commun., 335*, 154-61.

Editions

2016-01-27	Authored, Edited	Garapati, P V.

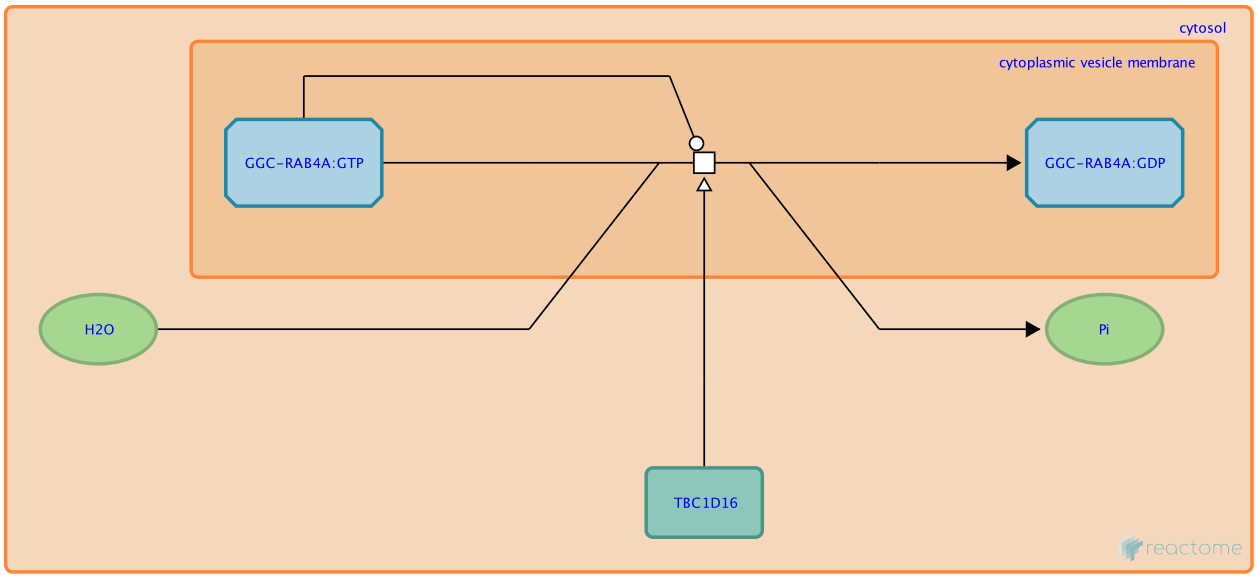
TBC1D16 accelerates GTP hydrolysis by RAB4A ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854604

Type: transition

Compartments: cytoplasmic vesicle membrane



RAB4A is a master regulator of receptor recycling from endocytic compartments to the plasma membrane. It is involved in transferrin receptor recycling and EGFR trafficking and signalling. TBC (Tre2/Bub2/Cdc16) domain family member 16 (TBC1D16), is a GTPase activating protein for Rab4A and enhances the intrinsic rate of GTP hydrolysis by RAB4A (Goueli et al. 2012).

Literature references

Goueli, BS., Powell, MB., Finger, EC., Pfeffer, SR. (2012). TBC1D16 is a Rab4A GTPase activating protein that regulates receptor recycling and EGF receptor signaling. *Proc. Natl. Acad. Sci. U.S.A., 109*, 15787-92. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

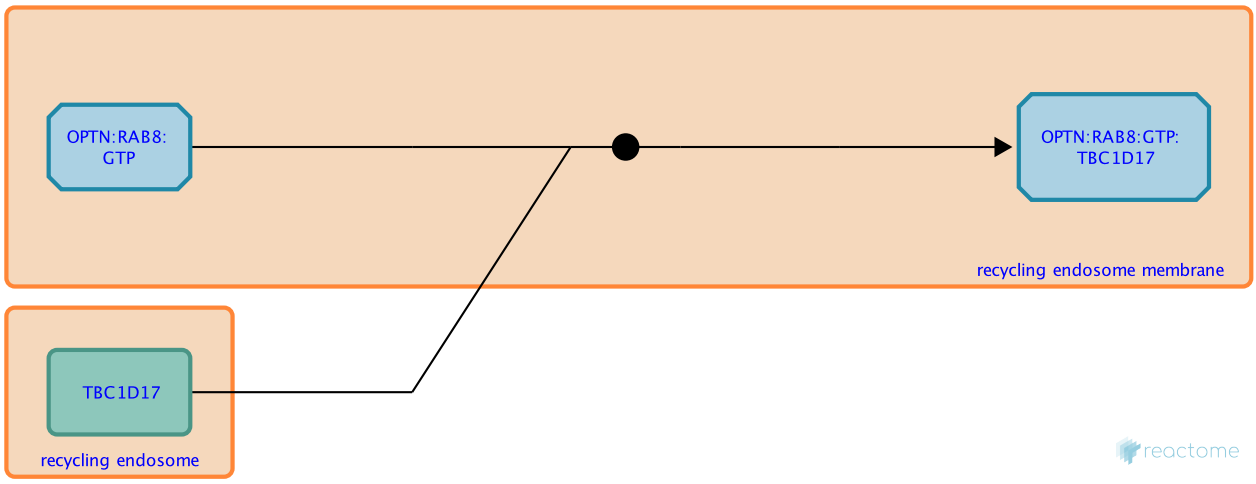
TBC1D17 binds OPTN:RAB8A ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854182

Type: binding

Compartments: recycling endosome membrane, recycling endosome



Rab8 is a small GTPase that is specifically involved in the regulation of secretory/recycling vesicles, modulation of the actin cytoskeleton, and cell polarity. TBC (Tre2/Bub2/Cdc16) domain family member 17 (TAB1CD17), a member of the Rab GTPase-activating protein, regulates Rab8-mediated endocytic trafficking of transferrin receptor through its interaction with optineurin (OPTN) (Vaibhava et al. 2012).

Literature references

Vaibhava, V., Nagabhushana, A., Chalasani, ML., Sudhakar, C., Kumari, A., Swarup, G. (2012). Optineurin mediates a negative regulation of Rab8 by the GTPase-activating protein TBC1D17. *J. Cell. Sci., 125*, 5026-39. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

TBC1D20 binds NS5A ↗

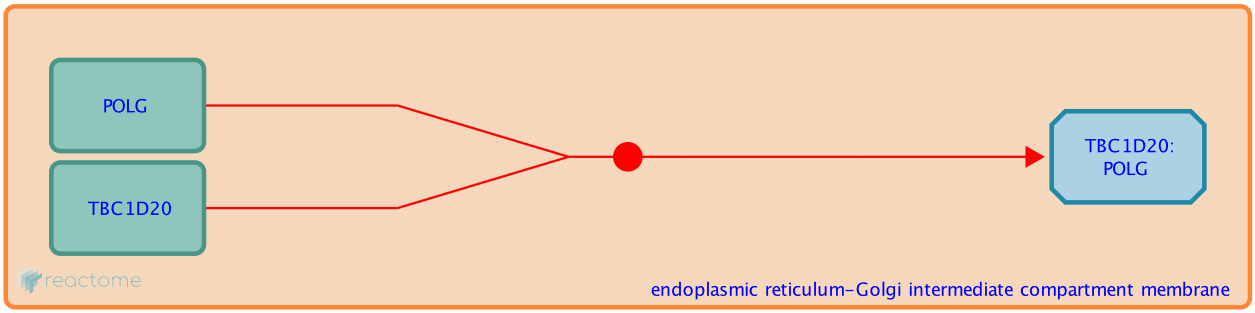
Location: TBC/RABGAPs

Stable identifier: R-HSA-8854290

Type: binding

Compartments: endoplasmic reticulum-Golgi intermediate compartment membrane

Diseases: hepatitis



TBC (Tre2/Bub2/Cdc16) domain family member 20 (TBC1D20), is a member of the Rab GAP for Rab1, the Rab involved in the regulation of ER-to-Golgi transport. TBC1D20 also interacts with Hepatitis C virus (HCV) nonstructural protein NS5A and this interaction is necessary for efficient HCV infection. It has been proposed that the TBC1D20:NS5A interaction locally inactivates Rab1 at sites of nascent viral protein synthesis to promote redirection from a Golgi-bound pathway to the virus-induced membrane structures, supporting HCV RNA replication (Sklan et al. 2007).

Literature references

Sklan, EH., Serrano, RL., Einav, S., Pfeffer, SR., Lambright, DG., Glenn, JS. (2007). TBC1D20 is a Rab1 GTPase-activating protein that mediates hepatitis C virus replication. *J. Biol. Chem., 282,* 36354-61. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

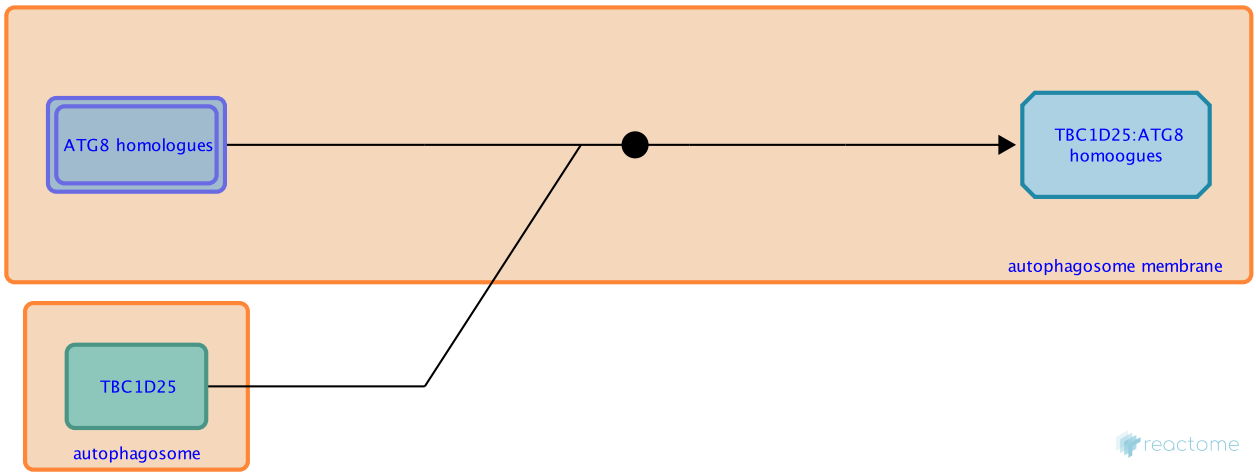
TBC1D25 (OATL1) binds ATG8 homologues ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854588

Type: binding

Compartments: autophagosome membrane, autophagosome



TBC (Tre2/Bub2/Cdc16) domain family member 25 (TBC1D25 also referred as OATL1), a putative GTPase activating protein (GAP), is recruited to autophagosomes through an interaction with ATG8 homologues (LC3, GABARAP and GATE-16), and is involved in the fusion between autophagosomes and lysosomes through its GAP activity. OATL1 delays autophagosomal maturation by inhibiting the encounter between autophagosomes and lysosomes (Itoh et al. 2011).

Literature references

Itoh, T., Kanno, E., Uemura, T., Waguri, S., Fukuda, M. (2011). OATL1, a novel autophagosome-resident Rab33B-GAP, regulates autophagosomal maturation. *J. Cell Biol., 192*, 839-53. ↗

Editions

2016-01-27	Authored, Edited	Garapati, P V.

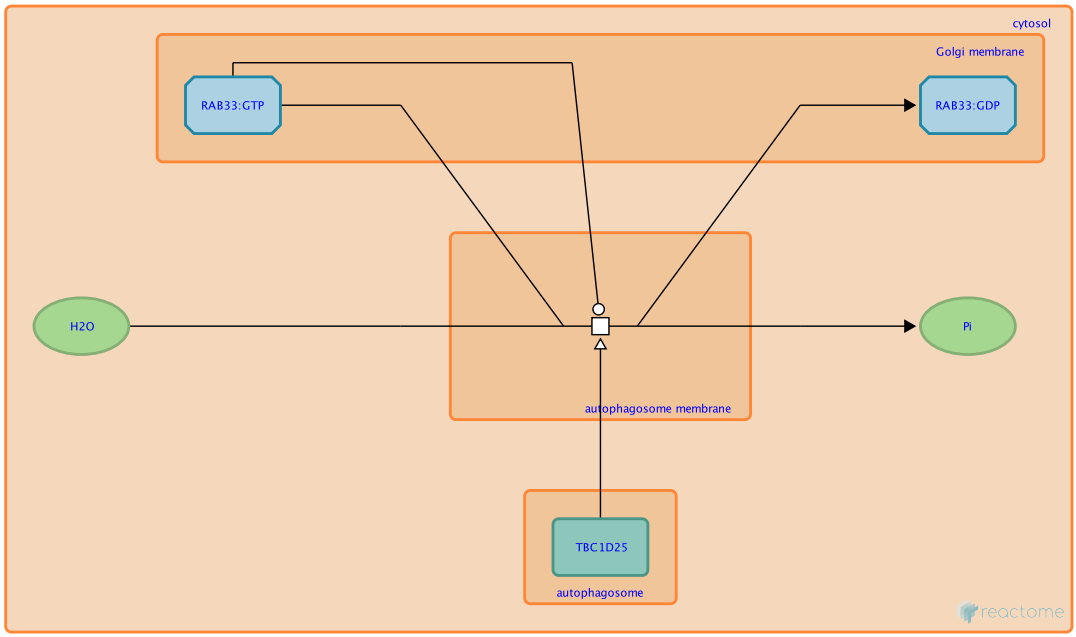
TBC1D25 accelerates GTP hydrolysis by RAB33B ↗

Location: TBC/RABGAPs

Stable identifier: R-HSA-8854612

Type: transition

Compartments: autophagosome membrane



RAB33B a medial Golgi-resident Rab involved in retrograde transport, is a target of TBC1D25 (OATL1). TBC1D25 significantly accelerates the GTP hydrolysis activity of RAB33B in a dose-dependent manner (Itoh et al. 2011).

Literature references

Itoh, T., Kanno, E., Uemura, T., Waguri, S., Fukuda, M. (2011). OATL1, a novel autophagosome-resident Rab33B-GAP, regulates autophagosomal maturation. *J. Cell Biol., 192*, 839-53. ↗

Editions

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