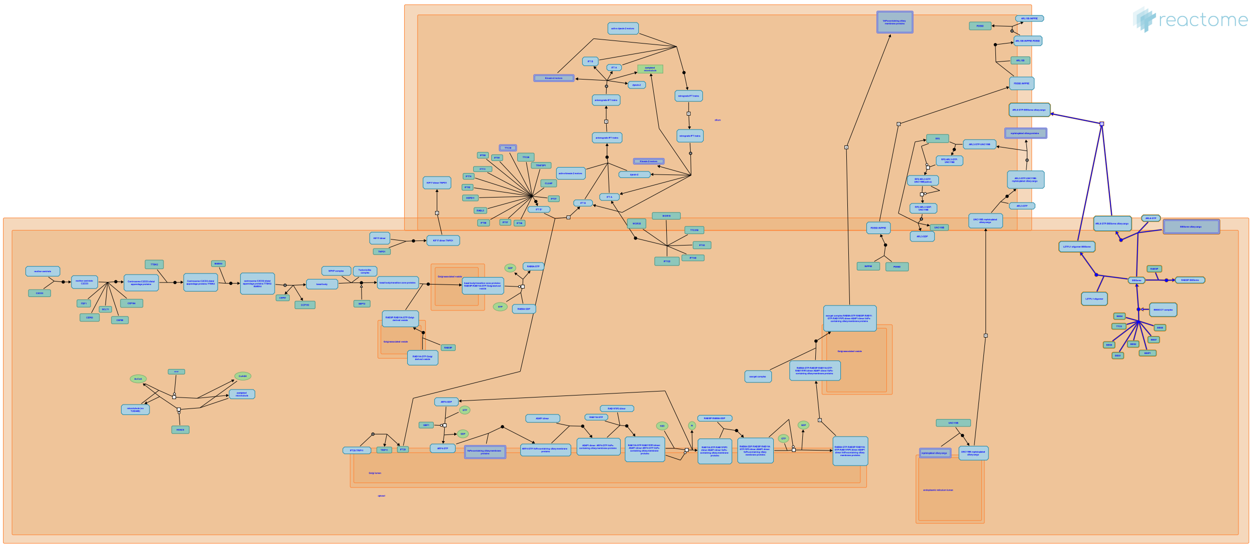
BBSome-mediated cargo-targeting to cilium



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

18/05/2024

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.

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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. ↗

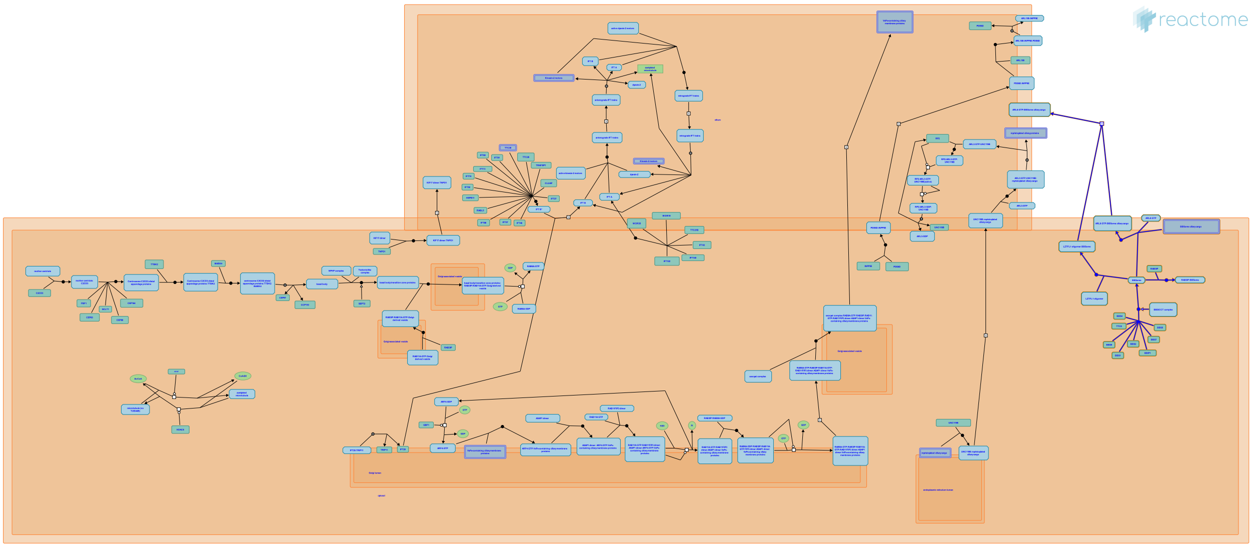
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 5 reactions (see Table of Contents)

BBSome-mediated cargo-targeting to cilium ↗

Stable identifier: R-HSA-5620922



The BBSome is a stable complex consisting of 7 Bardet-Biedl proteins (BBS1, 2, 4, 5, 7, 8 and 9) and BBIP10 that has roles in promoting IFT and trafficking proteins to the cilum (Blacque et al, 2004; Nachury et al, 2007; Loktev et al, 2008; Jin et al, 2010; reviewed in Sung and Leroux 2013). The BBSome is the primary effector of ARL6/BBS3, a small GTPase that binds the BBSome in complex with associated membrane proteins that are destined for the ciliary membrane (Jin et al, 2010; Nachury et al, 2007; Zhang et al, 2011; Seo et al, 2011). Components of the BBSome are enriched in TPR and beta-propeller motifs and are thought to form a linear coat on membranes that functions with ARL6 to target proteins to the cilium (Jin et al, 2010; reviewed in Nachury et al, 2010).

Literature references

Leroux, MR., McCarthy, J., Plasterk, RH., Quarmby, LM., Reardon, MJ., Mah, AK. et al. (2004). Loss of C. elegans BBS-7 and BBS-8 protein function results in cilia defects and compromised intraflagellar transport. *Genes Dev., 18*, 1630-42. ↗

Aguiar, M., Shida, T., Jin, H., Gygi, SP., Nachury, MV., White, SR. et al. (2010). The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell, 141*, 1208-19. ↗

Seo, S., Rahmouni, K., Bugge, K., Vogel, T., Morgan, DA., Stone, EM. et al. (2011). Bardet-Biedl syndrome 3 (Bbs3) knockout mouse model reveals common BBS-associated phenotypes and Bbs3 unique phenotypes. *Proc. Natl. Acad. Sci. U.S.A., 108*, 20678-83. ↗

Seo, S., Searby, CC., Bugge, K., Zhang, Q., Sheffield, VC., Nachury, MV. et al. (2011). A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet., 7*, e1002358. ↗

Sung, CH., Leroux, MR. (2013). The roles of evolutionarily conserved functional modules in cilia-related trafficking. *Nat. Cell Biol., 15*, 1387-97. ↗

Editions

2014-08-22	Authored	Rothfels, K.
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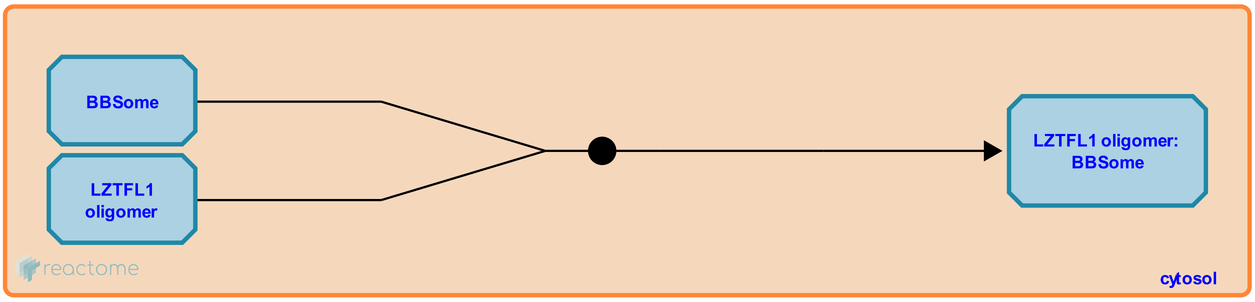
LZTFL1 binds the BBSome and prevents its traffic to the cilium ↗

Location: BBSome-mediated cargo-targeting to cilium

Stable identifier: R-HSA-5624129

Type: binding

Compartments: cytosol



LZTFL1 was identified as a tumor suppressor and as a protein that interacts with components of the BBSome (Wei et al, 2010; Seo et al, 2011). LZTFL1 forms cytosolic complexes with the BBSome and negatively regulates its entry into the cilium without affecting the assembly or stability of the BBSome complex. Both the BBSome and LZTFL1 have been shown to regulate the localization of the Hh signaling protein SMO (Seo et al, 2011). A recent study suggests that LZTFL1 may additionally play a role in coordinating the interaction between the BBSome and the IFT B component IFT27 and in this way contribute to the traffic of Hh pathway proteins into and out of the cilium (Eguether et al, 2014).

Preceded by: Formation of the BBSome

Literature references

Seo, S., Searby, CC., Bugge, K., Zhang, Q., Sheffield, VC., Nachury, MV. et al. (2011). A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet., 7*, e1002358. ↗

Pazour, GJ., San Agustin, JT., Keady, BT., Johnson, CA., Tobita, K., Francis, R. et al. (2014). IFT27 links the BBSome to IFT for maintenance of the ciliary signaling compartment. *Dev.Cell, 31*, 279-290. ↗

Cao, J., Wang, L., Zhou, W., Gao, B., Wang, W., Liu, ZP. et al. (2010). Tumor-suppressive functions of leucine zipper transcription factor-like 1. *Cancer Res., 70*, 2942-50. ↗

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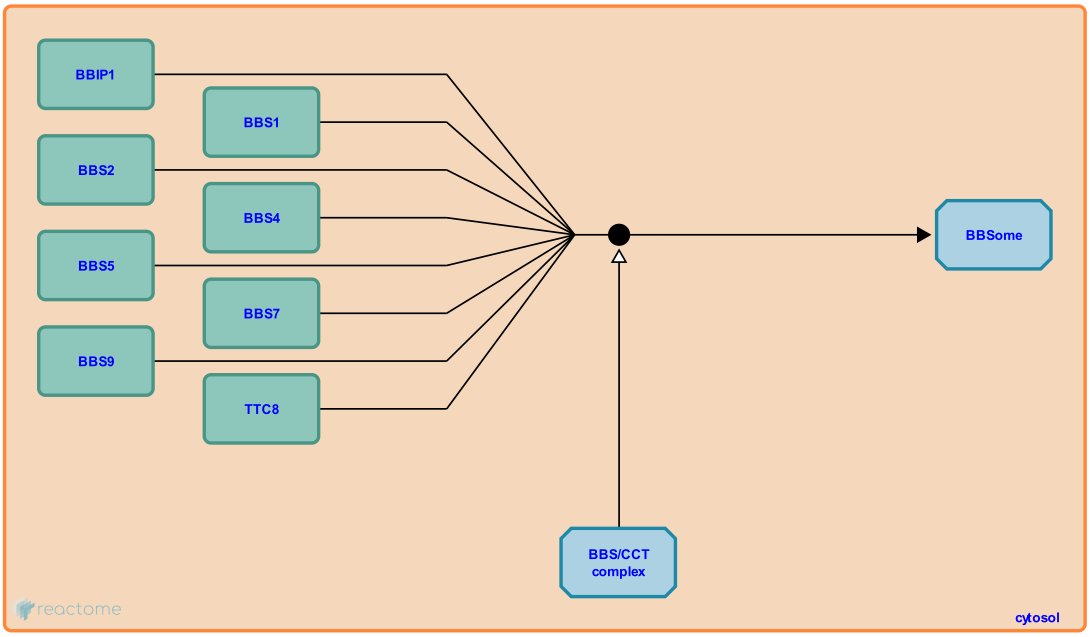
Formation of the BBSome ↗

Location: BBSome-mediated cargo-targeting to cilium

Stable identifier: R-HSA-5624125

Type: binding

Compartments: cytosol



The BBSome is a complex of 8 conserved proteins with roles in ciliary trafficking (Nachury et al, 2007; Loktev et al, 2008; reviewed in Nachury et al, 2010; Hsiao et al, 2012). Mutations in the BBS genes leads to Bardet-Biedl syndrome, a heterogeneous ciliopathy characterized by obesity, blindness, cystic kidney disease, retinitis pigmentosa, polydactyly, mental retardation, and renal failure in some cases (reviewed in Tobin and Beales, 2009). The BBSome is the primary effector of ARL6/BBS3, a small GTPase that recruits the BBSome and associated membrane proteins destined for the cilium to membranes (Jin et al, 2010; Nachury et al, 2007; Zhang et al, 2011; Seo et al 2011). The BBSome also interacts with the RAB8A guanine nucleotide exchange factor RAB3IP, and in this way promotes the recruitment of RAB8A to the cilium (Nachury et al, 2007). Components of the BBSome are enriched in beta propeller and TPR domains and have been shown to form linear arrays on liposomes (Jin et al, 2010). Where these arrays form, and how they contribute to ciliary targeting remains to be elucidated (Jin et al, 2010; reviewed in Nachury et al, 2010).

In mammalian cells, formation of the BBSome depends on a BBS/CCT complex that consists of MKKS/BBS6, BBS10, BBS12 and 6 members of the CCT/TRiC family of chaperonins. The BBS/CCT complex interacts with a subset of the BBSome protein and plays a role in the BBS7 stability, promoting the formation of an intermediate "BBSome core complex" (Seo et al, 2010; Jin et al, 2010; Zhang el al, 2012).

Followed by: LZTFL1 binds the BBSome and prevents its traffic to the cilium

Literature references

Aguiar, M., Shida, T., Jin, H., Gygi, SP., Nachury, MV., White, SR. et al. (2010). The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell, 141*, 1208-19. ↗

Beales, PL., Tobin, JL. (2009). The nonmotile ciliopathies. *Genet. Med., 11*, 386-402. ↗

Hsiao, YC., Tuz, K., Ferland, RJ. (2012). Trafficking in and to the primary cilium. *Cilia, 1*, 4. ↗

Seo, S., Rahmouni, K., Bugge, K., Vogel, T., Morgan, DA., Stone, EM. et al. (2011). Bardet-Biedl syndrome 3 (Bbs3) knockout mouse model reveals common BBS-associated phenotypes and Bbs3 unique phenotypes. *Proc. Natl. Acad. Sci. U.S.A., 108*, 20678-83. ↗

Seo, S., Searby, CC., Bugge, K., Zhang, Q., Sheffield, VC., Nachury, MV. et al. (2011). A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet., 7*, e1002358. ↗

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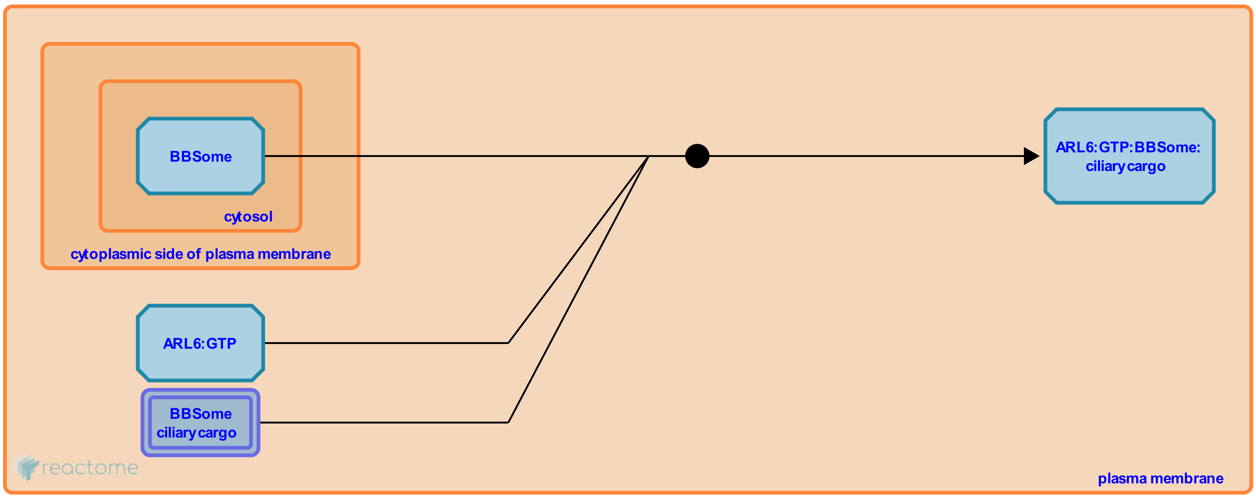
ARL6:GTP and the BBSome bind ciliary cargo ↗

Location: BBSome-mediated cargo-targeting to cilium

Stable identifier: R-HSA-5624126

Type: binding

Compartments: plasma membrane



ARL6 is a small GTPase that was also identified as BBS3, a gene that when mutated gives rise to the ciliopathy Bardet-Biedel syndrome (Chiang et al, 2004; Fan et al, 2004). In its GTP-form, membrane-associated ARL6 recruits the BBSome along with BBSome-associated cargo such as SSTR3, MHCR1 or SMO to the cilium (Jin et al, 2010; Zhang et al, 2011; Seo et al, 2011). Binding of IFT27 to the nucleotide-free form of ARL6 may also play a role in promoting the exit of the BBSome from the cilium (Liew et al, 2014). The BBSome, a complex consisting of BBS1, BBS2, BBS4, BBS5, BBS7, BBC9, TTC8/BBS8 and BBIP10 is thought to contribute to ciliary targeting, either by promoting budding of vesicles from the secretory pathway or through lateral diffusion of BBSome-enriched 'rafts' from the plasma membrane as indicated in this reaction (Jin et al, 2010; reviewed in Li et al, 2012; Sung and Leroux, 2013; Nachury et al, 2010). The interaction between the BBSome and ARL6 is mediated by the N-terminal B-propeller domain of BBSome component BBS1 (Jin et al, 2010). BBSome function is negatively regulated by LZTFL1, which forms a complex with the BBSome in the cytosol and inhibits its traffic to the cilium (Seo et al, 2011).

Followed by: ARL6:GTP and the BBSome target cargo to the primary cilium

Literature references

Casavant, T., Stone, EM., Carmi, R., Elbedour, K., Sheffield, VC., Chiang, AP. et al. (2004). Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (BBS3). *Am. J. Hum. Genet., 75*, 475-84. ↗

Aguiar, M., Shida, T., Jin, H., Gygi, SP., Nachury, MV., White, SR. et al. (2010). The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell, 141*, 1208-19. ↗

Seo, S., Rahmouni, K., Bugge, K., Vogel, T., Morgan, DA., Stone, EM. et al. (2011). Bardet-Biedl syndrome 3 (Bbs3) knockout mouse model reveals common BBS-associated phenotypes and Bbs3 unique phenotypes. *Proc. Natl. Acad. Sci. U.S.A., 108*, 20678-83. ↗

Ye, F., Aguiar, M., Nager, A R., Gygi, S., Murphy, J P., Liew, G M. et al. (2014). The intraflagellar transport protein IFT27 promotes BBSome exit from cilia through the GTPase ARL6/BBS3. *DevCell, 31*, 265-278. ↗

Seo, S., Searby, CC., Bugge, K., Zhang, Q., Sheffield, VC., Nachury, MV. et al. (2011). A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet., 7*, e1002358. ↗

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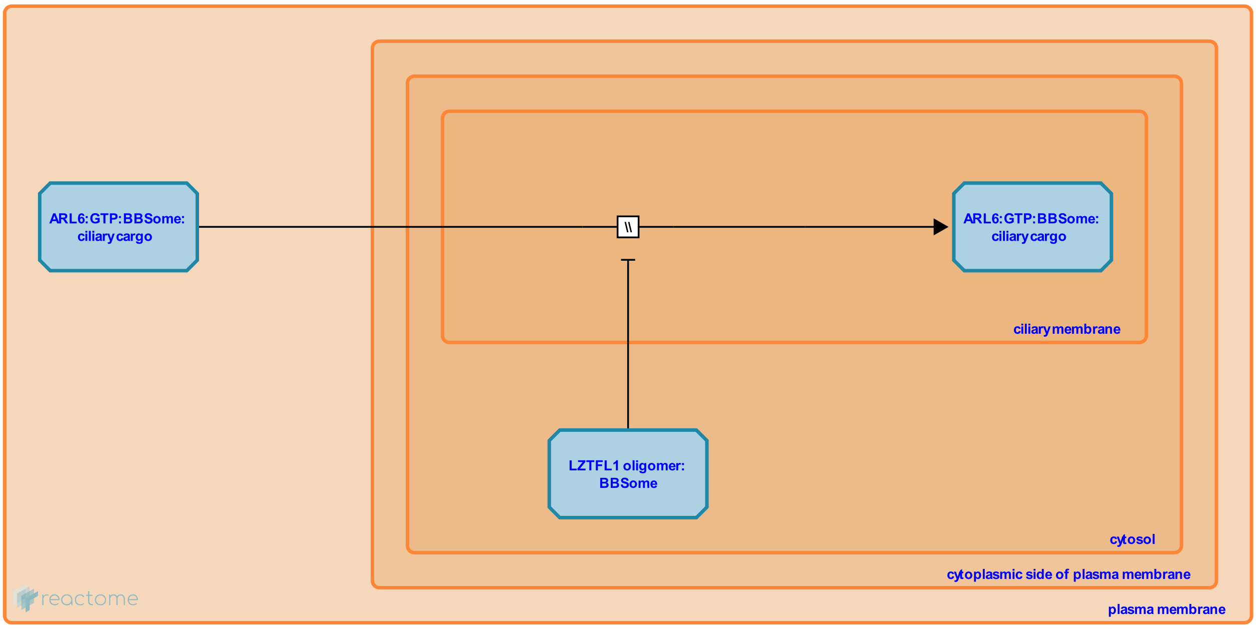
ARL6:GTP and the BBSome target cargo to the primary cilium ↗

Location: BBSome-mediated cargo-targeting to cilium

Stable identifier: R-HSA-5624127

Type: omitted

Compartments: ciliary membrane


ARL6:GTP:BBSome: ciliary cargo
ARL6:GTP:BBSome: ciliary cargo
LZTFL1 oligomer: BBSome
ciliary membrane
cytosol
cytoplasmic side of plasma membrane
plasma membrane
reactome

ARL6:GTP and the BBSome complex are required for the ciliary accumulation of proteins such as SSTR3, MHRC1 and SMO (Zhang et al, 2011; Jin et al, 2010; Seo et al, 2011; reviewed in Nachury et al, 2010; Sung and Leroux, 2013). BBSome localization to the primary cilium is negatively regulated by LZTFL1, and ciliary accumulation of some BBSome cargo is increased by LZTFL1 depletion (Seo et al, 2011).

Preceded by: ARL6:GTP and the BBSome bind ciliary cargo

Literature references

Aguiar, M., Shida, T., Jin, H., Gygi, SP., Nachury, MV., White, SR. et al. (2010). The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell, 141*, 1208-19. ↗

Seo, S., Rahmouni, K., Bugge, K., Vogel, T., Morgan, DA., Stone, EM. et al. (2011). Bardet-Biedl syndrome 3 (Bbs3) knockout mouse model reveals common BBS-associated phenotypes and Bbs3 unique phenotypes. *Proc. Natl. Acad. Sci. U.S.A., 108*, 20678-83. ↗

Seo, S., Searby, CC., Bugge, K., Zhang, Q., Sheffield, VC., Nachury, MV. et al. (2011). A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet., 7*, e1002358. ↗

Sung, CH., Leroux, MR. (2013). The roles of evolutionarily conserved functional modules in cilia-related trafficking. *Nat. Cell Biol., 15*, 1387-97. ↗

Seeley, ES., Jin, H., Nachury, MV. (2010). Trafficking to the ciliary membrane: how to get across the periciliary diffusion barrier?. *Annu. Rev. Cell Dev. Biol., 26*, 59-87. ↗

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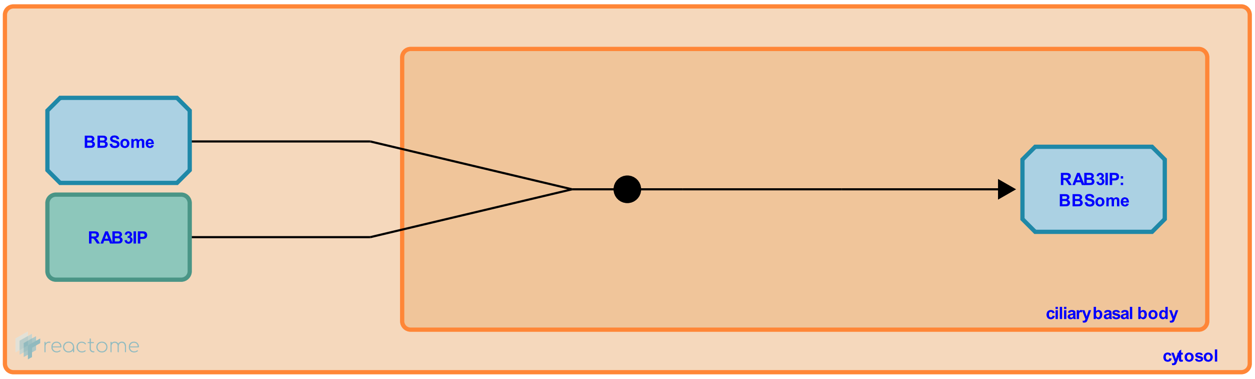
BBSome binds RAB3IP ↗

Location: BBSome-mediated cargo-targeting to cilium

Stable identifier: R-HSA-5617815

Type: binding

Compartments: ciliary basal body



The BBS1 component of the BBSome complex binds RAB3IP, a GEF for the small GTPase RAB8A. RAB3IP is required for RAB8A to localize to the cilium, and depletion of RAB3IP compromises cilia formation (Nachury et al, 2007; Loktev et al, 2008). GTP-bound RAB8A may promote ciliogenesis by promoting the traffic of post-Golgi vesicles to the base of the cilium (Nachury et al, 2007; reviewed in Zerial and McBride, 2001; Ishikawa et al, 2011; Hsiao et al, 2012; Sung and Leroux, 2013).

Literature references

Ishikawa, H., Marshall, WF. (2011). Ciliogenesis: building the cell's antenna. *Nat. Rev. Mol. Cell Biol., 12*, 222-34. ↗

Hsiao, YC., Tuz, K., Ferland, RJ. (2012). Trafficking in and to the primary cilium. *Cilia, 1*, 4. ↗

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Zerial, M., McBride, H. (2001). Rab proteins as membrane organizers. *Nat. Rev. Mol. Cell Biol., 2*, 107-17. ↗

Westlake, CJ., Loktev, AV., Zhang, Q., Sheffield, VC., Scheller, RH., Slusarski, DC. et al. (2007). A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell, 129*, 1201-13. ↗

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2014-08-07	Authored	Rothfels, K.
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