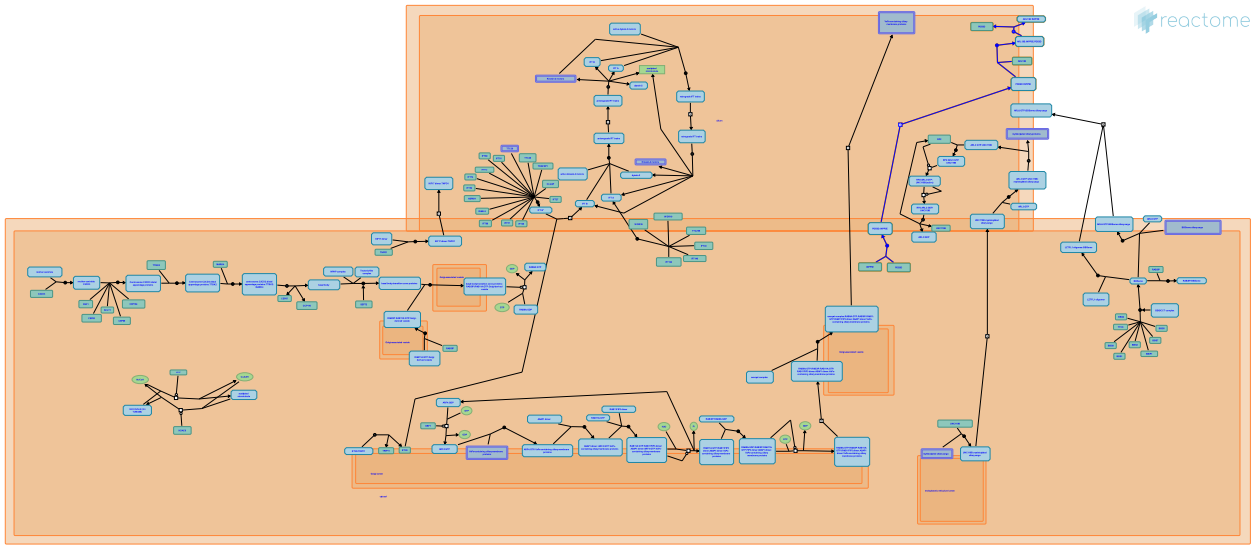
ARL13B-mediated ciliary trafficking of INPP5E



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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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

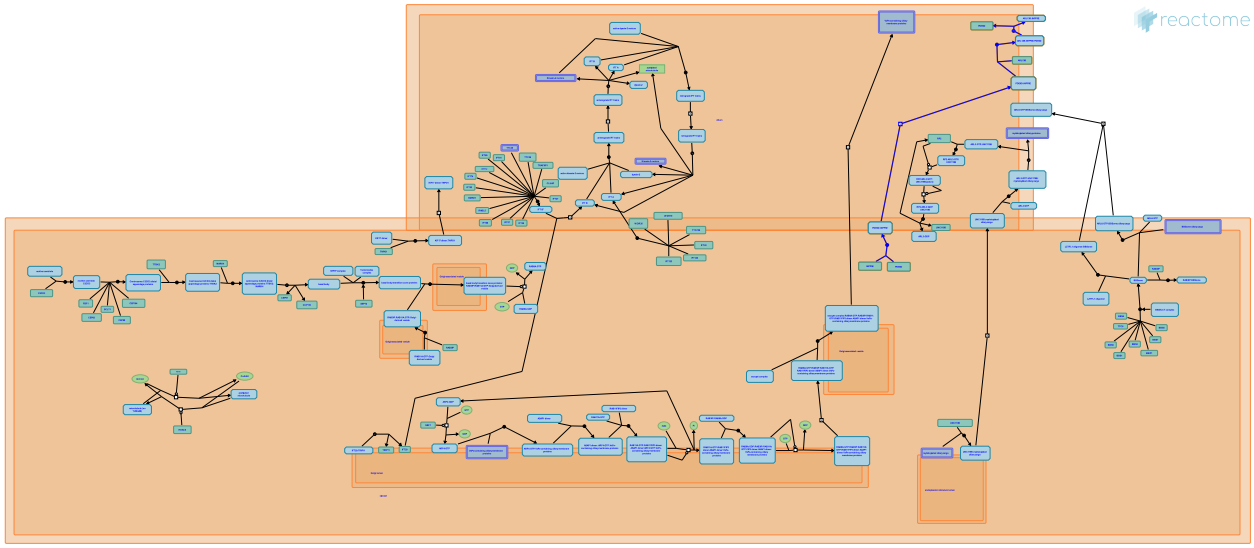
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

ARL13B-mediated ciliary trafficking of INPP5E

Stable identifier: R-HSA-5624958



ARL13B is a ciliary-localized small GTPase with an atypical C-terminus containing a coiled coil domain and a proline rich domain (PRD) (Hori et al, 2008). Mutations in ARL13B are associated with the development of the ciliopathy Joubert's Syndrome (Cantagrel et al, 2008; Parisi et al, 2009). Studies in C. elegans and vertebrates suggest that ARL13B may play a role in stabilizing the interaction between the IFT A and B complexes and the kinesin-2 motors during anterograde traffic in the cilium (Cevik et al, 2010; Li et al, 2010; Cevik et al, 2013; reviewed in Li et al, 2012; Zhang et al, 2013). Recent work has shown an additional role for ARL13B in trafficking the inositol polyphosphate-5-phosphatase E (INPP5E) to the cilium through a network that also involves the phosphodiesterase PDE6D and the centriolar protein CEP164 (Humbert et al, 2012; Thomas et al, 2014; reviewed in Zhang et al, 2013). Mutations in INPP5E are also associated with the development of Joubert syndrome and other ciliopathies (Bielas et al, 2009; Jacoby et al, 2009; reviewed in Conduit et al, 2012).

Literature references

Parisi, MA. (2009). Clinical and molecular features of Joubert syndrome and related disorders. *Am J Med Genet C Semin Med Genet, 151*, 326-40.

Kikko, Y., Kobayashi, T., Katada, T., Kontani, K., Hori, Y. (2008). Domain architecture of the atypical Arf-family GTPase Arl13b involved in cilia formation. *Biochem. Biophys. Res. Commun., 373*, 119-24.

Ling, K., Hu, J., Li, Y. (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. *J. Cell. Biochem., 113*, 2201-7.

Seo, S., Searby, CC., Li, Y., Pope, RM., Sheffield, VC., Humbert, MC. et al. (2012). ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19691-6.

Mans, DA., Kida, K., Hetterschijt, L., Sanders, AA., Ueffing, M., van Reeuwijk, J. et al. (2013). Active transport and diffusion barriers restrict Joubert Syndrome-associated ARL13B/ARL-13 to an Inv-like ciliary membrane subdomain. *PLoS Genet., 9*, e1003977.

Editions

2014-09-19	Authored	Rothfels, K.
2014-10-13	Edited	Jassal, B.
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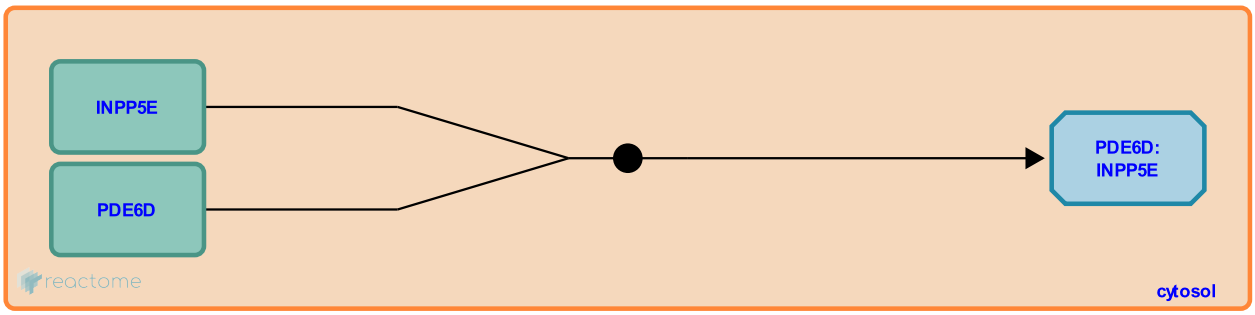
PDE6D binds INPP5E ↗

Location: ARL13B-mediated ciliary trafficking of INPP5E

Stable identifier: R-HSA-5624956

Type: binding

Compartments: cytosol



The inositol polyphosphate phosphatase INPP5E is a ciliary localized peripheral membrane protein with a CaaX prenylation motif in its C-terminus (Jacoby et al, 2009; Bielas et al, 2009; Humbert et al, 2012). This motif is downstream of the ciliary targeting sequence and prenylation is not required for the ciliary localization of INPP5E. The CaaX motif is required for the interaction between INPP5E and the phosphodiesterase PDE6D, and PDE6D is required for the ciliary localization of full length INPP5E but not a truncated solubilized form. These data suggest that PDE6D may play a role in extracting prenylated INPP5E from a donor membrane prior to ciliary targeting (Humbert et al, 2012).

Followed by: INPP5E translocates to the primary cilium

Literature references

Ayub, M., Compère, P., Kisseleva, MV., Hampshire, DJ., Cox, JJ., Gergely, F. et al. (2009). INPP5E mutations cause primary cilium signaling defects, ciliary instability and ciliopathies in human and mouse. *Nat. Genet., 41*, 1027-31 . ↗

Seo, S., Searby, CC., Li, Y., Pope, RM., Sheffield, VC., Humbert, MC. et al. (2012). ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19691-6. ↗

Schurmans, S., Kayserili, H., Gayral, S., Brancati, F., Dallapiccola, B., Jacoby, M. et al. (2009). Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. *Nat Genet, 41*, 1032-6. ↗

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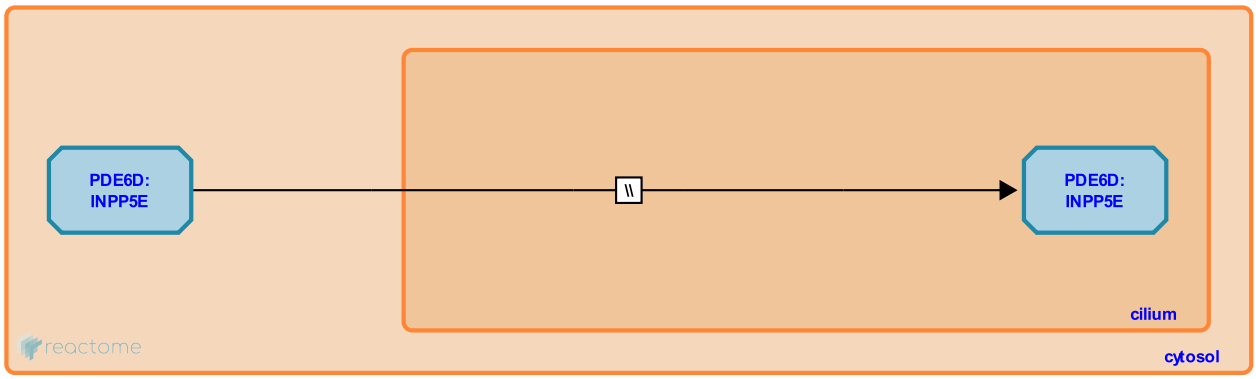
INPP5E translocates to the primary cilium ↗

Location: ARL13B-mediated ciliary trafficking of INPP5E

Stable identifier: R-HSA-5624954

Type: omitted

Compartments: cilium



INPP5E is a ciliary peripheral membrane protein that is associated with the ciliopathy Joubert's Syndrome (Bielas et al, 2009; Jacoby et al, 2009). Ciliary localization of the full-length protein depends on a targeting sequence and interactions with PDE6D and ARL13B, although the detailed mechanism remains unresolved (Humbert et al, 2012).

Preceded by: PDE6D binds INPP5E

Followed by: ARL13B binds INPP5E

Literature references

Ayub, M., Compère, P., Kisseleva, MV., Hampshire, DJ., Cox, JJ., Gergely, F. et al. (2009). INPP5E mutations cause primary cilium signaling defects, ciliary instability and ciliopathies in human and mouse. *Nat. Genet., 41*, 1027-31 . ↗

Seo, S., Searby, CC., Li, Y., Pope, RM., Sheffield, VC., Humbert, MC. et al. (2012). ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19691-6. ↗

Schurmans, S., Kayserili, H., Gayral, S., Brancati, F., Dallapiccola, B., Jacoby, M. et al. (2009). Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. *Nat Genet, 41*, 1032-6. ↗

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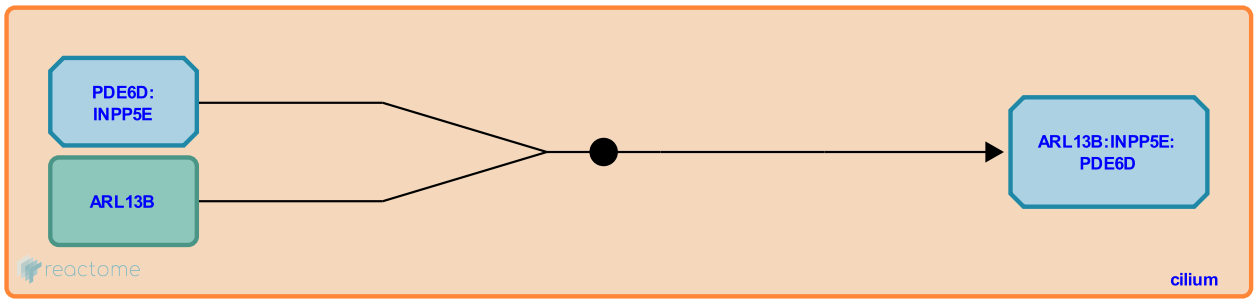
ARL13B binds INPP5E ↗

Location: ARL13B-mediated ciliary trafficking of INPP5E

Stable identifier: R-HSA-5624953

Type: binding

Compartments: cilium



The small GTPase ARL13B is required for the ciliary localization of INPP5E. ARL13B binds directly to INPP5E and is thought to displace PDE6D from the complex (Humbert et al, 2012).

Preceded by: INPP5E translocates to the primary cilium

Followed by: PDE6D dissociates from ARL13B:INPP5E

Literature references

Seo, S., Searby, CC., Li, Y., Pope, RM., Sheffield, VC., Humbert, MC. et al. (2012). ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19691-6. ↗

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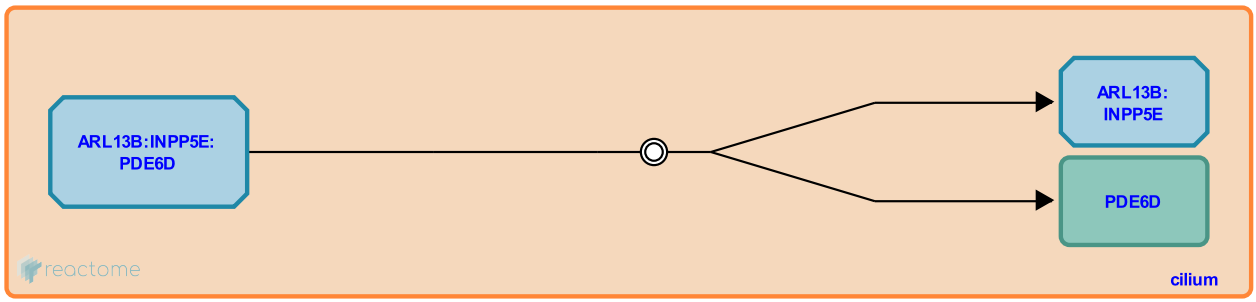
PDE6D dissociates from ARL13B:INPP5E ↗

Location: ARL13B-mediated ciliary trafficking of INPP5E

Stable identifier: R-HSA-5638012

Type: dissociation

Compartments: cilium



ARL13B promotes the ciliary localization of INPP5E by interacting with it directly and displacing PDE6D from the complex (Humbert et al, 2012).

Preceded by: ARL13B binds INPP5E

Literature references

Seo, S., Searby, CC., Li, Y., Pope, RM., Sheffield, VC., Humbert, MC. et al. (2012). ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19691-6. ↗

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