Cargo trafficking to the periciliary membrane

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14/12/2022
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


Reactome database release: 83

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https://reactome.org
Cargo trafficking to the periciliary membrane

Stable identifier: R-HSA-5620920

Proteomic studies suggest that the cillum is home to approximately a thousand proteins, and has a unique protein and lipid make up relative to the bulk cytoplasm and plasma membrane (Pazour et al, 2005; Ishikawa et al, 2012; Ostrowski et al, 2002; reviewed in Emmer et al, 2010; Rohatgi and Snell, 2010). In addition, the cilium is a dynamic structure, and the axoneme is continually being remodeled by addition and removal of tubulin at the distal tip (Marshall and Rosenbaum, 2001; Stephens, 1997; Song et al, 2001). As a result, the function and structure of this organelle relies on the directed trafficking of protein and vesicles to the cilium. Small GTPases of the RAS, RAB, ARF and ARL families are involved in cytoskeletal organization and membrane traffic and are required to regulate the traffic from the Golgi and the trans-Golgi network to the cilium (reviewed in Deretic, 2013; Li et al, 2012). ARF4 is a Golgi-resident GTPase that acts in conjunction with a ciliary-targeting complex consisting of the ARF-GAP ASAP1, RAB11A, the RAB11 effector FIP3 and the RAB8A guanine nucleotide exchange factor RAB3IP/RABIN8 to target cargo bearing a putative C-terminal VxPx targeting motif to the cilium. A well-studied example of this system involves the trafficking of rhodopsin to the retinal rod photoreceptors, a specialized form of the cilium (reviewed in Deretic, 2013). ARL3, ARL13B and ARL6 are all small ARF-like GTPases with assorted roles in ciliary trafficking and maintenance. Studies in C. elegans suggest that ARL3 and ARL13B have opposing roles in maintaining the stability of the anterograde IFT trains in the cilium (Li et al, 2010). In addition, both ARL3 and ARL13B have roles in facilitating the traffic of subsets of ciliary cargo to the cilium. Myristoylated cargo such as peripheral membrane protein Nephrocystin-3 (NPHP3) is targeted to the cilium in a UNC119- and ARL3-dependent manner, while ARL13B is required for the PDE6-dependent ciliary localization of INPP5E (Wright et al, 2011; Humbert et al, 2012; reviewed in Li et al, 2012). ARL6 was also identified as BBS3, a gene that when mutated gives rise to the ciliopathy Bardet-Biedl syndrome (BBS). ARL6 acts upstream of a complex of 8 other BBS-associated proteins known as the BBSome. ARL6 and the BBSome are required for the ciliary targeting of proteins including the melanin concentrating hormone receptor (MCHR) and the somatostatin receptor (SSTR3), among others (Nachury et al, 2007; Loktev et al, 2008; Jin et al, 2010; Zhang et al, 2011). Both the BBSome and ARL6 may continue to be associated with cargo inside the cilium, as they are observed to undergo typical IFT movements along the axoneme (Fan et al, 2004; Lechtreck et al, 2009; reviewed in Li et al, 2012).

Literature references


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VxPx cargo-targeting to cilium

Location: Cargo trafficking to the periciliary membrane

Stable identifier: R-HSA-5620916

A number of membrane proteins destined for the ciliary membrane are recognized by ARF4 in the trans-Golgi network, initiating the formation of a ciliary targeting complex that directs the passage of these cargo to the cilium (Mazelova et al, 2009; Geng et al, 2006; Jenkins et al, 2006; Ward et al, 2011; reviewed in Deretic, 2013). Although there is some support for the presence of a VxPx or related motif in the C-terminal tail of cargo destined for ARF4-mediated transport to the cilium, the details of this have not been definitively established and other ciliary targeting sequences have also been identified (reviewed in Deretic, 2013; Bhogaraju et al, 2013).

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BBSome-mediated cargo-targeting to cilium

Location: Cargo trafficking to the periciliary membrane

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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).

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A number of myristoylated proteins have been shown to traffic to the cilium in a myristoyl- and UNC119B:ARL3:RP2-dependent fashion. These include the ciliary proteins Nephrocystin 3 (NPHP3) and Cystin 1 (CYS1) (Wright et al, 2011; reviewed in Schwarz et al, 2012). Myristoyl-binding by the ARL3 effector UNC119B is required in an unknown fashion for the transport of the myristoylated cargo to the cilium. At the cilium, a GTPase cycle involving the ARF-like small GTPase ARL3 and its GAP protein RP2 promote the release of the myristoylated proteins into the ciliary membrane and the recycling and ciliary exit of UNC119B (Wright et al, 2011; reviewed in Schwarz et al, 2012). ARL3 plays additional roles in the cilium coordinating the association of IFT A and IFT B complexes with the kinesin motors (Li et al, 2010; reviewed in Li et al, 2012).

**Literature references**


ARL13B-mediated ciliary trafficking of INPP5E

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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).

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