

POSTER PRESENTATION

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The X-linked Retinitis Pigmentosa protein RP2 facilitates traffic of cilia target proteins

N Schwarz^{1,2*}, TV Novoselova¹, R Wait³, AJ Hardcastle¹, ME Cheetham¹

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Photoreceptors are specialized ciliated sensory neurons and aberrant traffic of proteins to the outer segment causes photoreceptor cell death. RP2 is a GTPase activating protein (GAP) for the small GTPase Arl3 and both proteins facilitate protein trafficking to primary cilia. We used GST-RP2 pull down from retinal lysates and identified the G β subunit of transducin (G β 1) as a novel RP2 interacting protein. RP2 competes with G γ 1 for G β 1 binding and does not interact with the G β :G γ heterodimer. In SK-N-SH cells, overexpression of G β 1 resulted in the cytoplasmic accumulation of the protein, whereas co-expression of G β 1 with either RP2 or G γ 1 restored membrane association of G β 1. Depletion of RP2 in ARPE19 cells by siRNA resulted in a shift of G β 1 from the membrane to the cytosol, confirming that RP2 facilitates the membrane association of G β 1. This shift in G β 1 localization was rescued by G γ 1 overexpression. Membrane targeting of G β 1 required RP2 N-terminal myristoylation and occurs via the co-factor C (TBCC) homology domain. The interaction was disrupted by the pathogenic RP2 mutation R118H, which blocks Arl3 GAP activity. Arl3-Q71L competed with G β 1 for RP2 binding suggesting that RP2 GAP activity on Arl3 would release G β 1. RP2 stimulated the association of G β 1 with Rab11, an important GTPase for post-Golgi vesicle trafficking of photoreceptor proteins. Collectively our data support a role for RP2 in facilitating membrane association and traffic of G β 1. Combined with other recent evidence, this suggests that RP2 may co-operate with Arl3 and its effectors in cilia associated trafficking of G proteins.

Author details

¹UCL, Institute of Ophthalmology, UK. ²ORBIT, UK. ³Kennedy Institute of Rheumatology Division, Imperial College London, UK.

* Correspondence: n.schwarz@ucl.ac.uk

¹UCL, Institute of Ophthalmology, UK

Full list of author information is available at the end of the article

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