

Prostaglandin-D2 synthase localises to centrioles and primary cilium, and interacts with TOPORS, implicated in retinal ciliopathy

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Objective

Prostaglandin-D2 synthase (*PTGDS*; MIM#176803) is a novel protein-partner of TOPORS (*TOPORS*; MIM#609507), a ubiquitously expressed nuclear and ciliary protein, implicated in retinitis pigmentosa. This study investigated the localisation of *PTGDS* and its potential mechanism-of-association with TOPORS.

Methods

Yeast two-hybrid screens, using TOPORS as bait, were performed against human retinal cDNA libraries. Validation and interaction-characterisation were performed in yeast, and by co-immunoprecipitation (co-IP) from HeLa cell extracts. Co-localisation studies were performed in hTERT-RPE1 cell line, and in murine retina cryo-sections. *PTGDS* expression was validated by RT-PCR.

Results

Co-IP demonstrated *PTGDS* was found in endogenous protein complexes with TOPORS, whereas in yeast *PTGDS* interacted most strongly with TOPORS' residues 1-380, comprising the RING-domain conferring its E3-ubiquitin-ligase activity. *PTGDS* co-localised with TOPORS, and centriolar markers in dividing cells, and was observed at basal body and along ciliary axoneme in ciliated cells. In mouse retina *PTGDS* was observed in several cell layers, partly overlapping with TOPORS in the photoreceptor layer. In human retina, RT-PCR studies demonstrated expression of several *PTGDS* isoforms.

Conclusion

PTGDS, a novel component of the primary cilium, could be involved in centriolar-ciliary homeostasis. This putative

role of prostaglandin synthases, is additionally supported by independent findings on the role of prostaglandin-E2 in ciliogenesis. Results suggest TOPORS could regulate *PTGDS* levels at the cilium by marking it for degradation by the ubiquitin-proteasome system, providing a basis for understanding the retinal ciliopathy associated with *TOPORS* mutations.

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