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Et al.

Prenylated retinal ciliopathy protein RPGR regulates ciliary localization of Joubert Syndrome-associated protein INPP5E in cooperation with PDE6δ

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Ciliary dysfunction is an underlying cause of severe human disorders (collectively called ciliopathies), such as retinitis pigmentosa (RP), Joubert Syndrome (JBTS), and Bardet-Biedl Syndrome. Ciliary proteins form distinct functional networks for localization to cilia as well as regulation of ciliary function. However, not much is known about the mechanism of ciliary localization and function of RPGR (retinitis pigmentosa GTPase regulator), a ciliary protein frequently associated with RP worldwide. Using tandem mass spectrometry analysis, we show that RPGR interacts with two JBTS-associated proteins: PDE6Π (delta subunit of Phosphodiesterase; a prenyl-binding protein) and INPP5E (inositol polyphosphate-5-phosphatase 5E; a ciliary cargo). Whereas PDE6Π binds in a prenylation-dependent manner to the C-terminus of RPGR, INPP5E associates with the N-terminus of RPGR. Prenylation and interaction of RPGR with PDE6Π are critical for its localization to cilia. We further show that loss of RPGR results in reduced amount of INPP5E in cilia of fibroblasts and in photoreceptor outer segment, a modified sensory cilium. Overall, our results suggest that RPGR, in complex with PDE6D, regulates the trafficking of ciliary cargo INPP5E and implicate reduction in ciliary INPP5E in the pathogenesis of RPGR-ciliopathy.

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