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Mechanisms controlling the cilia localization of INPP5E, a phosphoinositide 5-phosphatase mutated in MORM and Joubert syndromes.

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Introduction: INPP5E is a ciliary phosphoinositide 5-phosphatase whose mutations are the cause of two human ciliopathies, Joubert (JBTS) and MORM syndromes, and whose activity supports Hedgehog-dependent tumor progression. We previously showed that INPP5E is a critical regulator of ciliary phosphoinositide levels, which in turn control ciliary protein composition and Hedgehog signaling (Garcia-Gonzalo et al. 2015 Dev Cell). However, the mechanisms controlling INPP5E ciliary localization remain unclear.

Material and methods: We have used site-directed mutagenesis to examine how INPP5E cilia localization is controlled.

Results: We find that INPP5E cilia localization depends on two separate regions located at the beginning and end of its catalytic domain. These two regions, albeit separated by circa 300 residues, come together as a concave surface on the folded catalytic domain. Several residues on this surface are needed for INPP5E to bind ARL13B, a JBTS-causative ciliary protein known to be required for INPP5E to localize to cilia. Since INPP5E is reported to leave cilia in response to mitogenic signals, we also studied whether INPP5E ciliary targeting is regulated by phosphorylation. We find that INPP5E undergoes tyrosine phosphorylation, and that a mutant mimicking phosphorylation of a tyrosine on the above-mentioned surface prevents INPP5E cilia localization.

Conclusions: We conclude that INPP5E cilia localization is controlled by a ciliary targeting signal (CTS) present in its folded catalytic domain. This CTS acts, at least partly, by allowing INPP5E to interact with ARL13B. Moreover, our preliminary data suggest that CTS phosphorylation can interfere with INPP5E cilia localization.

Keywords: INPP5E, Joubert syndrome, MORM, ARL13B, cilia, phosphorylation.
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