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ARTICLE

Ubiquitin links smoothened to intraflagellar transport to regulate Hedgehog signaling

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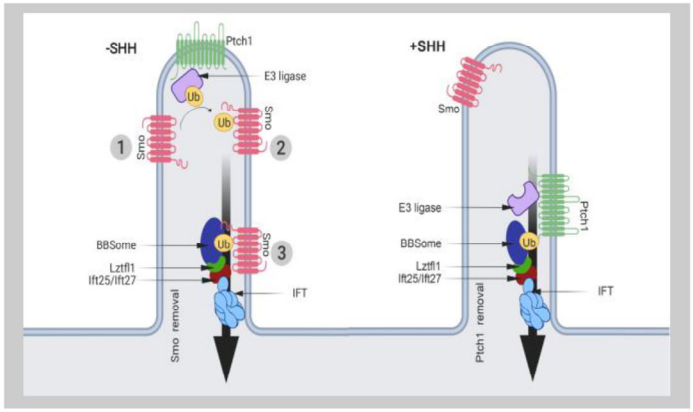

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Paurav Desai is a post doc in the Pazour lab. He works on primary cilia to understand the mechanism of intraflagellar transport (IFT) and how it plays a role in cell signaling, disease, and development. He received his Ph.D. in Cell & Dev Bio and Anatomy from Upstate Medical University, where he studied the mechanism of outer dynein arm in motile cilia, and his M.Sc. in Microbiology from Sardar Patel University in India.

Cilium play an important biological role. Improper functioning of cilium leads to variety of disorders that affect vision, kidney, heart, and developing embryo. Cilium monitors extracellular environment by numerous receptors of various signaling pathways it harbors and allows the cell to coordinate its physiology with surrounding cells. Hedgehog (HH) signaling plays fundamental roles during development and many of the developmental defects caused by ciliary dysfunction are attributed to abnormal HH signaling.

In the basal state, patched-1 (Ptch1) accumulates in cilia and prevents smoothened (Smo) ciliary accumulation and activation. On ligand binding, Ptch1 exits the cilium, Smo is derepressed and accumulates in the cilium, subsequently activating the downstream signaling. Mechanisms regulating these dynamic movements poorly understood. Their movement is partly facilitated by intraflagellar transport (IFT) and perturbing IFT disrupts HH signaling.

IFT, which is critical for ciliary assembly and and maintenance, involves motor driven transport of IFT particles: IFT-A, IFT-B, and BBSome. The IFT particle provides binding sites for diverse ciliary cargoes. Ift25 and Ift27, subunits of IFT-B, are not required for ciliary assembly. Instead, they work with Lztfl1 and the BBSome to regulate HH signaling and maintain proper levels of Smo and Ptch1 in cilia. Defects in IFT components cause Smo to accumulate in cilia without pathway activation.

We find that in the absence of ligand-induced pathway activation, Smo is ubiquitinated and removed from cilia, and this process is dependent on Ift27 and BBSome components. The activation of Hedgehog signaling decreases Smo ubiquitination and ciliary removal, resulting in its ciliary accumulation. Blocking ubiquitination of Smo by an E1 ligase inhibitor or by mutating two lysine residues in intracellular loop three causes Smo to aberrantly accumulate in cilia without pathway activation. Based on this data, we propose a model where Smo that enters the cilium at the basal state becomes ubiquitinated by an unknown E3 ligase. Ubiquitinated Smo is recognized as cargo for retrograde IFT leading to its ciliary exit and preventing Smo accumulation in cilia in the absence of pathway activation. Ptch1 may be regulated by a similar mechanism working after pathway activation.