

SPOTLIGHT

The primary cilium as a gatekeeper of FGFR2 function

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In this issue, Nita et al. (<https://doi.org/10.1083/jcb.202311030>) show that the primary cilium regulates FGFR2 signalling through spatial compartmentalization, enabling selective downstream activation. Disruption of ciliary localization in disease-linked FGFR2 variants highlights the role of the cilium as a signalling gatekeeper in development and disease.

Cells constantly sense their environment, receiving essential information that guides development, growth, physiology, and metabolism. However, cells encounter an overwhelming array of signals, making it challenging to respond appropriately to specific cues (1). One mechanism cells employ to manage this complexity is through the primary cilium, a specialized organelle protruding from the apical surface of most vertebrate cells. Acting like an antenna, the primary cilium receives signals and transmits information internally (2). It does this by providing a compartmentalized and privileged environment where specific transmembrane receptors and intracellular effectors are trafficked, concentrated, and activated (3, 4). Disruptions of genes associated with transport into cilia (such as the intraflagellar transport [IFT] complex), or ciliary architecture (such as the BBsome complex), underlie a wide range of developmental disorders and diseases and frequently result from abnormal signal transduction (5).

Several receptor systems rely on ciliary localization for proper functioning, thereby modulating critical physiological processes. Recent findings have expanded the list of cilium-resident receptors to include FGFR1 and FGFR2, two key members of the FGF receptor family (6). FGFR1 has previously been localized to the kinocilium of mechanosensory hair cells in the inner ear, where it contributes to polarity and morphogenesis (7). FGFR2, as shown in a recent study by Nita et al. (2025), exhibits a striking

dependence on ciliary localization for its signalling function. To unravel the complete FGFR2 signalling cascade, Nita et al. (2025) demonstrate that upon ligand induction by FGF10, FGFR2 activates downstream signalling molecules specifically within primary cilia. Through detailed tracking over a 24-h period, they reveal a dynamic cycle of FGFR2 localization. Initially, activated FGFR2 exits the cilium, becomes internalized through LAMP1-positive compartments, and eventually recycles back into the cilium by 24 h after induction (Fig. 1). To establish a direct link between ciliary localization and the activation of FGFR2, the authors inhibited ciliogenesis, either by knocking down the IFT172 gene or treating with ciliobrevin A (to trigger deciliation), noting a reduction in the expression levels of FGFR2 downstream signalling molecules, including pFRS2, pMEK1, pERK1/2, and pp38 levels (8). Mechanistically, FGFR2 ciliary entry hinges on a conserved juxtamembrane motif (428VTVSAE433), specifically the T429V430 sequence. Loss of this motif abolishes FGFR2's ciliary localization and signalling capacity. The study further identifies essential trafficking regulators, notably IFT144 and BBS1, along with kinase GRK2, which fine-tune FGFR2 ciliary trafficking and signalling. Interestingly, comparing the localization of FGFR1 and FGFR2 in epithelial cell line (IMCD3) versus mesenchymal cell lines (NIH3T3 and 3T3-L1) suggests that there are cell-specific ciliary trafficking mechanisms for different FGFRs.

One of the most compelling aspects of this study is the association with disease. Activating FGFR2 mutants are associated with a range of congenital disorders as well as an increased predisposition to cancer (9, 10, 11). The link with ciliary localization raised the possibility that some FGFR2 may be associated with dysregulated ciliary localization. The authors examined the localization of pathogenic FGFR2 variants in relation to primary cilia, discovering that variants p.N550K (associated with cancer) and p.P253R (linked to Apert syndrome) fail to localize to cilia, raising the possibility that this facet contributes to disease development. Remarkably, treatment with the selective FGFR2 inhibitor RLY-4008 enhanced ciliary localization of these mutants, offering a possible therapeutic strategy. However, ciliary localization defects in other pathogenic variants, p.C342R (Crouzon syndrome) and p.M391R (bent bone dysplasia), appeared to result from distinct, unrelated mechanisms.

This study underscores a broader principle: the primary cilium acts not only as a passive receiver but as a spatially constrained decision-making hub. For FGFR2, ciliary localization may provide spatial insulation that ensures precise effector engagement, an emerging concept also seen in FGFRs (12). The findings raise important questions for future exploration. How does the cilium selectively gate signalling outcomes? Can defects in ciliary localization explain phenotypic variability in FGF-related

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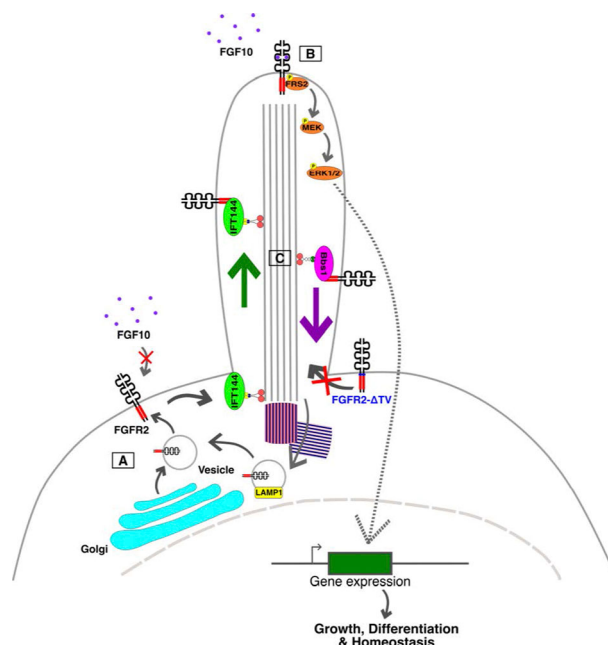


Figure 1. **Schematic representation of primary cilium-dependent FGFR2 signalling.** (A) FGFR2 is transported to the plasma membrane from the Golgi through intracellular vesicles, which get activated only after translocation to the primary cilium. (B) After FGF10 stimulation, FGFR2 transduces the signal through MEK and ERK1/2 kinases and activates the downstream genes to control tissue growth, differentiation, and homeostasis. (C) FGFR2 expression in the primary cilium is maintained by IFT144 and Bbs1 molecules before targeting it to the LAMP1 vesicles.

syndromes? And can cilia-directed therapies rescue signalling fidelity in disease?

Answering these questions will not only advance our understanding of FGFR biology

but also illuminate general principles of how spatial compartmentalization within the cell governs developmental signalling fidelity and how its disruption leads to disease.

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