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Dissecting Intraflagellar Transport, One Molecule at a Time

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Intraflagellar transport (IFT) is required for proper function of cilia, although many of the mechanistic details underlying this process are obscure. Two studies in this issue of *Developmental Cell* illuminate key functions of one IFT protein, IFT27, and offer clues into how IFT cargo is selected and transported.

Intraflagellar transport (IFT), the regulated movement of cargo along the ciliary axoneme, is critical for ciliary biogenesis and function (Pedersen and Rosenbaum, 2008). Complete disruption of IFT leads to either failure of ciliogenesis or severe distortion of ciliary architecture, both of which are incompatible with life, while hypomorphic mutations give rise to severe multi-organ pathologies that, in humans, manifest in acute neonatal disorders (Davis and Katsanis, 2012). In this issue of *Developmental Cell*, Eguether et al. (2014) and Liew et al. (2014) provide molecular insights into the mechanisms underlying IFT cargo selection and hint at regulated interactions between some IFT components and other ciliary complexes to regulate paracrine signaling (Eguether et al., 2014; Liew et al., 2014).

Initial biochemical studies of IFT defined two key particles, IFT-B and IFT-A. IFT-B is composed of 16 core members mounted on kinesin motors and is responsible for cargo transport from the base of the cilium to the tip (anterograde transport). IFT-A, the retrograde core particle, is composed of six core proteins driven by dynein motors (Pedersen and Rosenbaum, 2008). Some, but not all, IFT proteins also participate in non-ciliary transport, in a cell-type-specific manner (Garcia-Gonzalo et al., 2011). The two reports in this issue of *Developmental Cell* reveal further complexity and suggest that IFT27, historically considered a dedicated anterograde transport protein, may also participate in retrograde transport (Eguether et al., 2014; Huet et al., 2014; Liew et al., 2014). These findings additionally highlight a link between IFT and the BBSome, a complex of proteins that, when mutated, cause Bardet-Biedl syndrome (BBS; Nachury et al., 2007). While the BBSome is critical for the sorting of membrane proteins, including components of the sonic hedgehog (SHH) signaling pathway, into the cilium (Seo et al., 2011), the mechanisms facilitating the selective transport of such proteins out of the cilium are unclear.

Eguether and colleagues (2014) investigated the molecular underpinnings of the ciliopathy phenotypes observed in a new *Ift27*$^{-/-}$ mouse model, including polydactyly, cardiac malformations, *situs inversus*, and craniofacial defects. The authors noted that although *Ift27*$^{-/-}$ mouse embryonic fibroblasts (MEFs) do not display overt structural defects indicative of disrupted IFT, they exhibit attenuated SHH signaling concomitant with the accumulation of SHH components, including the transmembrane receptors patched (PTCH), smoothened (SMO), and the SHH G protein-coupled receptor intermediate GPR161. Moreover, in the absence of IFT27, the authors observed aberrant ciliary localization of multiple BBSome components, as well as BBSome-associated proteins such as ARL6/BBS3 and LZTFL1/BBS17. The authors also found that cells lacking *Lztfl1*, another causative BBS gene that participates in BBSome-mediated protein trafficking (Seo et al., 2011), accumulate BBSome proteins but not IFT27. As such, they propose that LZTFL1 cooperates with IFT27 to facilitate retrograde transport of BBS and SHH proteins.

In a parallel study, Liew et al. (2014) utilized ciliated in vitro models coupled with biochemical analyses to examine the interaction of IFT27 with the BBSome. First, the authors found that IFT27 binds to ARL6. ARL6 is a GTPase, like IFT27, and a known effector of the BBSome, required for its targeting to the cilium. In addition, cells with both suppressed *Ift27* expression and *Ift27*$^{-/-}$ MEFS were found to accumulate BBSome components and ARL6 in their cilia. Finally, and consistent with a previously suggested role for the BBSome in sorting SHH signaling components entering the cilium upon pathway activation (Seo et al., 2011), lack of IFT27 resulted in the ciliary accumulation of transmembrane receptors PTCH, SMO, and GPR161, presumably because these proteins fail to exit. The authors propose that, in addition to a canonical role in anterograde transport in cooperation with the IFT-B complex, IFT27 can dissociate from IFT-B to bind and activate ARL6, a process necessary for targeted removal of SHH components from the cilium.

Together, these two studies hint at a previously underappreciated interaction between two of the most highly characterized ciliary modules, the IFT machinery, and the BBSome, and provide important new clues about trafficking of signaling moieties from the ciliary compartment to the cell (Figure 1). However, the biological reality is likely to be even more complex. For instance, suppression of *ift27* in *Chlamydomonas* or *Trypanosoma* caused a reduction of IFT-A and IFT-B amounts (Huet et al., 2014; Qin et al., 2007) and concomitant shortening of the axoneme, arguing for a role of IFT27 in IFT particle stability. This was not observed in the models used by Eguether et al. (2014) and Liew et al. (2014), suggesting that either this IFT27 function has been lost in higher vertebrates or that it might only exist in cell types not interrogated in the current studies. In addition, the defects in SHH component trafficking raises the question of whether IFT27 is dedicated to responding to SHH activation or whether this method of removing proteins from the cilium might also apply to other signaling molecules. All of these

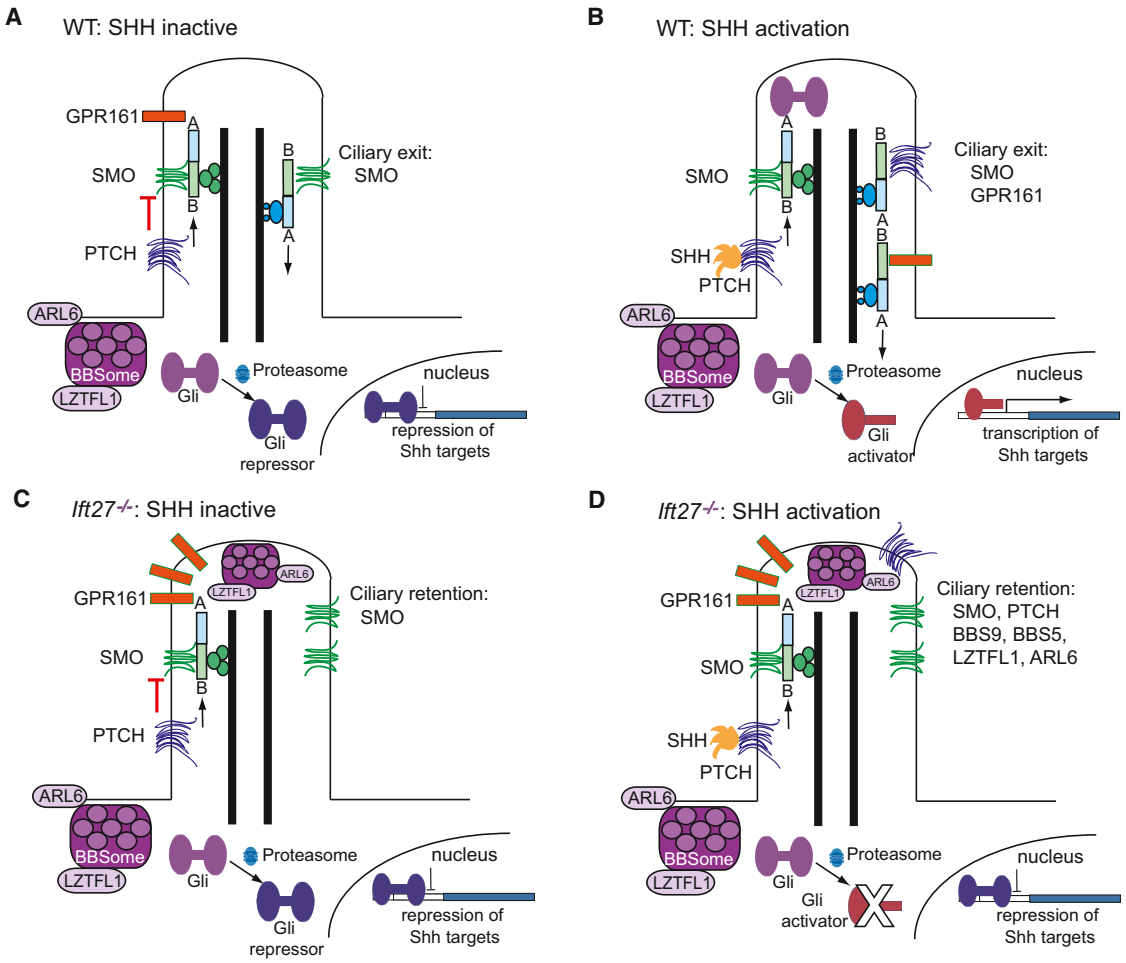

Figure 1. Ciliary Effects of *Ift27* Depletion

(A and B) SHH signaling in wild-type (WT) cells. (A) Transmembrane receptor patched (PTCH) represses smoothened (SMO) in the absence of ligand, and Gli repressor maintains suppression of SHH targets in the nucleus. (B) SHH ligand binds to PTCH, SMO is derepressed by bound PTCH, Gli localizes to the cilium, and then signal is transduced to the nucleus to induce target gene transcription. SHH intermediate G protein-coupled receptor 161 (GPR161) is trafficked normally in the cilium. BBS-related proteins remain at the basal body. IFT-B (green rectangle) and IFT-A (blue rectangle) conduct anterograde and retrograde movement of cargo, respectively. (C and D) SHH signaling in *Ift27*$^{-/-}$ cells. (C) BBS-associated proteins mislocalize to the cilium, SMO and PTCH are retained, and an excess of GPR161 is localized to the cilium, likely due to a failure of retrograde transport facilitated by IFT27. (D) In the presence of ligand, Gli fails to activate, likely due to mislocalization of signaling proteins in the cilium.

questions must be placed in the broader context of ciliary function in different tissues and developmental time points.

Finally, it will be important to place these findings in the context of human genetic disease. *Ift27*$^{-/-}$ mice exhibit severe ciliopathy hallmarks and cannot survive past birth (Eguether et al., 2014), while patients with apparent loss-of-function alleles in the same molecule have BBS, an intermediate ciliopathy (Aldahmesh et al., 2014). These discordant observations may be driven by allelic differences or by non-identical functions of IFT27 in mice and humans. Ultimately, the synthesis of data from diverse cell types, organisms, and developmental and homeostatic contexts will be required to gain a deeper appreciation of the diverse roles of IFT proteins, their accessory subunits, their cargo, and, more broadly, the complexity that underpins ciliary function.

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