unclear whether these proteins are truly metamorphic and can interconvert between the different conformations.

Metamorphic proteins may not be as rare as it currently seems. It may even be, as argued by Tuinstra et al. (1), that most structural biology efforts have inadvertently selected against their detection. If so, then we may find more manifestations of this phenomenon as new proteins are studied and old proteins reexamined. Such discoveries will enhance our understanding of protein folding, function, and evolution.

References and Notes
13. The structures have been determined by the Joint Center for Structural Genomics (www.jcsg.org) with Protein Data Bank entries 2OOK and 2O3L.

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CELL BIOLOGY

Arrestin’ Movement in Cilia
Rajat Rohatgi1,2 and Matthew P. Scott1

Most cells in our bodies bear immotile hairlike protrusions called primary cilia (1). Only a few micrometers long, they are marvelously complex sensors, detecting and interpreting signals from the environment, such as light, odorants, fluid flow, and proteins that signal between cells. In each case, the receptor for the signal, along with some of the proteins that transmit the message into the cell, are localized in cilia. Their movement into and out of cilia controls signaling pathways that ultimately trigger responses such as cell division and differentiation. Thus, a central challenge is to understand how transmembrane proteins, especially receptors, are targeted to primary cilia. In humans, defective trafficking to cilia can cause pathological conditions ranging from cystic kidney disease to brain malformations and obesity (2). On page 1777 of this issue, Kovacs et al. (3) describe a new mechanism for the movement of the transmembrane protein Smoothed (Smo) into primary cilia. Smo is a component of the signaling pathway that responds to secreted proteins in the Hedgehog (Hh) family. The Hh pathway has been previously linked to cilia (4–6) and plays fundamental roles in development, stem cell function, and carcinogenesis (7).

Sonic Hedgehog (Shh) is a secreted ligand that initiates signaling by binding to its receptor Patched 1 (Ptc1). In the absence of Shh, Ptc1 is concentrated in cilia and inhibits Smo activity (8). Shh binding to Ptc1 inactivates the receptor and causes Ptc1 to move out of cilia.

This allows the activation of Smo, which accumulates within the ciliary membrane (4). The movement of Smo to cilia brings it near other components of the signaling pathway, resulting in activation of transcription factors in the Gli family that regulate gene expression (9).

Smo is a seven-pass transmembrane protein that resembles heterotrimeric GTP-binding protein (G protein)–coupled receptors. Such receptors transmit signals either through trimeric G proteins or through β-arrestin proteins and G protein–coupled receptor kinases (Grks) (10). The roles of β-arrestins are quite broad. Recruited to receptors by ligand binding and Grk phosphorylation, they can desensitize receptors to further stimulation and assemble protein complexes that have trafficking and signaling functions (10).

Molecular motors, such as those belonging to the Kinesin family, transport proteins into and out of cilia. To examine this process, we first measured the distance Smo and Ptc1 travel from the basal body to the ciliary tip of cultured cells (Fig. 1, A and B). Ptc1 moves continuously throughout the exposure time, whereas Smo is stationary for most of the exposure time. We then examined the activity of β-arrestin, a protein involved in the internalization of G protein–coupled receptors (11). We focused on β-arrestin 2 (Grk2), which is recruited to cilia (12). The presence of Grk2 is a sensitive indicator of Shh signaling (13). In the absence of Shh, Smo activity is low, and β-arrestin 2 activity is high, indicating that Smo interacts with β-arrestin 2 and is not internalized. In Shh–stimulated cells, Smo activity increases, β-arrestin 2 is internalized, and Smo activity is reduced (Fig. 1C). By combining these measurements, we could see how Smo and β-arrestin 2 move in response to Shh signaling.

To understand these movements, we monitored the localization of β-arrestins in cilia of Kif3A motor complex–deficient cells (Fig. 1D). In Kif3A motor complex–deficient cells, β-arrestin was retained in cilia, and Smo localization was altered (Fig. 1E). These changes in the localization of β-arrestin and Smo were observed only in Shh–stimulated cells (Fig. 1F). This suggests that the Kif3A motor complex is required for typical cilia movements.

References and Notes
13. The structures have been determined by the Joint Center for Structural Genomics (www.jcsg.org) with Protein Data Bank entries 2OOK and 2O3L.

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A signaling protein localizes to primary cilia through its interaction with a complex that contains a motor protein.
depletion of Grk2 and β-arrestin 2 in cultured mammalian cells and zebrafish embryos blocks Hh signaling (11–13). Smo activation leads to the Grk2-mediated association of β-arrestin 2 with Smo, which then triggers the internalization (endocytosis) of Smo (12).

Kovacs et al. investigate the next important question: How does recruitment of β-arrestin 2 to Smo activate signaling? Using RNA interference in cultured mouse fibroblasts, the authors show that depletion of β-arrestin 1 or 2 prevents the movement of Smo to cilia as well as subsequent target gene transcription. The authors propose that Smo trafficking to cilia is mediated by Shh-enhanced association of the Smo–β-arrestin complex with the type II kinesin motor Kif3A. The finding that β-arrestin is required for both endocytosis and ciliary targeting of Smo seems contradictory; however, vesicles that carry Smo to the cilia may originate from the plasma membrane as recycling endosomes rather than directly from an intracellular source (the Golgi).

Kif3A, a component of the kinesin II motor complex, transports protein cargos within cilia. Materials are conveyed along microtubules at the core of the cilium by an elaborate intraflagellar transport system (1). This system is composed of a Kif3A-driven motor complex that moves toward the tip of the cilium and a second complex driven by the motor protein dynein that moves back toward the base. The link between cilia and Hh signaling emerged from the observation that mouse embryos lacking intraflagellar transport components, including Kif3A, have damaged Hh signaling (5).

Mice carrying mutations in the genes encoding Kif3A and other intraflagellar transport proteins suffer from developmental abnormalities caused by a lack of both Gli activator function (such as neural tube defects) and Gli repressor function (such as limb defects) (6). Does the discovery of a Smo–β-arrestin–Kif3A complex shed light on these complex phenotypes? The role of Kif3A in activating Gli proteins is consistent with its role in promoting Smo movement to cilia. However, Kif3A has a second role in Hh signaling that is probably independent of Smo. In the absence of Shh, Kif3A promotes conversion of Gli3 into a truncated repressor form, Gli3R (6). Thus, Kif3Apresses target genes by promoting Gli3R formation in the absence of Shh, but promotes Gli activator formation by transporting Smo into cilia in the presence of Shh (see the figure). The switch between these two states may be triggered by the formation of the Smo–β-arrestin–Kif3A complex. This is reminiscent of the dual role played by the motor protein Costal2 in Hh signaling in the fly Drosophila melanogaster (7).

Several seven-transmembrane receptors, such as those for somatostatin and serotonin, are located in primary cilia, so an important question is whether these receptors also rely on a β-arrestin–Kif3A complex for their localization. In mammalian photoreceptor cells, Kif3A transports arrestin and the seven-transmembrane receptor opsin through a specialized variant of primary cilia (14). Because many seven-transmembrane receptors associate with β-arrestin, but only a small number localize in cilia, additional factors must control ciliary localization. The Bardet-Biedl syndrome protein complex controls trafficking of seven-transmembrane receptors to cilia (15, 16). Unraveling how these and other mechanisms together regulate movement of transmembrane proteins to cilia will continue to shed light on Hh and other signaling pathways in primary cilia, illuminating new aspects of cell biology and potentially new paths to disease therapies.

References and Notes
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PERSPECTIVES

ATMOSPHERIC SCIENCE

Himalaya—Carbon Sink or Source?

Jerome Gaillardet1 and Albert Galy2

Chemical analysis of hot springs in the Himalaya suggest that the carbon released from mountain forming regions may warm Earth.

In 1845, the French mining engineer Joseph Ebelmen described how atmospheric CO2 reacts with rock minerals to form dissolved salts and bicarbonate. He envisioned the possibility of a global carbon cycle, in which the CO2 injected into the atmosphere by volcanoes is first transformed into soluble bicarbonate and then participates in the precipitation of carbonates in the ocean.

Today, the global carbon cycle and its influence on the long-term (million to billions of years) evolution of climate are still a matter of research. The theory of plate tectonics gave a better framework for the concept of sediment recycling (1). The role of silicate weathering as a climate regulator has been strengthened by modeling of the carbon cycle (2, 3), a better understanding of the interrelationships with other biogeochemical cycles, and the accumulated data from the geological archive. In addition to this, previously unconsidered CO2 inputs to the atmosphere by the Himalayan range have been recently discovered (4, 5).

The key idea of today’s carbon cycle models is that Earth sequesterates CO2 degassed from Earth’s interior in limestone, thus preventing it from being released into the atmosphere and causing warming. The only valid sequestration mechanism at geological time scales is the weathering of Ca-Mg silicates and subsequent precipitation of carbonate in the ocean. Photosynthesis, weathering of carbonate rocks, and the burial of organic carbon into sediments are all sequestering processes that are balanced by return fluxes (respiration, precipitation of carbonates in the ocean, and oxidation of inland organic matter). But these processes occur on a time scale shorter than millions of years. The most recent estimate of pre-anthropogenic CO2 consumption flux by silicate weathering reaction is 0.07 PgC/year (6) (see the figure).

Numerous uncertainties in this geological carbon cycle still remain, the principal of those being the amount of carbon entering the atmosphere now and in the past. The degassing flux was estimated based on the flux emitted by volcanoes in different geodynamic contexts and

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