Hedgehog Signaling

Philip W. Ingham

Institute of Molecular and Cell Biology, Singapore 138673

Correspondence: pingham@imcb.a-star.edu.sg

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The Hedgehog (Hh) proteins belong to one of a small number of families of secreted signals that play a central role in the development of most metazoans. *hh* itself was originally identified as a mutation that causes a “segment polarity” phenotype in *Drosophila*—as were most of the core components of the Hh signal transduction pathway (Ingham et al. 2011). These components have been highly conserved between flies and vertebrates (Figs. 1 and 2); however, mammals express three related proteins, Sonic hedgehog (Shh), Indian hedgehog, and Desert hedgehog (Dhh), and genetic analysis in mice has uncovered a vertebrate-specific role of the primary cilium in Hh signaling (Goetz et al. 2009).

An unusual feature of Hh proteins is their covalent coupling to cholesterol, which occurs during autocleavage of the proprotein to yield the signaling moiety, HhN (Beachy et al. 1997). HhN is also palmitoylated at its amino terminus by an acyl transferase encoded by the *Drosophila* *skinny hedgehog* gene (*Skn*). Secretion of lipidated HhN requires the function of a large multipass transmembrane protein, Dispatched, that is structurally related to the Hh receptor Patched (Ptc1) (Ingham et al. 2011). Binding of HhN to Ptc1 is promoted by two other transmembrane proteins, CDO and BOC (known as IHOG and BOI in *Drosophila*), which act redundantly to bind HhN via one of several fibronectin III (FnIII) motifs in their extracellular domains (Beachy et al. 2010). In its unbound state, Ptc1 localizes to the primary cilium (Rohatgi and Scott 2007), where it acts via a poorly characterized mechanism, thought to involve the transport of one or more lipids, to suppress the activity of the G-protein-coupled receptor (GPCR)-like protein Smoothened (Smo) (Ayers and Théron 2010).

The principal response of cells to HhN is the activation of target genes by the Gli zinc finger proteins. Gli2 and Gli3 (but not Gli1) are bifunctional transcription factors: their full-length forms function as transcriptional activators, but they can be converted into lower-molecular-weight transcriptional repressors. This is promoted by the phosphorylation of a series of motifs within the carboxy-terminal

domain of the protein. These motifs are sequentially phosphorylated by PKA, GSK3, and CKI to generate recognition signals for the F-box protein bTrCP, a component of the SCF complex. This in turn catalyzes the ubiquitylation of the carboxyl terminus, targeting it for degradation by the proteasome to yield the truncated amino-terminal repressor forms, Gli2/3R (Ingham et al. 2011). These bind to Hh target genes to repress their transcription. Gli2/3 proteins appear to shuttle up and down the primary cilium in association with the Cos/Kif7 and SuFu proteins; in the absence of Smo activity, this association seems to promote their processing at the base of the primary cilium. Inactivation of Ptc by HhN results in Smo being transported to the tip of the primary cilium (a process that requires Kif3a and β -arrestin activity), where its activity promotes the dissociation of the Gli2/3-Cos-SuFu complex (Tukachinsky et al. 2010), releasing the full-length highly labile forms

Figure 1. Hedgehog signaling (simplified view).

Figure 2. Hedgehog signaling.

of the Gli proteins. These translocate to the nucleus and activate transcription of target genes, such as *Ptch1*, which attenuates the signal, *Gli1*, which amplifies the signal, and the genes encoding the cell cycle regulators, Myc, cyclin D, and E.

Figures 1 and 2 adapted, with permission, from Cell Signaling Technology (<http://www.cellsignal.com>).

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