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Perspective

The contrasting roles of primary cilia and cytonemes in Hh signaling

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ABSTRACT

Hedgehog (Hh) is a paracrine signaling protein with major roles in development and disease. In vertebrates and invertebrates, Hh signal transduction is carried out almost entirely by evolutionarily conserved components, and in both, intercellular movement of Hh is mediated by cytonemes – specialized filopodia that serve as bridges that bring distant cells into contact. A significant difference is the role of primary cilia, a slender, tubulin-based protuberance of many vertebrate cells. Although the primary cilium is essential for Hh signaling in cells that have one, most Drosophila cells lack a primary cilium. This perspective addresses the roles of primary cilia and cytonemes, and proposes that for Hh signaling, the role of primary cilia is to provide a specialized hydrophobic environment that hosts lipid-modified Hh and other components of Hh signal transduction after Hh has traveled from elsewhere in the cell. Implicit in this model is the idea that initial binding and uptake of Hh is independent of and segregated from the processes of signal transduction and activation.

Text

Cytonemes are specialized types of signaling filopodia that are actin-based (Ramírez-Weber and Kornberg, 1999) (Fig. 1). They extend from both the apical and basal surfaces of polarized cells (Hsiung et al., 2005) and they ferry signaling proteins such as Hedgehog (Hh) and Decapentaplegic (Dpp) between source and target cells (Bilioni et al., 2012; Bischoff et al., 2013; Callejo et al., 2011; Kornberg, 2011b; Roy et al., 2014a). The primary cilium is a microtubule-based structure that emanates from a cell's basal body. Almost every vertebrate cell has one, and primary cilia have roles in many signaling processes, including Hh signaling (reviewed in Goetz and Anderson, 2010). Yet, although both cytonemes and primary cilia are specialized cytoplasmic extensions and both function in Hh signaling, their roles in Hh signaling are probably distinct. The primary cilium is not a cytoneme in the sense that a primary cilium is not a conduit for transporting Hh between cells. And unlike a primary cilium, a cytoneme does not house components of Hh signal transduction and it is not a structure in which signals are transduced.

The importance of primary cilia to Sonic Hedgehog signal transduction was discovered when mouse mutants lacking functional primary cilia were found to be defective in Hh signaling (Huangfu et al., 2003) (for simplicity, the Hh abbreviation will be used here for both Hedgehog and Sonic Hedgehog). Subsequent work revealed that primary cilia contain some components of the Hh signal transduction pathway, including the Gli transcription factors, the Patched 1 (Ptc1) Hh receptor and the seven-transmembrane protein Smoothened (Smo) (Corbit et al., 2005; Haycraft et al., 2005; Rohatgi et al., 2007), and that Hh co-localizes with Ptc in the primary cilium (Rohatgi et al., 2007). Although these findings do not show whether Hh-dependent Ptc function controls pathway activation in cilia or elsewhere, they have supported the idea that the primary cilium has two roles in Hh signaling – to receive Hh after it has been released by Hh-producing cells and to initiate signal transduction in responding cells. There are a number of reasons to propose that the primary cilium does not have a direct role in Hh reception.

Although primary cilia have been implicated as signal sensing organelles, for instance in vertebrate left-right axis specification (Field et al., 2011; Kamura et al., 2011; McGrath et al., 2003; Pennekamp et al., 2002), they do not appear to be the site of Hh binding and uptake, for instance, in the neural tube of the mouse embryo where Hh patterns cell types in a concentration and time-dependent manner (reviewed in Jacob and Briscoe, 2003). At embryo stage E8.5, Hh is produced by the notochord, which is next to the basal surface of the cells of the ventral neural tube (Fig. 2A). Hh protein, detected with α-Hh antibody (Gritli-Linde et al., 2001) or by fluorescence of Hh:GFP (Chamberlain et al., 2008), distributes most prominently along the basal surface of the neural tube, with highest concentrations ventrally. Hh is also detected apically in the lumen of the neural tube, again with highest concentrations ventrally. These distributions are consistent with the idea that Hh emanates basally from the ventral notochord and then disperses basally along the basal surface of the neural tube. The route that leads Hh to the apical distribution in the neural tube is less obvious and must involve additional steps.

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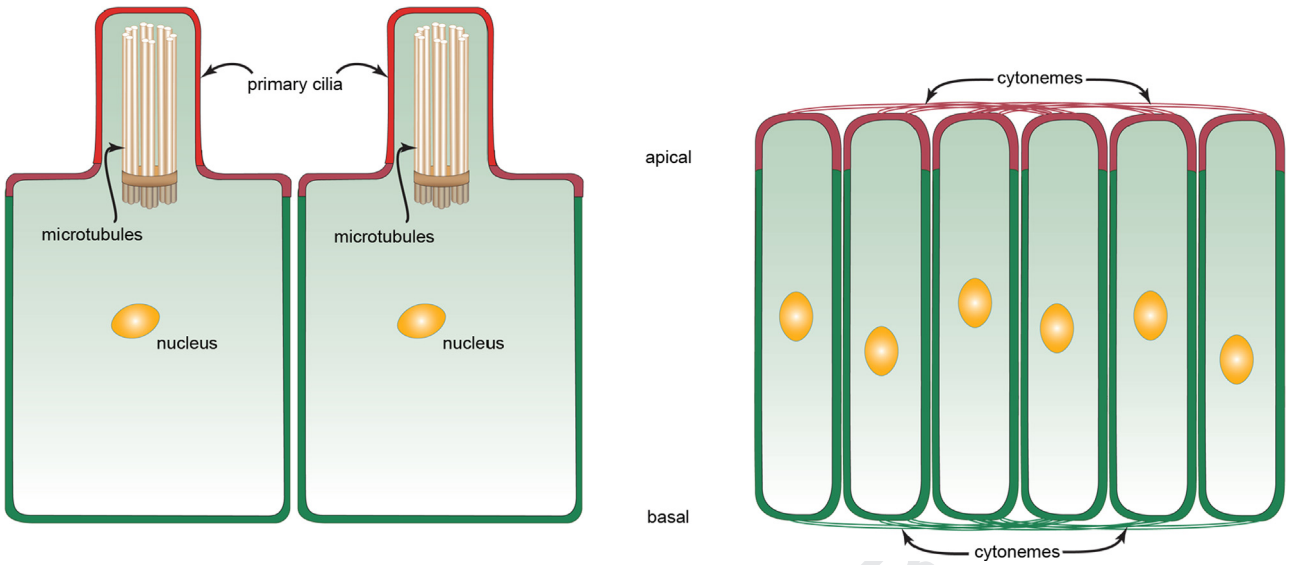

Fig. 1. Primary cilia and cytonemes in polarized cells. Drawings show ciliated cells (left) and non-ciliated cells (right) in a polarized epithelium, apical up and basal down. Ciliated cells extend a single primary cilium apically that contains 9 doublet pairs of microtubules linked to a basal body. These cells presumably have cytonemes that are not depicted in this drawing. Apical and basal cytonemes extend across both the apical and basal surfaces of the non-ciliated cells such as those of the wing imaginal disc.

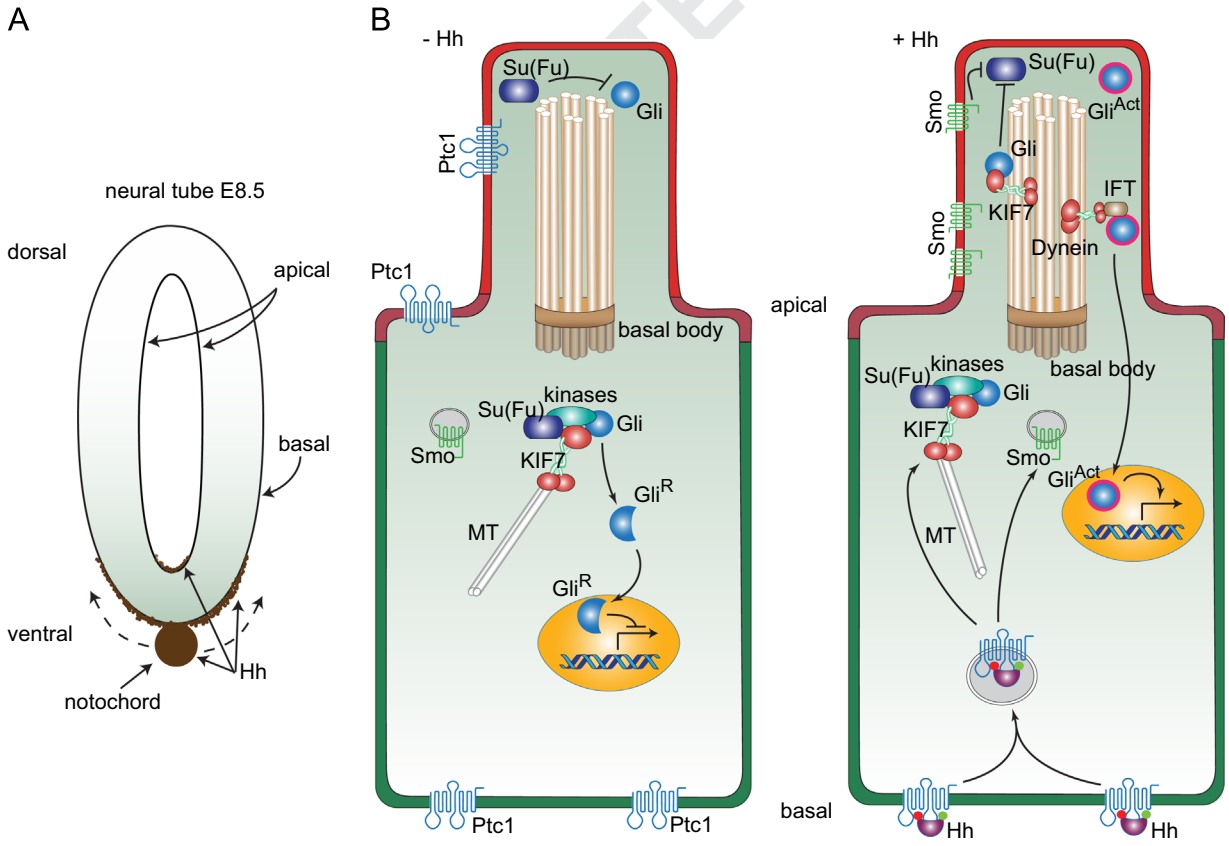

Fig. 2. Hh distributions in the neural tube of the mouse embryo and model for signaling in a ciliated mouse cell. (A) Drawing depitcs Hh expression (brown) in the notochord of an E8.5 mouse embryo. Hh expressed in the notochord moves dorsally and distributes along the basal surface of the neural tube; some accumulates at the apical surface. (B) A subset of the components involved in Hh signal transduction is depicted in a cell prior to receipt of Hh (−Hh; left), and in a cell active for Hh signal transduction (+Hh; right). The primary cilium contains a 9+0 bundle of doublet microtubules that extend from a basal body, and ferry components of Hh signal transduction with microtubule-binding KIF7 and Dynein motor proteins. The Ptc1 receptor (blue) is present in the apical plasma membrane, and in in non-signaling cells, in the plasma membrane of the primary cilium. Smo is only present in the plasma membrane of the primary cilium in Hh-signaling cells. In non-signaling cells, Smo is in intracellular vesicles and Gli is present both in the primary cilium where its inactive state is Su(Fu)-dependent and in the cytoplasm. In the cytoplasm it is associated with KIF7, Su(Fu) and several kinases and is processed to a proteolyzed repressor form that translocates to the nucleus. In signaling cells, shown as receiving Hh at the basal membrane, intracellular vesicles containing Ptc1 and Hh form, the process that generates Gli^R is inhibited, and in the primary cilium, Su(Fu)-dependent inactivation of Gli is inhibited and the transcriptional activator form of Gli is generated.

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