MIM and cortactin antagonism regulates ciliogenesis and hedgehog signaling.

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Public Summary:
Sonic hedgehog (Shh) is a secreted protein that activates specific cell membrane receptor protein and thereby activates and transports Shh messenger proteins into the nucleus to initiate cellular responses. Proper Shh signaling response is required for the development and regeneration of many organs, including the brain and bladder. Shh deficiency in humans can lead to developmental defects such as holoprosencephaly, a series of malformations of the brain and face. On the other hand, aberrantly activated Shh response results in a number of cancers, such as glioma and basal cell carcinoma. Primary cilium is a membrane protrusion of the mammalian cells that functions like an antenna to collect, concentrate, and channel the Shh signal messenger into the cell nucleus to program cellular responses. As such, defective primary cilium formation decreases Shh responsiveness. Primary cilium is constructed with a foundation called basal body, on which anchored and grew a tubular framework that generates the membrane protrusion. The basal body and the tubular framework are generated with one type of the cellular skeleton, the microtubules, albeit in different organization. In this report we show how a protein named Missing in Metastasis, or MIM, controls the formation of primary cilium and Shh response. MIM protein is associated with another type of cellular skeleton, the actin filaments. Using skin dermal cell as an experimental cell model, we show that MIM protein is required at the basal body to maintain primary cilium, Shh responsiveness, and hair follicle formation. MIM depletion in skin dermal cells resulted in the loss of primary cilia and Shh responsiveness. Using a hair follicle regeneration assay as a tissue regeneration model, in which hair follicles are generated with dermal and epidermal cells, we show that MIM depletion in the dermal cells decreases hair follicle formation. We further demonstrate that MIM controls primary cilium formation by antagonizing the activity of another actin-associated protein, Cortactin. Cortactin protein activity is modified by the addition of a series of phosphoryl group, by an enzyme Src that performs the phosphorylation. This is because MIM depletion resulted in increased Src phosphorylation activity. Likewise, Src inhibition or Cortactin depletion is able to counteract cilia formation defect caused by the loss of MIM. By contrast, increased Src production or phosphoryl-modification of Cortactin in cells, behaves like MIM depletion, which results in cilia formation defect. Our results suggest that MIM promotes cilia formation by antagonizing Src-dependent phosphorylation on Cortactin. Our study thus describes a mechanism linking the regulators of the actin cellular skeleton with primary cilia formation and Shh signal responsiveness in tissue regeneration.

Scientific Abstract:
The primary cilium is critical for transducing Sonic hedgehog (Shh) signaling, but the mechanisms of its transient assembly are poorly understood. Previously we showed that the actin regulatory protein Missing-in-Metastasis (MIM) regulates Shh signaling, but the nature of MIM's role was unknown. Here we show that MIM is required at the basal body of mesenchymal cells for cilia maintenance, Shh responsiveness, and de novo hair follicle formation. MIM knockdown results in increased Src kinase activity and subsequent hyperphosphorylation of the actin regulator Cortactin. Importantly, inhibition of Src or depletion of Cortactin compensates for the cilia defect in MIM knockdown cells, whereas overexpression of Src or phospho-mimetic Cortactin is sufficient to inhibit ciliogenesis. Our results suggest that MIM promotes ciliogenesis by antagonizing Src-dependent phosphorylation of Cortactin and describe a mechanism linking regulation of the actin cytoskeleton with ciliogenesis and Shh signaling during tissue regeneration.