Hedgehog signaling is controlled by Rac1 activity

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Abstract

Hedgehog (Hh) signaling critically regulates cell fate and proliferation in development and disease. The nuclear translocation of transcriptional factor family Glis (Gli1-3) is indispensable for Hh signaling activation; however, the mechanisms governing Glis nuclear translocation are not well understood. Here, we report that Glis translocation in response to Hh requires the small GTPase Rac1 inactivation; however, the mechanisms governing Glis nuclear translocation are not well understood.

Here, we report that Glis translocation in response to Hh requires the small GTPase Rac1 inactivation. We show that upon binding of Hh to its receptor Ptc1, receptor Smo dissociates from Ptc1 and binds to Vav2, resulting in decreased phosphorylation level of Vav2, which further inactivates Rac1. The role of Rac1 depends on regulation of phosphorylation levels of kinesin II family member 3A (Kif3A) with shortened primary cilia length, which in turn regulates intraflagellar transport 88 (IFT88) protein degradation and subsequently dampens the SuFu-Glis complex formation in primary cilia, resulting in release of Glis from primary cilia and translocation into nucleus. Moreover, in GFAP-Cre;Smo\textsuperscript{M2/−} transgenic mice cerebellum that develop medulloblastomas caused by hyper-activation of Smo, Vav2 phosphorylation is inhibited and Rac1 is inactivated; genetic ablation of Rac1 in the mice embryonic limb bud ectoderm (Prx1-Cre;Rac1\textsuperscript{f/f}) promotes Hh signaling activation through Glis translocation. Together, these results uncover Rac1 inactivation and subsequent Glis translocation as a hitherto uncharacterized mechanism controlling Hh signaling and may provide additional targets for therapeutic intervention of this important pathway.

Results

Figure 1. Activation of Rac1 inhibits Hh signaling.

Figure 2. Hh-Smo regulates Rac1 activity through Vav2.

Figure 3. Activation of Rac1 enhances Gli-SuFu complex formation.

Figure 4. Activation of Rac1 promotes IFT88 degradation through regulation of phosphorylation levels of Kif3A.

Figure 5. Genetic Rac1 ablation in the mice embryonic limb bud ectoderm promotes Gli1 nuclear translocation.

Conclusion

These results uncover Rac1 inactivation and subsequent Glis translocation as a hitherto uncharacterized mechanism controlling Hh signaling and provide additional targets for therapeutic intervention of this important pathway.