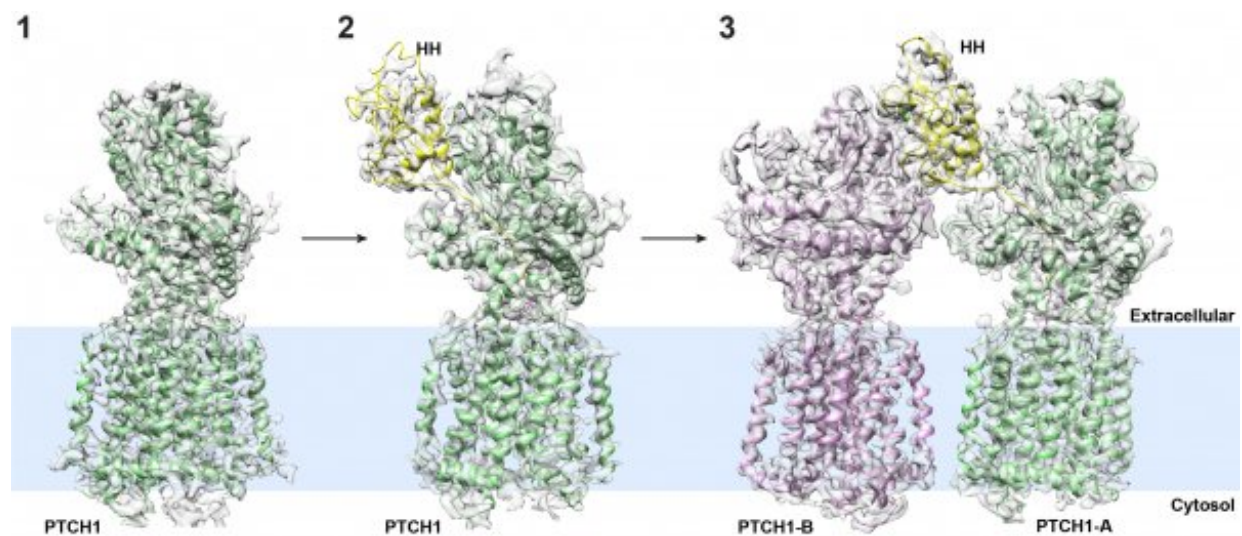


Researchers determine atomic structure of molecular complex associated with birth defects

August 24 2018



Cryo-EM structures illuminate the molecular mechanism of Hedgehog signaling. 1. PTCH1 alone. 2. 1-to-1 ratio PTCH1-HH complex (Nature 560:128-132). 3. 2-to-1 ratio PTCH1-HH complex. Credit: *Science*

In a study published today in *Science*, UT Southwestern and Rockefeller University researchers used advanced microscopes to determine at atomic resolution the structure of a molecular complex implicated in birth defects and several cancers.

The Hedgehog signaling pathway, which transmits information to embryonic cells, is crucial to human health. Insufficient signaling during development leads to [birth defects](#), while unrestrained Hedgehog signaling occurs in many cancers. Excessive signaling is implicated in [basal cell carcinoma](#) – the most common malignant [cancer](#) in humans – as well as in brain cancer, breast cancer, and prostate cancer, said Dr. Xiaochun Li, UT Southwestern Assistant Professor of Molecular Genetics and Biophysics and a Rita C. and William P. Clements, Jr. Scholar in Biomedical Research. Many pharmaceutical companies are developing drugs that target Hedgehog signaling. Having a clearer view of the structure could help those efforts, Dr. Li said.

The researchers, using cryo-electron microscopy (cryo-EM) technology, showed that two Patched-1 (PTCH1) molecules simultaneously engage a single Hedgehog (HH) molecule, but at two distinct sites. This unique 2-to-1 ratio PTCH1-HH complex is required for efficient Hedgehog signaling in [cells](#).

Cryo-EM uses enormous microscopes equipped with robotics to determine the structure of molecular samples that are frozen at temperatures so low that ice crystals cannot form.

In another paper published in *Nature* last month, Dr. Li's group reported a cryo-EM structure of the 1-to-1 PTCH1-HH complex. Their biochemical assays indicated that HH binding to one PTCH1 molecule may not be sufficient for full activity. HH may need to recruit either a different protein or another PTCH1 molecule, he said.

"In the current *Science* paper, we report a 2-to-1 PTCH1-HH complex in which one Hedgehog molecule binds to two of its receptors (PTCH1) at two different spots. We used our cell biology assay to verify that this 2-to-1 complex is indeed the signaling generator for Hedgehog signaling. Combined with the earlier study published in *Nature*, we hope our new

work will provide additional insights for physicians and scientists in this field," he explained.

More information: Xiaofeng Qi et al. Structures of human Patched and its complex with native palmitoylated sonic hedgehog, *Nature* (2018). [DOI: 10.1038/s41586-018-0308-7](https://doi.org/10.1038/s41586-018-0308-7)

Xiaofeng Qi et al. Two Patched molecules engage distinct sites on Hedgehog yielding a signaling-competent complex, *Science* (2018). [DOI: 10.1126/science.aas8843](https://doi.org/10.1126/science.aas8843)

Provided by UT Southwestern Medical Center

Citation: Researchers determine atomic structure of molecular complex associated with birth defects (2018, August 24) retrieved 25 April 2024 from <https://medicalxpress.com/news/2018-08-atomic-molecular-complex-birth-defects.html>

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