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Hedgehog, meet Patched

Proteoglycan ensures that the Hedgehog protein and its receptor make a connection.

Hedgehog protein and its receptor are made for each other, but even this perfect couple needs a little help to get together. Li et al. (1) reveal that a proteoglycan plays cupid for the molecules and sparks signal transduction through the Hedgehog pathway, a mechanism exploited by a type of childhood cancer.

During development, Hedgehog proteins are sculptors, helping to mold the embryo's limbs and other parts of the body. Later in life, however, the protein's ability to spur cell division can promote basal cell carcinomas and other cancers, which often rev up the Hedgehog pathway. Li et al. teased out a connection between Hedgehog proteins and rhabdomyosarcoma, a soft-tissue tumor that strikes children (2). Hedgehog proteins steer a cell's fate by latching onto the membrane receptor Patched-1. Also participating in this encounter are proteoglycans known as glypicans (3). In previous work, the researchers showed that glypican-3 curtails signaling by preventing Hedgehog proteins from binding to Patched-1 (4). Another group has demonstrated that rhabdomyosarcoma cells often overproduce glypican-5 (5), raising the possibility that this proteoglycan promotes tumor growth by stimulating the Hedgehog pathway.

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Li et al. put this idea to the test by modifying glypican-5 levels in rhabdomyosarcoma cells. They found that decreasing levels of glypican-5 by RNAi trimmed the amount of Gli1, a protein whose production is switched on by Hedgehog signaling. Boosting glypican-5 quantities had the opposite effect, raising Gli1 levels and speeding cell proliferation. Knowing that the primary cilium is necessary for Hedgehog signaling, Li et al. tracked glypican-5 to the ciliary membrane, where they suspect it links up with Patched-1. However, glypican-3 didn't show up in the cilium, which fits with its proposed function in intercepting Hedgehog molecules before they reach Patched-1.

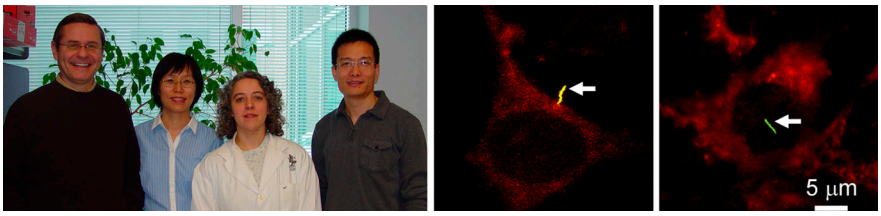
How do glypican-5 molecules perform their job? "Basically, they are acting like matchmakers," says senior author Jorge Filmus. He and his colleagues determined that glypican-5 binds to Sonic Hedgehog, one of the mammalian Hedgehog proteins, and to Patched-1. Glypican-5 also encouraged Sonic Hedgehog and Patched-1 to stick together.

The team then investigated whether one of the distinguishing features of glypicans—their glycosaminoglycan chains—affects Hedgehog signaling. Glypican-5 carries chondroitin sulfate and heparan sulfate chains. Enzymes that lop off the chondroitin sulfate molecules reduced glypican-5's ability to bind to Patched-1, and enzymes that remove the heparan sulfates had an even stronger effect. That suggests both kinds of chains are needed for Hedgehog signaling but that the heparan sulfate chains may be more important.

"This is a novel mechanism by which the Hedgehog signaling pathway can be activated," says Filmus. Yet how glypican-5 serves as a matchmaker remains unresolved. The proteoglycan might coax Hedgehog proteins and Patched-1 to interact or might strengthen their bond once they've already linked up. The researchers think that mammalian cells can use their six different glypicans to fine-tune their responses to Hedgehog signals. "Cells use these glypicans to decide which are their favored interactions, which ones they really want to happen," Filmus says. By making more glypican-3, for example, cells can reduce their sensitivity to Hedgehog proteins, or they can become more responsive by amplifying glypican-5.

The findings suggest two new approaches for rhabdomyosarcoma treatment. Drugs that inhibit the Hedgehog pathway—usually by blocking a protein downstream of Patched-1—are already in clinical trials as therapies for several kinds of cancer. These compounds may also benefit rhabdomyosarcoma patients. Another alternative, the researchers say, is developing novel drugs that target glypican-5.

Focal Point



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(Left to right) Jorge Filmus, Wen Shi, Mariana Capurro, and Fuchuan Li determined how glypican-5 proteoglycans fire up the Hedgehog pathway to promote the growth of rhabdomyosarcoma cells. At left, wild-type glypican-5 (red) settles in the primary cilium (green; arrow), which serves as an antenna for Hedgehog signaling. But glypican-5 molecules that lack glycosaminoglycan chains (right) largely remain outside the primary cilium.

1. Li, F., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201008087.
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4. Capurro, M.I., et al. 2008. *Dev. Cell.* 14:700–711.
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