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## Plant Compound Blocks Action of Cancer Genes

A plant compound that produces severe neural defects in developing embryos can block the action of mutated genes that produce basal cell skin carcinomas, the most common form of human cancer.

According to researchers at the Howard Hughes Medical Institute (HHMI) at The Johns Hopkins University School of Medicine, the studies in mouse cells suggest that the drug may be used to treat a number of cancers, including medulloblastomas in the brain and rhabdomyosarcomas in muscle. The finding also spotlights the promise of mechanism-based treatment approaches that target specific signaling pathways that are critical to a particular cancer. Conventional chemotherapy, in sharp contrast, kills cancer cells by attacking all proliferating cells-killing healthy tissue in the process.

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In an article in the August 31, 2000, issue of the journal *Nature*, HHMI investigator Philip A. Beachy and his colleagues reported that the plant compound cyclopamine interferes with the action of the protein encoded by the gene, *Smoothed*. When *Smoothed* or its regulator *Patched* are mutated in skin cells, the cells grow without their normal constraints, and cancer can arise. *Smoothed* and *Patched* play a role in sensing the signal produced by *Hedgehog*, a critical protein in embryonic development.

Beachy's co-authors on the *Nature* article included Jussi Taipale and colleagues at Hopkins, and HHMI investigator Matthew P. Scott and his colleagues at Stanford University School of Medicine.

"It had long been known that animals that consumed plants containing cyclopamine suffered severe neural birth defects, including malformations that produced a single cyclopic eye," said Beachy. "And when we knocked

out the mouse counterpart of the *hedgehog* gene, *Sonic hedgehog*, we saw an effect very much like that produced in animals by cyclopamine. So, that really rang a bell for us."

After initial experiments indicated that cyclopamine did not directly affect the Hedgehog protein, the scientists turned their attention to the two cellular targets that receive signals from Hedgehog-proteins produced by the genes *Smoothened* and *Patched*. While the Smoothened protein switches on cell division, the Patched protein acts as a cellular "brake," or tumor suppressor. Previous studies had shown that Hedgehog switches on cell division by binding to Patched, turning off its normal braking function, and allowing Smoothened to activate cell proliferation.

The scientists' experiments ruled out that cyclopamine might thwart proliferation by activating the Patched protein. They found instead that when they deleted the *Patched* gene from mouse cells, cyclopamine could still turn off cell division. "Thus, we'd eliminated two red herrings-that cyclopamine affected either Hedgehog or Patched," said Beachy.

To test whether Smoothened was cyclopamine's target, the scientists first produced mouse cells that expressed high levels of the Smoothened protein. Cyclopamine still suppressed activation of those cells. To investigate the limits of cyclopamine's suppression, the scientists next tested the drug's effects on mouse cells that possessed mutant activated forms of the Smoothened protein that were freed from control by Patched.

These mutant Smoothened-activated cells, the scientists found, proliferated regardless of cyclopamine treatment. Importantly, however, the mutant cells were suppressed by a more potent, synthetic form of cyclopamine.

"All these findings lead us to believe that Smoothened is the target of cyclopamine action, concluded Beachy. "And now that we have evidence that Smoothened is the target, we can further explore whether the interaction is direct or indirect."

Also, said Beachy, further experiments will test the effects of cyclopamine on tumors grown in mice that arise in cells lacking the Patched tumor suppressor.

Beachy emphasized that cyclopamine's potential as a cancer therapy also illustrates the enormous potential of mechanism-based cancer therapies. "There are many efforts being made in universities and pharmaceutical companies to identify critical signaling pathways in tumors that could represent specific therapeutic targets," he said. "And these efforts will certainly lead to treatments far more effective and less toxic than standard chemotherapeutic agents, which are basically cell poisons."