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Genetic Cause of Most Common Cancer Found

Institute researchers have learned that basal cell carcinoma, the most common human cancer, is caused by a defect in a gene that restrains cell growth. The finding could lead to new drugs—perhaps applied directly to the skin—to treat tumors.

Each year, about 750,000 people in the United States develop basal cell carcinoma. The tumors primarily strike pale-skinned people of Northern European ancestry during their middle or late years. Unlike many cancers, basal cell carcinoma grows locally but does not spread throughout the body. The newfound gene also plays a role in a rare but debilitating inherited condition called basal cell nevus syndrome (BCNS). People with this syndrome develop dozens to hundreds of basal cell carcinomas starting as early as age ten. Today, physicians treat BCNS and basal cell carcinoma with surgery, radiation, and other standard approaches. The new research—reported in the June 14, 1996, issue of the journal *Science*—offers promise for scientists pursuing either condition.

"The dark red stain in the left panel shows where *patched* is active in the developing and limbs in a mouse embryo. The dark blue stain in the right panel shows where *patched* is active in in a *Drosophila* wing imaginal disc. In both cases the high level of expression of the *patched* gene is a response to a secreted signaling molecule, hedgehog, that is sent from nearby cells. Activity of *patched* in human skin leads to controlled growth; it's absence leads to basal cell carcinoma."

Based on studies in the fruit fly, researchers believe their wayward gene—called *patched*—normally acts as a brake for another gene, *hedgehog*

, that instructs cells during development and growth. When *patched* is defective or missing, hedgehog goes unrestrained, causing cells to behave abnormally. In flies, this results in developmental defects and cell proliferation. "If these two genes work in humans as they do in flies, perhaps researchers will find a way to interfere with hedgehog's signaling—and as a result stop the tumors from forming," said Ronald Johnson, a postdoctoral fellow in developmental biology at Stanford University School of Medicine. Johnson worked with Matthew Scott of the Howard Hughes Medical Institute at Stanford and researchers from the University of California, San Francisco (UCSF), to identify the culprit gene.

Because the *patched* gene is crucial in fly development, the researchers hunted for it among human chromosomes. They pinpointed its location on human chromosome 9—in the same region harboring an unknown gene involved in BCNS. "At this point, we asked, Could a malfunction of the *patched* gene in humans lead to the BCNS and also to the basal cell carcinomas that many people get in their later years?" Johnson said. The HHMI/Stanford researchers began collaborating with Erwin Epstein at UCSF, who was searching for the gene that caused BCNS. Working together, the two groups examined DNA from people with BCNS or the common type of basal cell carcinoma.

They found that basal cell carcinomas arise when heavy exposure to sunlight damages both copies of the *patched* gene. In contrast, patients who inherit BCNS get one defective copy of *patched*.