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## Studies of Fly Tumor May Expand Understanding of Human Cancer

Howard Hughes Medical Institute (HHMI) researchers at Yale University have "rescued" fruit flies from cancerous tumors by inserting a cancer-suppressing human gene into the insects. The scientists believe that their achievement represents the first direct link between human tumor suppressor genes and those found in the fruit fly *Drosophila*.

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More broadly, the experiments demonstrate that even though flies and humans are separated by 800 million years of evolution, the insects can provide important new insights into human cancers, says HHMI investigator Tian Xu at Yale University School of Medicine.

Tumor suppressor genes produce proteins that normally stop cell proliferation. When such genes malfunction, they produce defective proteins that permit cells to proliferate endlessly, producing tumors.

In a paper published in the February 1999 issue of the journal *Nature Genetics*, the researchers showed that inserting the human "large tumor suppressor" (*LATS1*) gene into *Drosophila* that lacked the fly version of the gene (*lats*) prevented tumor formation. Flies with the human *LATS1* gene did not show the widespread tumors and early mortality caused by the non-functioning *lats* gene, suggesting that the two genes have the same function.

In addition, Xu and his colleagues uncovered evidence that *lats* is a new kind of tumor suppressor that blocks a specific stage of cell proliferation. "We believe this finding represents a major advance in understanding cell cycle

regulation, and thus cancer biology, because these LATS molecules are a new type of negative regulator for the enzymes that drive the cell cycle," said Xu. Thus, he said, the finding hints that further explorations into the molecular signaling machinery involving LATS1 may yield insights into little-understood cancers and perhaps lead to new cancer therapies.

In another set of experiments, which were described in a second paper in the February 1999 issue of *Nature Genetics*, Xu's team disrupted the *LATS1* gene in mice. The scientists found that mice developed ovarian tumors, soft-tissue sarcomas and pituitary disorders.

"This finding is important because it is the first example showing that an invertebrate tumor suppressor is also a tumor suppressor in mammals," said Xu. "This also suggests that some human cancers may be caused by a mutation of the *LATS1* gene, although the correlation between mice and humans is not that good in terms of the types of tumors caused by a particular mutation."

In a commentary on the two papers, cancer researcher Christopher Kemp of the Fred Hutchinson Cancer Research Center in Seattle noted that even though many tumor suppressor genes have been identified in flies, they "had not gained broad acceptance or notice in the mammalian cancer genetics community."

But the two papers by Xu and his colleagues, "take the study of fly cancer to a new level," wrote Kemp in the February 1999 issue of *Nature Genetics*. "These show, apparently for the first time, that a gene functions as a tumor suppressor in both invertebrates and vertebrates. In two fell swoops, the authors have thrust a previously obscure fly mutation to the center of the cell cycle and mammalian cancer."

A key to the experiments was Xu's team's technique for producing "genetic mosaic" fruit flies. In such mosaics, researchers can manipulate selected cells to give them two copies of a defective tumor suppressor.

"These mosaic flies are like cancer patients, in that very few cells possess mutated tumor suppressors, consequently developing tumors," explained Xu. "Most of the cells in both the flies' and the human patients' bodies carry normal copies of these genes.

"We believe that with this new technique we have shown that just as in many other aspects of biology, *Drosophila* will prove an excellent model to study tumor development, and that the process in flies will prove directly relevant to what happens in mammals, including humans," said Xu.