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Fly Genes Provide Model for Understanding How Cancer Spreads

Howard Hughes Medical Institute (HHMI) researchers have developed a method for using the fruit fly *Drosophila* as a model to understand the genes that drive the spread of cancer. The screening test is already proving beneficial in identifying novel combinations of genetic malfunctions that contribute to metastatic cancer.

Metastasis occurs when cells from a primary tumor break off and invade another organ. It is the deadliest transformation that a cancer can undergo, and therefore researchers have been looking for specific genes that propel metastasis. If they can identify distinctive metastatic gene programs for different cancers, it may be possible to slow or halt metastases by targeting the proteins produced by those genes.

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— Tian Xu

HHMI investigator Tian Xu and graduate student Raymond Pagliarini at Yale University School of Medicine have used their genetic screening method to reveal unexpected combinations of genetic malfunctions that are required for metastasis. Xu and Pagliarini report their studies in an article published in the October 10, 2003, issue of the journal *Science*.

"*Drosophila* is an excellent model for studying metastasis because genes in *Drosophila* are remarkably similar to the ones in humans and some seventy percent of the known human disease genes are present in *Drosophila*," said Xu. "Secondly, powerful genetic techniques have been developed in *Drosophila*. This is especially important in understanding metastasis, because late-stage cancers have accumulated so many mutations, those responsible for metastatic progression have been difficult to pinpoint."

Pagliarini and Xu began their studies with a mutant form of *Drosophila*, in which an activated cancer gene called *Ras* produces easily observable, non-metastatic tumors in the developing embryonic eye. Mutated *Ras* also plays a central role in many human cancers. The researchers tagged these

tumor cells with a green fluorescent protein, which enabled them to track tumor metastasis.

When the researchers generated a broad array of additional gene mutations in the *Ras* -activated flies, they discovered that a gene called *scrib* seemed to trigger spread of the cancer cells when it was mutated. But the researchers also found that mutations of *scrib* alone were not sufficient to produce tumors in the flies.

To confirm that what they were seeing was true metastasis and not simply an overgrowth of tumors that had invaded neighboring tissues, the researchers conducted additional experiments. Their studies showed distinctive cellular changes in the mutant flies that mimicked metastatic changes observed in human cancers. Specifically, they found degradation of a structure outside tissues or organs called the “basement membrane,” which encapsulates tissues. Human cancer cells break down the basement membrane before spreading into other tissues.

The researchers also detected in the *Ras / scrib* -mutant flies a reduction in the level of a protein called E-cadherin that helps cells adhere to one another. Reductions in E-cadherin function are also seen in malignant human cancers. By restoring the level of E-cadherin, the researchers found that they could suppress the metastatic behavior of tumors in the mutant flies.

“Such findings not only show that the process we observed in the fly is very similar to human malignant cancer, but also that our system provides the ability to screen for factors that can block metastasis,” said Xu.

“Overall, these findings are important to understanding metastasis, because previously investigators had looked for genes that only promote metastasis,” said Xu. “They excluded genes that also contribute to tumorigenesis, a good example being *Ras* . But we found that oncogenic change, such as that caused by *Ras* , also directly contributed to metastasis. So, the genes have to work together.

“This finding has important implications for explaining why tumors of different origins can have vastly different and distinctive metastatic potential,” said Xu. “Now it makes sense. The answer appears to be because they depend on the kind of mutations that it took them to become tumors, and their metastatic potential had already been dictated by those.”

Xu said that the findings offer real opportunity for development of new anti-metastatic cancer treatments. “It was previously thought that targeting *Ras* was important only in preventing tumor initiation,” said Xu. “But now, we know that *Ras* —as well as *scrib* and the other cell-polarity mutations we studied—is important for tumor progression. So they may all be drug targets for blocking metastasis.”

Xu and his colleagues are now screening for additional mutations in their fly model that not only induce mutation, but also block it. They are also introducing human cancer-related genes into flies to test the genes' effects on

metastasis. And, they will also screen compounds in their fly model for those that block metastasis.