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Mutations in Different Cells Cooperate to Set the Stage for Cancer

According to modern biology textbooks, a single genetic mutation is rarely enough to cause cancer. It is generally thought that cells must accumulate a series of mutations that work together to trigger tumor development. Now, Howard Hughes Medical Institute (HHMI) researchers have shown that distinct cancer-causing mutations in neighboring cells can cooperate to produce tumors.

Cancer biologists have long known that it takes the cooperation of multiple cancer-causing genes - or oncogenes -- to cause cancer. "It was assumed that these mutations have to occur in the same cells to drive tumorigenesis," said HHMI researcher Tian Xu at Yale University. "We have now discovered that the oncogenic mutations don't have to be in the same cells to drive development of cancer. Distinctive mutations occurring in different neighboring cells could cooperate to promote tumorigenesis."

Xu, graduate student Ming Wu, and postdoctoral researcher José Carlos Pastor-Pareja, both of whom work in Xu's lab at Yale University, are coauthors of the study published in *Nature* on January 13, 2010. The findings may open up a new avenue of research into the molecular origins of cancer. They also help to clarify how ordinary cellular stresses, such as wounds or inflammation, may promote cancer development.

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Xu's team set out to study the interaction of two mutant genes often detected together in tumors. One of these, *Ras*^{V12}, is a growth-promoter. *Ras* mutations are well known for their ability to cooperate with other mutations

to cause cancer. On its own, however, *Ras*^{V12} causes only a mild overgrowth of cells. The other gene, *scrib*-, a non-functioning mutant of a tumor-suppressor gene known as *scrib*, by itself causes cells to die. When the two mutant genes are found in single cell, they cooperate to produce tumors.

Xu and his colleagues were curious about what would happen when *Ras*^{V12} exists in one group of cells, and *scrib*- exists in a nearby group of cells. They decided to find out, using the fruit fly *Drosophila melanogaster*, a model organism that has been a workhorse of geneticists over the years. To its surprise, Xu's group discovered that the two mutations, existing in adjacent clusters of *Drosophila* larval eye cells, somehow interacted to turn the entire group of cells into a large invasive tumor. The results were dramatic, Xu says. It was just as if the two mutations had existed in a single cell.

"No one has ever shown before that different oncogenic mutations in different cells can interact to produce a tumor," said Xu. "People have just assumed that when they take the DNA from a tumor, the various mutations they see are combined in each cell. But they could be in different cells. Nobody really knows."

The team observed a similar result when they grew cells with the *Ras*^{V12} mutation together with cells that harbored a dysfunctional mutant of another tumor-suppressor gene, *lgl*. That led them to wonder whether the old paradigm of oncogenesis - that cancer-causing mutations must exist in the same cell -- might be in need of revision.

Since their results indicated that the genetic "cooperation" long thought to be necessary for tumor formation could actually occur between cells, Xu's team wanted to find out how this could happen. By sifting through some of the genes activated in the *Ras*^{V12} plus *scrib*- combination, they found the signaling pathway that mediates the interaction. They showed that cells that contain the *scrib*- mutation activate a signal protein called JNK, which in turn drives a signaling pathway that promotes cellular proliferation. When this JNK-driven activity reaches cells that contain *Ras*^{V12}, the combination of these two cell-proliferating influences appears to be enough to push the cells into tumorigenesis.

Intriguingly, the JNK activity seems to spread from *scrib*- cells via a mysterious, domino-type effect. "The signal is relayed from cell to cell," Xu said. "So if we stop it in one cell, then the signal no longer propagates."

Xu and his colleagues say that the *scrib*- mutation is not the only thing that can spur JNK signaling. JNK is a stress-response signal, which is activated when tissues are wounded or inflamed, and it appears to be necessary for wound healing. Thus relatively ordinary stress, in concert with a *Ras*^{V12} mutation, might be enough to trigger cancer.

"It has been suspected that stress contributes to cancer because individuals that are frequently exposed to stressed conditions such as inflammation are more likely to develop cancer," said Xu. "We have learned that indeed stress can help tumor development and it does so by activating the JNK stress signaling process. Now we know this, we can consider targeting it with therapeutics."