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Single Cancer Gene Has Profound Effects

Howard Hughes Medical Institute researchers have discovered that a gene commonly mutated in a wide range of cancers can single-handedly trigger pre-cancerous changes in cells. The discovery demonstrates that the oncogene, *K-ras*, can initiate tumor development in ways that were previously unappreciated.

The finding that mutant *K-ras* alone can cause rapid cell proliferation challenges one of the central tenets of cancer biology—that the cooperative action of two oncogenes is required to initiate the transformation of cells to a cancerous state.

According to the study's senior author, [Tyler E. Jacks](#) of the Howard Hughes Medical Institute (HHMI) at MIT, the new data suggest that drugs that affect the action of K-ras should be considered to control the development of pre-cancerous lesions before they progress to late-stage cancer.

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- Tyler Jacks

The results of these experiments challenge previous studies that showed that introducing mutated *ras* genes into cells caused cells to stop dividing and even undergo senescence. The researchers believe the new studies provide a better picture of what is really happening in the early stages of cancer because they have subtly manipulated their model system to replicate the conditions found in real cancers more accurately.

The researchers, led by HHMI's Jacks, published their findings in the April 2004 issue of the journal *Cancer Cell*. Jacks and his colleagues at MIT collaborated on the studies with researchers from the University of Pennsylvania, the Dana-Farber Cancer Institute, MD Anderson Cancer Center, Tufts University School of Medicine and Veterinary Medicine and

Children's Hospital, Boston.

According to Jacks, the *ras* family of oncogenes is important to study because a high percentage of cancers show mutations in a member of that family. Overall about 30 percent of cancers show *ras* mutations, including 50 percent of colon cancers and 90 percent of pancreatic cancers.

Previous studies showed that the introduction of mutated *ras* genes inhibited cell division or led to premature senescence of the cells. But these results gnawed away at Jacks and his colleagues because they knew the findings were incompatible with evidence that *ras* mutations were present in certain pre-neoplastic lesions, such as those found in pancreatic cells. One explanation for the discrepancy, according to Jacks, is that the earlier studies did not accurately reflect the physiological conditions under which oncogenes cause cancer because the researchers introduced the oncogenes from outside cells at high levels of activity.

Jacks and his colleagues, who have worked for years to develop better mouse models of cancer, take a different approach. "The more work we do, the more we realize how important it is to carefully manipulate biological systems in such studies to recapitulate the mechanism of human cancers," he said.

In an attempt to mimic more closely the real pre-cancerous process, Jacks and his colleagues created a mutated version of one of the most prevalent types of the *ras* gene, called *K-ras*. The researchers created a small mutation of the *K-ras* gene that would not alter the structure of the resulting protein in any substantial way, to mimic the kind of mutation that would be found in a naturally occurring *K-ras* oncogene. The mutant form of the gene would remain inactive until turned on inside cells. When turned on, it would be expressed at physiological levels, just as an oncogene might abruptly appear in pre-cancerous cells.

"We think this feature is important because the levels of expression of genes that encode signaling molecules are clearly important in determining their effect on cell biology, cell growth, cell death, and other properties relevant to cancer," said Jacks.

When the researchers activated the mutant *K-ras* gene in cultured mouse cells, they found that the manipulation led to two well known pre-cancerous properties: enhanced proliferation and immortalization of cells.

"It's from those observations that we argue that the delicate balance of signaling pathways that emerges from *ras* is critically important in determining the cellular outcome," said Jacks. "And my suspicion is that the earlier work led to inappropriately high levels of signaling through one particular pathway, and that's what led to the cell cycle arrest and premature cell senescence."

Working with cultured cells, the researchers also studied the effects of additional gene mutations on the system—such as those that eliminated the protective effect of the tumor suppressor gene *p53*. In combination with the mutated *K-ras*, such mutations produced evidence that cells underwent full transformation to a cancerous state.

And when the researchers introduced the conditional *K-ras* gene into mice, they found that restricted expression in the lung and colon produced the kind of pre-cancerous cell proliferation seen in human cancers. Widespread expression of the gene in embryonic mice was lethal.

Jacks said that the studies emphasize the importance of anti-*ras* drugs in treating cancers at the earliest stages. “This work shows that *ras* mutations can and are likely to be early drivers of proliferation in pre-neoplastic lesions,” he said. “This should focus attention on inhibiting *ras* pathways not only in cancer therapy, but in cancer prevention—trying to prevent the development of pre-neoplastic lesions, which can lead to a more advanced cancer,” he said.

He said that the group's experiments also revealed that the signaling pathway through which *ras* is known to trigger cell proliferation was not obviously activated by the mutant K-*ras*.

“We're still investigating mechanistically how that happens,” he said. “But it would suggest that there are other pathways downstream of *ras*—known or unknown—that are actually driving the proliferation of these cells. If we can understand what those are, it might direct our attention to other therapeutic opportunities to inhibit proliferation of *K-ras* mutant cells.”