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## Cancer "Brake" Keeps Growth in Check

Researchers have identified a protein that activates the well-known tumor suppressor gene *p53* to prevent the division of cells that have damaged DNA. When the enzyme *Chk2* is missing or defective, the "brakes" on proliferation of DNA-defective cancer cells are released and the cells are free to multiply and possibly form tumors.

Since *Chk2* normally activates *p53*, a gene that is mutated in more than half of human cancers, the researchers speculate that mutations in *Chk2* could also cause cancer. "These findings that *Chk2* mutations behave like *p53* mutations in causing cancer is very important," said Stephen Elledge, an HHMI investigator at Baylor College of Medicine. "*Chk2* is now a strong candidate for the gene mutation in the half of cancers that do not have mutations in *p53*."

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— **Stephen J. Elledge**

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A research team that included Atashi Hirao and Tak Mak of the University of Toronto and Elledge reported the discovery in the March 10, 2000, issue of the journal *Science*.

The discovery that *Chk2* is a tumor suppressor began with studies in Elledge's laboratory, where researchers were examining the "checkpoint" pathway in yeast. The checkpoint pathway is a crucial surveillance system that allows dividing cells to suspend cell division in order to repair damaged DNA. Cells that divide before DNA damage is repaired may form tumors. "We had discovered a yeast checkpoint enzyme called Rad53 and subsequently cloned a human homolog that we named *Chk2*," said Elledge. "We reasoned that *Chk2* might play the same role in humans."

Elledge contacted Mak to initiate a collaboration to further explore *Chk2*'s role in DNA damage repair. Researchers in Mak's laboratory generated embryonic mouse cells deficient in *Chk2* and exposed them to gamma radiation to damage their DNA. While examining the irradiated cells, the

scientists discovered that these cells could not maintain the normal arrested state needed to repair damaged DNA.

The scientists also wanted to know whether Chk2 directly affected p53. To test this hypothesis they used a Chk2-deficient version of another kind of mouse immune cell, called a thymocyte. In normal thymocytes, p53 induces a suicide response, called apoptosis, when the cells are exposed to radiation or DNA-damaging drugs. In the mouse thymocytes that lacked Chk2, the cells survived doses of gamma radiation that would normally be sufficient to trigger the p53-induced apoptosis.

The scientists found that drugs or radiation increased the amount of p53 in normal cells, but not in the Chk2-deficient cells. Reintroducing the Chk2 gene, however, increased p53 levels in these cells.

In test tube studies, the scientists also showed how the Chk2 enzyme could maintain p53 activation by attaching a phosphate to a particular area on the p53 protein. The addition of this phosphate protects p53 from destruction by another regulatory enzyme, thereby keeping the cell cycle shut down, said Elledge. Chk2 is a type of enzyme known as a kinase, which triggers the action of other proteins by adding phosphates to them.

"These studies showed that Chk2 is a strong regulator of p53, and is among its most important regulators," said Elledge. "There is also clinical evidence that it has a role in cancer because two cancer-prone families have recently been found that show a familial mutation in the *Chk2* gene. The cancer in those families strongly resembles those caused by mutations in p53."

While loss of Chk2 function likely contributes to a wide range of cancers, said Elledge, it is not likely to be as powerful a cancer promoter as loss of p53.

"While they are equally effective as tumor suppressors, the genetic properties of p53 make its loss more likely to generate tumors," said Elledge. "There are certain types of *p53* mutation in one of the two copies of the gene that will cause the mutant gene to interfere with the normal gene and promote tumor formation. *Chk2* behaves more like a classical tumor suppressor.

"Thus, *Chk2* may play an important role in inherited cancers in which both genes are mutated, while *p53* will also be particularly important in spontaneous tumors, in which loss of one gene interferes with the good gene and causes aggressive tumor growth," said Elledge.

But, Elledge added, Chk2's role in responding to DNA damage is not limited to controlling p53. "Cells from tumors that show loss of *Chk2* may have new vulnerabilities not present in tumors that have mutations in *p53*," he said. "We may be able to exploit that vulnerability to selectively kill those cancers."