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Cell Death Protein Hampers Effectiveness of Cancer Drug

Human colon cancer cells that lack a specific programmed cell death trigger can avoid being killed by a drug that is widely used to prevent the development of colon cancer. The finding suggests that drug therapy aimed at preventing cancer might be improved by taking into consideration the ability of cancer cells to produce mutations that shut down normal cell death pathways.

"These studies provide one of the first good clues that a single gene can completely control the effect of chemopreventive agents in a human cancer cell," said [Bert Vogelstein](#), a Howard Hughes Medical Institute investigator at The Johns Hopkins University Oncology Center. "This finding implies that multiple cancer-preventive drugs will likely be a strategy of choice in chemoprevention, especially in tumors that are highly mutable," he said.

In an article published in the November 3, 2000, issue of the journal *Science*, Vogelstein and his colleagues at Hopkins showed that knocking out the *Bax* gene in colon cancer cells causes those cells to become completely resistant to standard doses of sulindac, a non-steroidal anti-inflammatory drug (NSAID) that helps prevent colon polyps from becoming cancerous.

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"We have never seen as dramatic and profound an effect as this total resistance to sulindac generated by knocking out a single gene," said Vogelstein. "We saw complete resistance, both to the death-promoting effect

of the drug and to its long-term growth-inhibiting effects. When we have looked at the effects of knocking out other genes in these same cells, we have seen only an attenuation of the response."

According to Vogelstein, the findings were a surprise because previous studies did not indicate that deleting BAX would protect colorectal epithelial cells against programmed cell death, which is also called apoptosis. This may have been because the studies were done in mouse cells, while the new studies were performed in human cells

Vogelstein's team approached the problem using human cancer cells to explore the apoptotic response of knockout cells to the chemotherapeutic compound 5-fluorouracil. The cells used in the experiment were colorectal cancer cells that are commonly used for gene knockout studies. The scientists used three different methods to disrupt the *Bax* genes in the cancer cells, to demonstrate rigorously that BAX deficiency was responsible for making the cells resistant to sulindac.

Additional experiments revealed that altering the ratio of the pro-apoptotic BAX and an anti-apoptotic protein known as Bcl-X_L generated resistance to sulindac. "For years it has been known that the ratio of pro- and anti-apoptotic members of this family of genes can be a controlling factor in apoptosis," said Vogelstein. "We now have found that these NSAIDs don't affect BAX expression; they simply reduce the expression of Bcl-X_L. When normal cells are treated with these drugs, the ratio of BAX to Bcl-X_L goes up and they die. But if you've knocked out the *Bax* gene, then the ratio is zero, and no matter whether the Bcl-X_L goes down or not, the cells live."

Vogelstein said that this kind of detailed understanding of cancer cell responses to cancer-preventive drugs is important if chemopreventive strategies are to be successful. "So far, the amount of effort, whether measured in hours or dollars spent is perhaps a million-fold more for cancer therapy than for preventive approaches," he said. "Many researchers are now beginning to believe that it is at least as reasonable, and perhaps more so, to try to identify ways to prevent cancer. But we must make a substantial effort to understand why the few known chemopreventive agents work."