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Study says normal but out-of-control enzyme may be culprit that signals some cells to become cancer

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Working with human colorectal cancer cells, a University of Minnesota team, led by cancer biologists Zigang Dong and Ann Bode, has found the potential culprit among a network of enzymes that relay signals inside cells to regulate such functions as cell growth, cancer development and programmed cell death. The work suggests that drugs designed to disable the enzyme, known as TOPK, could have anti-cancer benefits. The study appears in the July issue of the journal *Gastroenterology*.

“Colorectal [cancer] is the second leading cause of cancer mortality, and the molecular pathways [by which it develops] remain incompletely understood,” said Dong, a McKnight Presidential Professor in cancer prevention and director of the university’s Hormel Institute in Austin, Minn. “In this study, we provided evidence showing that TOPK promotes transformation [of normal cells to cancerous ones] in colorectal carcinoma.”

The story begins with the frequent observation by researchers that members of this enzyme network are overactive in the cells of several human cancers. The function of all these enzymes is to activate other enzymes and proteins, which makes them ideal for passing along signals.

For example, a cancer-causing agent or a hormone may find its way from the bloodstream to the outer membrane of a cell. After its arrival, it sets off a chain of reactions, or signals, inside the cell. Some of these

signals take the form of certain enzymes activating others. Eventually, the “news” reaches the genetic material inside the cell nucleus, where changes resulting in uncontrolled growth--cancer--or some other cell behavior are made.

It was thought that some form of an enzyme called MEK, which belongs to the family of signaling enzymes, was the culprit. But to cause cancer, an enzyme or other agent is expected to be active all the time, like a light with no off switch. MEK, however, is never active all the time in nature; only if kept artificially active can it lead to cancer. Therefore, researchers theorized that a related enzyme was activating others in the network and keeping the signaling process going.

Dong and his colleagues examined the role of TOPK. This enzyme is not very active in normal tissues, but it is quite active in cancerous cells taken from blood, breast, prostate and colorectal tumors, among others. The onset of cancer could trigger the permanent turning-on of TOPK. One piece of evidence for this is that while TOPK is similar to MEK in structure, TOPK has features that suggest it is easier to keep turned on all the time.

The team performed several experiments to determine whether high TOPK activity could lead to cancer.

- When they engineered mouse skin cells to produce excessive amounts of the enzyme and then injected the cells into other mice, those mice developed tumors. Control mice had none.
    - After they had “silenced” the gene for TOPK in human colorectal cancer cells, growth of the cells was significantly slowed compared to control colorectal cancer cells.
        - The researchers also found that TOPK and a related enzyme (not MEK) activated each other in

growing human colorectal cancer cells.

Taken together, these and other findings suggested that TOPK is, in effect, the key cancer-causing member of the network for which researchers have been searching, Dong said. Also, the fact that TOPK seems active mainly in cancer cells--not normal ones--means it could make a good target for chemotherapy.

How TOPK gets turned on is not known, but it appears to happen as a result of abnormal activity in cells that stems from genetic mutations in certain well-known genes. Such genes, called oncogenes, generally don't cause any trouble until mutations occur in them.

Source: University of Minnesota