

## Do suicidal cells prevent colon cancer?

Cancer may kill, but its deadliness depends upon the ability to keep alive the dividing cells that feed its malignant growth. It's not surprising, then, that cancer cells often have mutations that prevent them from undergoing apoptosis, a form of cellular suicide.

Beyond their role in sustaining tumors, mutations that hinder apoptosis may initiate certain cancers. A new report suggests that precancerous polyps form in the colon because defects in a gene called *APC* stop the cells that line the colon from dying when they should.

"It's the first link between *APC* and programmed cell death," says Patrice J. Morin, an author of the report.

Investigators discovered *APC* while studying familial adenomatous polyposis (FAP). People with this rare inherited disorder commonly have thousands of polyps lining their colon. Because the polyps frequently progress to cancer, some FAP patients resort to having their colon removed as a preventive measure.

In 1991, researchers announced that people with FAP inherit a mutation in one of their two *APC* genes (SN: 8/10/91, p. 86). When mutations strike their second *APC* gene, cells in the colon can turn into polyps. The tumors of people struck at random by colon cancer almost always have *APC* mutations.

What does *APC* do in the cell that is so important? It encodes a protein that cells need to undergo apoptosis, contends Morin of the Howard Hughes Medical Institute at John Hopkins Medical Institutions in Baltimore. Morin, along with Hopkins colleagues Bert Vogelstein and Kenneth W. Kinzler, presents evidence supporting that assertion in the July 23 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

The researchers introduced functioning versions of *APC* into some colon cancer cells growing in petri dishes. These cells normally lack *APC*, the gene's protein, because both of their copies of the gene are mutated. The colon cancer cells making *APC* did not proliferate as quickly as the unaltered cancer cells. On a closer look, the investigators discovered that the cancer cells making *APC* were undergoing apoptosis.

Combining that discovery with recent research showing that *APC* turns on in colon cells only when they near the inner surface of the colon, the researchers offer a possible role for the gene's protein.

Like the skin, the inner lining of the colon is self-renewing. The oldest layers are continuously sloughed off and replaced by newer cells. As a cell nears the surface of the lining, it may synthesize *APC* in order to commit suicide, say the investigators. If the gene is mutated, however, the cell doesn't die and can form a polyp that may turn cancerous.

Linking *APC* to apoptosis may help explain the apparent ability of aspirin, ibuprofen, and similar drugs to prevent the formation of polyps and thus ward off colon cancer (SN 9/9/95, p. 165). Known collectively as nonsteroidal anti-inflammatory drugs, recent research indicates that they induce colon cells to undergo apoptosis. In effect, says Morin, they may substitute for *APC*.

The new findings, says David E. Fisher of the Dana Farber Cancer Institute in Boston, "suggest *APC* plays a role in life-death decisions. It's a very enticing result, but there's a lot more to do with this observation in terms of verifying the mechanism by which this happens."

The gene's role in apoptosis may simply be that its protein transmits the complex signal to commit suicide. Another molecule that may be involved in that death signal is beta-catenin, to which *APC* binds tightly.

Yet investigators caution that *APC* probably does more than command cells to die. "*APC* is an enormous protein. It has the potential to interact with many other proteins in a cell," notes Jeffrey I. Gordon of the Washington University School of Medicine in St. Louis, who suggests that *APC*'s interactions may also influence cell proliferation and migration.

— J. Travis