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New function for colon cancer gene found

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Dartmouth Medical School geneticists have discovered a striking turnabout role for a gatekeeper known to put on the brakes for colon cancer. Flaws in a gene called adenomatous polyposis coli (APC), which normally prevents excessive cell growth, are thought to trigger development of most colorectal cancers.

But in an about face, the tumor suppressor gene also has a second task, the researchers found, as a gas pedal that accelerates signaling between cells. This novel duality is reported in the January 18 issue of *Science* by a team led by Dr. Yashi Ahmed, assistant professor of genetics at DMS.

“Colon cancer is the second most frequent cause of cancer-related death in the United States,” said Ahmed. “Understanding the normal role of APC and what’s happening to cells that have lost the gene can help us identify therapeutic targets for drug action against this common cancer.”

APC was first identified in families with a hereditary predisposition to develop colon cancer. Family members are born with an error in one of their two APC gene copies, but are fine as long as the other gene copy is normal. However, many of their colon cells develop a second defective gene. As a result, by their teens and twenties these individuals get hundreds to thousands of colon growths--called polyps--some of which invariably progress to cancer, so their colon is usually removed when they are in their twenties.

But these types of polyps that have a strong association with cancer are not limited to hereditary colon cancer. By age 60, according to Ahmed,

up to 40 percent of the general population will have at least one such polyp with mutations in both APC genes. Fortunately, with a colonoscopy to view the colon many polyps can be removed in their early stages, before they become cancer.

APC is part of a vital signaling pathway that coordinates cell growth in all animals—from flies through people. During embryonic development, this pathway causes cells to grow and differentiate to become the kind of cells they should be. In many adult cells, however, the pathway should be turned off, and APC puts the brakes on the pathway to stop cell growth.

The researchers devised strategies to explore the molecular workings of APC in the fruit fly, a simple animal with rapid breeding time that offers many advantages in the laboratory. When they remove or reduce APC, they see fruit flies with no wings, peculiar abdomens and many other oddities.

However, APC defects found in colonic polyps have an unusual feature. Generally, gene mutations can disrupt an entire protein, but in colon cancers, only half the APC protein is lost, while the other half remains, Ahmed explains. Her work in fruit flies suggests a reason for this unexplained phenomenon.

“We found that APC has a second, new job. It not only puts the brake on cell signaling, but also gives some gas. These two functions are controlled by different parts of the protein. In the colon cancers, the brake part of the APC protein is lost, but there is strong pressure to retain the give-it-some-gas portion,” Ahmed said.

Indeed, the DMS team’s data suggest that this new “gas” facet is also present in the human APC protein, reinforcing APC’s role as a regulator that promotes or suppresses cell growth. Future studies on how APC balances signals may help benefit treatments not only for colon tumors,

but also for birth defects, since the signaling pathway regulated by APC affects nearly all tissues during development.

Source: Dartmouth Medical School