JON GILBERT FOX

Yashi Ahmed, center—with postdocs Hassina Benchabane, left, and Carter Takacs, right—study fruit fly genes.

Tumor suppressor gene has a dual role

The molecular mesh of a fruit fly's eye has given DMS geneticists new insight into a gene long known for putting the brakes on colon cancer. While it normally slows down or stops excessive cell growth, this gene—adenomatous polyposis coli (APC)—turns out to also step on the gas, firing up other genes to increase signaling between cells.

Accelerator: APC's accelerator function, according to Yashi Ahmed, M.D., Ph.D., may contribute to the development of colorectal cancers. Her team's findings were published in the January 18 issue of the prestigious journal *Science*.

The APC gene was first identified in families with a hereditary predisposition to having colon cancer. But colonic polyps that may become malignant do not occur only in those suspectible to hereditary colorectal cancer. According to Ahmed, 40% of the U.S. populace will, by age 60, develop colon polyps that exhibit mutations in both of the human APC genes. And that can lead to cell overgrowth and colon cancer.

APC is part of a signaling pathway that communicates to cells what their next step should be—whether to grow, divide, stop dividing, or die. From the time a human embryo is formed through childhood and adolescence, the pathway is turned on so that cells can grow. But in most adult cells, APC puts the brakes on the pathway to stop cell growth. Both the pathway and APC are virtually the same in all animals, from humans to frogs to worms—to the fruit fly *Drosophila*, which the DMS team has used as its model organism. "The beauty of this is you can look at this signaling pathway in a living organism as opposed to something that is very far removed," says Ahmed.

The researchers knew about APC's role as a brake—Ahmed had played a part in identifying that function in the late 1990s. So they decided to study the fly's whole genome, looking at the organism's various body parts to figure out which genes were crucial for activating the pathway and how that occurred.

"The last thing we expected to find was APC," says Ahmed.

Mutated: A fruit fly has a compound eye with 800 parts called "unit eyes." Within each unit eye are retinal neuron cells that detect light. The fly has two copies of the APC gene: APC1 and APC2. The team isolated flies with an APC1 gene that was mutated and no longer able to function as a brake. With APC1 disabled, the signal pathway was turned up too high in the retinal neuron cells, so all those cells died and the flies became blind. The researchers then took similar APC1 mutant flies and reduced the level of APC2. To their surprise, the flies did not go blind. This meant APC2 didn't act as a brake but kept the signal pathway turned on.

"That was a big shock," says Ahmed. "We were just looking in the whole genome for genes that are important for activation of the pathway, and the last thing we expected to find was APC."

As a check, the researchers reduced the level of APC in flies with different APC mutations. They found that flies with lower levels of APC grew only one wing instead of two. Other flies had abdomens with less shiny surfaces and bristles with an abnormal, coarse look. So in the wings and abdomen, it was clear that APC was important for normal development, while in the eyes APC could contribute to too much signaling.

Genes: The team then determined that APC controls another protein called beta-catenin, a transcriptional activator that turns on specific target genes in the pathway. APC's job is to keep "beta-catenin levels in just the right window so it doesn't get to be too much or too little," says Ahmed. "The established role of APC is to prevent too much signaling," adds Carter Takacs, a postdoctoral fellow and the lead author of the study. "Now we've shown that in some context, APC is actually important for promoting signaling. So it's this yin and yang."

The team's recent findings suggest that APC's accelerator function is present in human colon cancer as well. "When you look at a colon tumor, you nearly always find that a piece of APC is still present," says Ahmed. "And that suggests to people that you need that piece of APC to get the tumor, maintain it, and allow it to grow."

Now the trick will be to figure out a way to turn that knowledge to putting the brakes on the tumor. MATTHEW C. WIENCKE