'One-hit' event provides new opportunity for colon cancer prevention, say Fox Chase researchers

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More than 30 years ago, Alfred Knudson Jr., M.D., Ph.D., revolutionized the field of cancer genetics by showing that a person must lose both their paternal and maternal copies of a particular class of cancer-inhibiting genes, called tumor-suppressor genes, in order to develop cancer. This theory, called the two-hit hypothesis, guided scientists around the globe in their quest for tumor suppressor genes.

Now Knudson, a Fox Chase Cancer Center Distinguished Scientist and senior advisor to the Center president, and colleagues offer evidence that a "one-hit" event is enough to change the cells and increase the likelihood they would become cancerous.

By studying people who have inherited the first hit in every cell in the body, the Fox Chase researchers believe they may have discovered a source for some of the earliest known molecular changes that signal the presence of colorectal cancer, the second leading cause of cancer-related death in the United States. Their findings are presented in the September 15 issue of the journal Cancer Research.

"We hypothesized that an inherited one-hit gene mutation can, by itself, lead to changes in the proteins of normal-looking cells" says Anthony Yeung, Ph.D., lead author of the paper and a tenured member of the Fox Chase scientific staff. "While these cells are just another hit away from becoming cancerous, their altered patterns of protein production may

represent new biomarkers of cancer and novel targets for preventive and therapeutic drugs – a chance to strike at cancer before a second hit can happen."

The Fox Chase researchers studied patients with familial adenomatous polyposis (FAP), an inherited disorder that also serves as a classic model in support of the two-hit hypothesis. Patients with FAP, which predisposes people to colon cancer, carry mutations in one of their two copies of the adenomatous polyposis coli (APC) tumor-suppressor gene. The APC gene acts to prevent the colon cells from growing out of control and becoming cancerous. The APC gene is also mutated in most cases of sporadic colorectal cancer.

According to Yeung, the proteome, the sum total of proteins a cell will create from the genome, offers an insight into the physical state of cells. "We see that a single hit, in this case an inherited mutation, can have many repercussions within the entire cell even if it doesn't cause cancer itself," Yeung says. "The 'one-hit' event makes a second mutation that much more likely to push the cell over the edge into cancer."

This is the first time the human colon proteome has been characterized to this depth, made possible by samples of high quality and purity donated by research participants. Approximately 13 percent of 1,695 identified proteins were abnormally produced in the colon of APC mutation carriers, indicating that a colon cell under the one-hit state is already abnormal. Many of the changes affect molecular pathways consistent with the function of the APC protein as a tumor suppressor, including how the cell moves, interacts with other cells, divides, responds to free radical damage and, ultimately, self-destructs when growth threatens to go out of control.

"The two-hit hypothesis is applicable to most cancers because there are hundreds of tumor-suppressor genes," Yeung says. "The knowledge

acquired in this study on the proteome of precancerous one-hit cells could be an opportunity to devise rational strategies, based on drugs or dietary changes, that may delay a second hit from occurring and thus prevent cancer from happening entirely."

Source: Fox Chase Cancer Center