Different drug combinations work best for prevention versus treatment of colorectal tumors

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Colorectal cancer is the second leading cause of cancer-related deaths in the United States. Once colorectal cancer has spread to other parts of the body, only 11 percent of patients will survive five years from the date of their diagnosis. Most colorectal cancers are adenocarcinomas—cancers that begin in cells that make and release mucus and other fluids. Adenocarcinomas begin as benign tumors called adenomas, which become malignant over time. By treating adenomas before they become cancerous, it could be possible to prevent colorectal cancer.

Researchers at Fox Chase Cancer Center have tested the effectiveness of two promising drugs in preventing and treating colorectal adenomas in mice. A team led by Wen-Chi Chang, PhD, assistant research professor at Fox Chase, found that the effect of these drugs, which have already been approved by the Food and Drug Administration for the treatment of other conditions, depends on whether adenomas are present when drug treatment begins. Chang will present these findings at the AACR Annual Meeting 2013 on Sunday, April 7.

"We often get focused on either the preventive or therapeutic setting and don't think about how these drugs are maybe serving more than one purpose," says senior author on the study Margie L. Clapper, PhD, co-leader of the Cancer Prevention and Control Program at Fox Chase. "The most exciting thing for us was to be able to track these tumors and for the first time distinguish between prevention and chemotherapy, and

to show that one agent is maybe effective in both settings if used appropriately, or in this case, in combination with another agent."

Past studies in animals have shown that colorectal tumors can be suppressed by combined treatment with two drugs: a non-steroidal anti-inflammatory compound called sulindac and a cholesterol-lowering medication called atorvastatin—whose brand name is Lipitor. But in those studies, tumors were induced in an unnatural way—through exposure to carcinogenic chemicals—whereas in humans, cancer often has genetic origins.

To evaluate the effectiveness of sulindac and atorvastatin in an animal model more relevant to humans, Chang, Clapper and their colleagues used a unique mouse that had genetic alterations that cause them to develop multiple colorectal adenomas, without exposure to carcinogens. "No one had previously tested the effectiveness of this drug combination against colorectal cancer originating from alterations in the genome," Clapper says. "In some ways, using this type of preclinical tumor model represents a new paradigm for doing prevention studies and therapeutic studies."

In the new study, the researchers treated the mice with either drug alone or in combination for 100 days and used colonoscopic examinations to evaluate the presence and size of tumors before and after treatment. In mice that had tumors prior to treatment, only combination therapy reduced the number of adenomas in the colon by the end of the treatment period.

The results were strikingly different in mice that were tumor-free when treatment began. In these mice, exposure to atorvastatin alone or in combination with sulindac resulted in about a three-fold increase in the percentage of mice that were tumor-free by the end of the treatment period. Among these mice, 44 percent of those treated with atorvastatin

alone and 30 percent of those treated with both drugs did not develop tumors, compared with 13 percent of mice that received no treatment and nine percent that received sulindac alone. Moreover, atorvastatin treatment completely inhibited the formation of microscopic adenomas in these mice.

The findings demonstrate that the effectiveness of the two drugs at preventing and treating colorectal adenomas depends on whether tumors are present prior to the onset of treatment. "Based on this study, we're able to say that if you don't have a tumor to begin with, maybe Lipitor is best, but if you do have a tumor to begin with, you need the combination therapy," Chang says. "We can start to tailor clinical care based upon the disease state as well as the establishment of tumors."

Moving forward, the researchers plan to study the specific genetic alterations in this particular mouse model, with the goal of identifying molecular pathways that could be targeted with therapies.

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