

## Scientists identify a gene that may suppress colorectal cancer

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In today's online edition of *Genome Research*, a husband-and-wife research team from Thomas Jefferson University report the discovery of a gene that, when mutated, may suppress colorectal cancer. To conduct the study, the researchers used a strain of mice that develop polyps, or small growths of tissue, in the digestive tract—the harbingers of cancer. When these mice possessed one copy of the mutated gene, the incidence of small intestinal and colon polyps were reduced by about 90%.

"This gene may give us a novel target to aid in the diagnosis, prevention, and/or treatment of cancer," says Dr. Arthur Buchberg, one of the cosenior authors on the report.

The gene is called *Atp5a1*, and encodes an essential component of the cell's energy-production machinery. Mice with two copies of mutated *Atp5a1* die early in embryonic development—probably due to insufficient energy. The identification of a gene critical for energy production in the cell opens up an array of potential new targets for therapy.

The research team identified a duplication of DNA—only four bases in length—in a critical part of the *Atp5a1* gene. This mutation, which results in decreased levels of *Atp5a1* gene expression, is the first mutation identified in the mouse *Atp5a1* gene. In trypanosomes (tiny parasitic protozoa that cause African sleeping sickness), the loss of *Atp5a1* gene function leads to death. To date, no mutations in the human *ATP5A1* gene have been identified—further supporting its essential role



in the cell.

"In humans, *ATP5A1* is located on chromosome 18, in a region that often exhibits genetic alterations in colon tumors," says Dr. Linda Siracusa, the other co-senior investigator on the project. "A better understanding of the biological function of *ATP5A1* will provide insights concerning its potential role in human cancer."

Colorectal cancer is currently ranked as the second leading cause of cancer death in the United States. But scientific progress in cancer research is challenged by the array of environmental and genetic influences on tumor initiation, development, and progression in the human population. Therefore, scientists have turned to mouse models, which have nearly identical genetic backgrounds and are housed in controlled conditions.

The scientists used a strain of mice called Min (multiple intestinal neoplasia). Min mice carry mutations in the Apc gene, which causes the development of intestinal tumors. Inactivation of the corresponding gene (*APC*) in humans is considered a key event in the development of colorectal cancer.

Tumor development is regulated by modifier genes, which may function to enhance or suppress tumor initiation, growth and/or progression. *Atp5a1* is a modifier gene, and it is located on the same chromosome as *Apc* in mice. Interestingly, the results suggest that the mutant *Atp5a1* gene caused the death of tumor cells, primarily when it was present on the same chromosome as the mutant *Apc* gene.

Source: Cold Spring Harbor Laboratory



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