Mechanism for esophageal cancer uncovered

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A gene thought to be associated with cancer development can be a tumor suppressor gene in mice, researchers have discovered. Understanding which genes are involved in spreading cancer could lead to future therapies.

"For cancer to spread, some genes are activated, while others that would prevent cancer growth are prevented from doing their jobs. The cancer research community has thought that the gene p120, falls into the latter category," said Douglas Stairs, Ph.D., assistant professor of pathology, who completed this research at University of Pennsylvania and is now at Penn State College of Medicine. "In this research, the loss of the p120 gene led to the development of cancer."

Stairs worked with colleagues at Vanderbilt University to create a mouse model to study the gene. Called a knockout mouse, these specially bred mice do not have the p120 gene in their mouths and esophagi. Researchers then studied the mice to see if tumors formed in those areas. In 70 percent of p120 knockout mice, tumors formed.

Researchers observed that mice that had cancer had hyperactivated immune systems. Absence of p120 led to the production of immune cells that are pro-tumor generating and pro-cancer forming.

"For cancer, the immune system can both help and hurt the body," Stairs said. "Some immune cells help the body get rid of the cancer cells, while other immune cells help tumors to form. When p120 was absent, tumor promotion through the immune system was activated. The mice

produced the bad types of immune cells." The researchers published their results in the journal *Cancer Cell*.

Researchers learned through further investigation that these "bad" immune cells traveled to the esophagus and improperly activated fibroblasts. Fibroblasts are cells that create the support structure for tissues. They are most noticeably activated when tissue damage occurs and scarring is a result of the fibroblast cells activating. Fibroblasts are also activated in cancer patients.

By improperly activating the fibroblasts, the immune cells were able to stay active longer than normal.

"Each feeds off the other," Stairs said. "It creates an environment that is very permissive for cancer development."
Stairs is now working to identify which proteins are used to communicate between tumor cells and other cells in the tumor microenvironment -- the immune cells and fibroblasts. He aims to discover how cells that lose p120 interact with the immune system, which, in turn, interacts with the fibroblasts. "Once we know that," he said, "we can then potentially develop a strategy to break those relationships -- a therapy."

The creation of the p120 knockout mouse will also help other researchers, providing a model for esophageal cancer that did not exist before.

Provided by Pennsylvania State University

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