Scientists link two cancer-promoting pathways in esophageal cancer

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Identification of a non-traditional pathway for spiriting a cancer-promoting protein into the cell nucleus points to a possible combination therapy for esophageal cancer and indicates a mechanism of resistance for new drugs that attack the Hedgehog pathway.

A team of researchers at The University of Texas MD Anderson Cancer Center reports in the March 20 *Cancer Cell* that the mTOR molecular pathway promotes the activity of the Gli1 protein in esophageal cancer development and progression.

"The Hedgehog pathway is the established, or canonical, pathway for activating Gli1. We've shown a clear-cut mechanism to link all non-canonical activation of Gli1 through a single pathway, TOR," said senior author Mien-Chie Hung, Ph.D., vice president for basic research, professor and chair of MD Anderson's Department of Molecular and Cellular Oncology.

"Crosstalk between these two pathways is a challenge, but our experiments showed a combination of the mTOR inhibitor RAD-001 (Everolimus®) and the Hedgehog inhibitor GDC-0449 (Erivedge) steeply reduced the tumor burden in a mouse model of esophageal adenocarcinoma," Hung said.

Both drugs have been approved by the U.S. Food and Drug Administration for use in other types of cancer.

Both pathways active in aggressive human cancer

An analysis of 107 tissue samples of human esophageal cancer tumors showed that 80 (74.8 percent) had a marker of mTOR promotion of Gli1 and 87 (81.3 percent) had the version of Gli1 activated by Hedgehog.

Esophageal cancer is one of the most aggressive forms of cancer, with fewer than 20 percent of patients surviving for five years, the study notes. And it has become more frequent in the United States by 5 to 10 percent annually since the 1980s. Inflammation and obesity are thought to be driving factors in this increased incidence, Hung said.

The researchers used experiments with cell lines, mouse models and human tumor samples to demonstrate how Hedgehog and mTOR, both implicated in esophageal and a variety of cancers, converge on Gli1.

Slipping Gli1 into the nucleus

Gli1 is a transcription factor - a protein that moves into the cell nucleus where it binds to and activates other genes. Gli1 normally is held out of the nucleus by a protein called SuFu, which binds to it at a specific region.

Hung said the Hedgehog pathway frees Gli1 by activating a signaling protein called Smoothened (SMO), which blocks SuFu binding, allowing Gli1 to move into the nucleus and activate a variety of genes, including Hedgehog activators.

GDC-0449, approved in January by the FDA for treatment of metastatic basal cell carcinoma, inhibits SMO. Basal cell carcinoma is driven by mutations in the Hedgehog pathway, Hung said, but resistance to SMO inhibitors has emerged in clinical trials to treat other cancers, such as ovarian and pancreas.

"We now believe the mTOR pathway is one source of this resistance," Hung said.

How mTOR helps Gli1

Hung and colleagues started with Tumor Necrosis Factor Alpha (TNFa), an inflammatory protein connected to development of esophageal cancer. In a series of experiments, they found that TNFa

triggers Gli1 through the mTOR pathway by:

- Activating the kinase S6K1, which attaches a phosphate group to Gli1 rendering the phosphorylated Gli1 unable to bind to SuFu.
- With SuFu thwarted, the phosphorylated version of Gli1 moves into the nucleus and activates genes.

The team developed an antibody to identify the presence of phosphorylated Gli1, providing a possible biomarker of cancer resistant to Hedgehog inhibitors, Hung said.

The team treated mice with esophageal cancer with RAD-001, GDC-0449 or both. The mTOR inhibitor RAD-001 alone had almost no effect. The Hedgehog inhibitor GDC-0449 alone reduced tumor volume by 40 percent. Together, they reduced tumor volume by 90 percent.

Clinical trials of the combination for esophageal and other cancers could be guided by the antibody for phosphorylated Gli1 and the presence of plain Gli1, Hung said, which would indicate a need to use both drugs.

Earlier research by other labs indicates that the AKT and MAPK/ERK also activate the Hedgehog pathway. Hung and colleagues show that AKT and ERK, which both activate the mTOR pathway, appear to activate Gli1 via phosphorylation of S6K1 and Gli1.

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