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Cross Talk Between Oncogenes Suggests Treatment Combination in Esophageal Cancer

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(PhysOrg.com) -- Using a three-dimensional tissue culture system that mimics esophageal tissue growth of the particularly aggressive type of tumors known as ESCC (esophageal squamous cell cancer), Penn researchers have discovered molecular cross talk between two oncogenes and the tumor suppressor gene p53. The results highlight a targeted therapy that may hold promise for treating ESCC.

Esophageal squamous cell cancer (ESCC) is a particularly aggressive form of disease and is often metastatic at diagnosis. ESCC is a prototype of squamous cell cancers, which are the most common form of epithelial cancers. Using a three-dimensional (3-D) tissue culture system that mimics esophageal tissue growth, Anil K. Rustgi, MD, chief of Gastroenterology at the University of Pennsylvania School of Medicine, and colleagues have discovered molecular cross talk between the oncogene Met, which is overexpressed in the majority of these tumors; the epidermal growth factor receptor (EGFR) oncogene; and the tumor suppressor gene p53. The results highlight a targeted therapy that may hold promise for treating ESCC.

Using the 3-D culture system, the team identified a sequence of events that may lead to tumor formation and progression in this type of esophageal cancer. They hypothesized that a mutation in the p53 gene and overexpression of EGFR lead to tumor initiation and the start of tumor invasion by triggering expression of the Met protein. Once tumor

cells invade the surrounding tissue, signals secreted by neighboring non-cancerous cells further activate the Met receptor, which in turn stimulates more growth and invasion. Consistent with this model, Rustgi and colleagues find that inhibitors of Met activity in their 3-D system prevent this pattern of tumor invasion.

Those data, which the team presented on Sunday afternoon, April 18th at the American Association of Cancer Research meeting, suggest that treating patients with an EGFR inhibitor and a Met inhibitor may be more effective than treating them with just one inhibitor at a time. Also, the newly uncovered interaction between these key cancer-promoting genes may occur in other cancers and may suggest ways to improve targeted therapy combinations, Rustgi says. He discussed the development and use of the 3-D model system in a session on Saturday, April 17th.

“There has been a notion of an interrelationship between Met and EGFR oncogenes, and this work reveals also a potential link between Met and the p53 mutation,” Rustgi says. Specifically, Rustgi's team found that genetic changes or drugs that inhibit the Met receptor in epithelial cells or its binding partner, hepatocyte growth factor (HGF), block ESCC invasion. Additionally, Met activation increases when a cell overexpresses EGFR and has a mutated copy of p53, both of which are common genetic mutations in ESCC. "These results highlight the potential benefit of the therapeutic targeting of HGF/Met signaling in esophageal squamous cell cancer and potentially other squamous cancers where this pathway is deregulated."

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