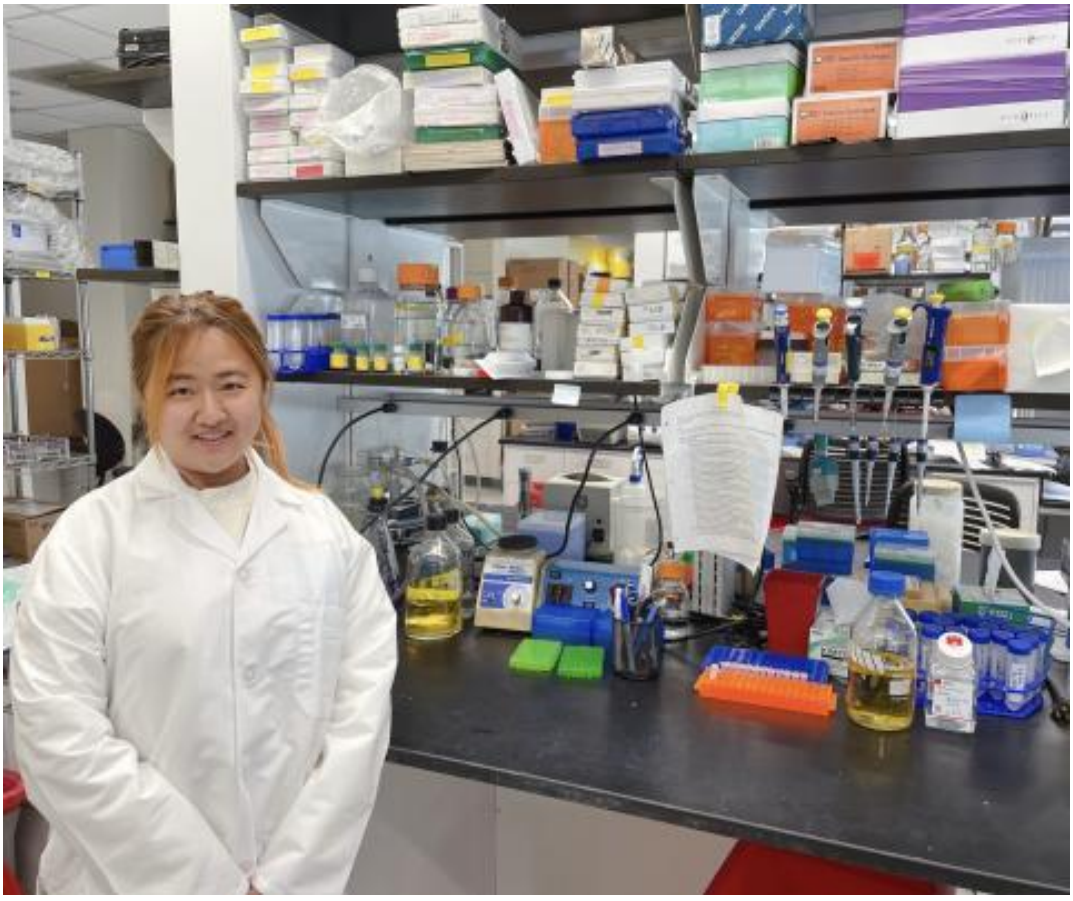
Columbia University
Herbert Irving Comprehensive
Cancer Center

A New Potential Therapeutic Target for Metastatic Esophageal Cancer



Qiaosi Tang, PhD, is a graduate student in Dr. Anil Rustgi's lab at Columbia and lead author on the study.

Researchers have found a new potential therapeutic target for lung metastasis of esophageal squamous cell carcinoma (ESCC). A recent study led by researchers at the Herbert Irving Comprehensive Cancer Center elucidates the role of the BIRC-5 gene and Survivin, the protein it encodes, in metastasis of ESCC, as well as potentially other Survivin-dependent cancers such as pancreatic adenocarcinoma (PDAC) and colorectal cancer.

A potential treatment for ESCC and beyond

Esophageal cancer is a highly aggressive cancer that affects nearly 570,000 people worldwide each year. The most common subtype of esophageal cancer is esophageal squamous cell carcinoma (ESCC), which typically has a poor prognosis. Many cases of ESCC are not detected until late stages, after the cancer has already metastasized, or spread, most often into the lungs.

“Unfortunately, the treatment options for metastatic ESCC have not significantly advanced in the past twenty years, although advances in immunotherapy are promising,” says Anil Rustgi, MD, director of the Herbert Irving Comprehensive Cancer Center and senior author on the paper. “Our study provides insights into new potential therapeutic targets that could hopefully build on those promising advances.”

In the study, recently published in *Genes and Development*, the researchers identified a pathway through which metastasis of ESCC is regulated by mutant p53, the most common genetic alteration in ESCC. P53 is also the most frequently mutated gene across all cancers, giving the researchers’ findings a potential broad application across a number of different cancers.


Dr. Anil K. Rustgi, director of the Herbert Irving Comprehensive Cancer Center (Photo: Barbara Alper)

Survivin is critical in GI cancer metastasis

Using mouse models, the researchers found that BIRC-5, a gene that encodes the anti-apoptic protein Survivin, is highly enriched in mutant p53 ESCC cells. Further tests showed that mutant p53 binds to YAP (Yes-associated protein), a transcriptional regulator, increasing binding to the BIRC-5 promoter and turning on the expression of Survivin. Survivin is a key regulator of mitosis and programmed cell death, which allows cancer cells to proliferate.

The researchers found that Survivin is upregulated – or expressed at a higher rate – not only in metastatic ESCC, but also in metastatic pancreatic and colon cancer. This is the first study to provide evidence of the role of Survivin in tumor metastasis and to identify mutant p53 as a key of part in regulating Survivin expression.

"These findings are exciting because current therapies for ESCC – chemotherapy, radiotherapy, surgery – may not be as effective in metastatic lesions," says Qiaosi Tang, PhD, a graduate student in Dr. Rustgi's lab and lead author on the paper. "Targeting Survivin could be an effective therapy for both primary and metastatic ESCC, as well as other cancers like pancreatic adenocarcinoma and colorectal cancer."

What's next

The researchers are looking to advance their findings into a preclinical study, testing the effectiveness of several compounds in modulating Survivin. Currently, there are a number of Survivin-targeting therapeutic approaches in various stages of development, including RNAi, antisense small nucleotides (ASO), small molecular inhibitors, and peptide vaccines. In addition to testing some of these existing compounds, the researchers will look to test a YAP inhibitor, as well as potentially develop a novel compound targeting Survivin.

The study is titled "Mutant p53 regulates Survivin to foster lung metastasis."

Other contributors (all at Columbia unless otherwise noted): Gizem Efe, Anna M. Chiarella, Jessica Leung (The Wistar Institute), Maoting Chen, Taiji Yamazoe (Abramson Cancer Center), Zhenyi Su, Jason R. Pitarresi (Abramson Cancer Center), Jinyang Li (Abramson Cancer Center), Mirazul Islam (Vanderbilt University), Tatiana Karakasheva (Abramson Cancer Center), Andres J. Klein-Szanto (Fox Chase Cancer Center), Samuel Pan, Jianhua Hu, Shoji Natsugoe (Kagoshima University), Wei Gu, Ben Z. Stanger (Abramson Cancer Center), Kwok-K Wong (New York University), J. Alan Diehl (Case Western University), Adam J. Bass, Hiroshi Nakagawa, Maureen E. Murphy (The Wistar Institute).

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