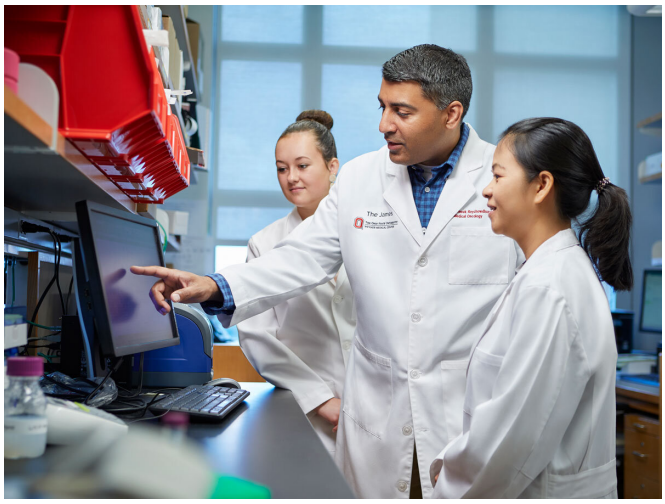
Study suggests new strategy for treating advanced, progressing bile duct cancer

14 January 2020



Credit: Ohio State University Medical Center

A new study led by researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) shows how resistance to a promising targeted drug develops in patients with a rare, lethal cancer of the bile ducts called cholangiocarcinoma.

The study, reported in the journal *Molecular Cancer Therapeutics*, also suggests that adding another drug at the time of progression might re-sensitize tumor cells to the initial drug, called an FGFR inhibitor.

"While the majority of patients with FGFR-positive cholangiocarcinoma benefit from new FGFR inhibitors in clinical trials, most patients unfortunately develop cancers resistant to the drugs," says study leader Sameek Roychowdhury, MD, Ph.D., a medial oncologist and researcher at the OSUCCC—James. "We believe that this study is an important step in understanding drug resistance, and improving the treatment of this and other cancers caused by abnormal FGFR gene mutations."

Findings also suggest that monitoring fragments of circulating tumor DNA for acquired mutations that cause resistance to FGFR inhibitors may reveal the presence of resistance mutations and mark the time a patient should begin taking the additional drug, an mTOR inhibitor.

The successful treatment of cholangiocarcinoma is challenging because the disease is usually diagnosed at an advanced stage that has a five-year survival rate of 2%. Patients diagnosed earlier also have low five-year survival due to high rates of disease recurrence. Abnormal activation of the FGFR gene happens in 15 to 20% of people with cholangiocarcinoma, and FGFR inhibitors show effectiveness in 70 to 80% of those patients until resistance develops. There are six studies of FGFR inhibitors in clinical trials at the OSUCCC—James.

"A better understanding of how treatment resistance develops and how to prevent it is critical for improving the treatment of cholangiocarcinoma and other cancers caused by FGFR mutations," says first author Melanie Krook, Ph.D., a postdoctoral fellow in Roychowdhury's lab.

"Our findings suggest that cholangiocarcinoma patients treated with an FGFR targeted therapy could potential benefit from combination therapies with other drugs such as mTOR inhibitors. Additional laboratory studies are needed to identify the optimal lead strategies for this combination," she adds.

For this study, Roychowdhury, Krook and colleagues examined the FGFR (fibroblast growth factor receptor) gene in the cancer cells of a cholangiocarcinoma patient who died after experiencing disease progression and developing resistance to the FGFR inhibitor infigratinib.

The researchers identified two acquired FGFR mutations in the patient's tumor cells that conferred resistance to FGFR inhibitors. They then used cancer cell lines to learn that the mutations led to activation of the mTOR biochemical pathway. This enabled the cancer cells to grow even in the presence of FGFR inhibitors. Adding an mTOR inhibitor to the cells restored their sensitivity to FGFR inhibitors.

Key findings

- Two acquired FGFR2 mutations, p.E565A and p.L617M, were shown to drive resistance to the FGFR inhibitor infigratinib.
- The p.E565A mutation upregulates the mTOR signaling pathway, which desensitizes cholangiocarcinoma cell lines to infigratinib and other FGFR inhibitors.
- A drug that inhibited the mTOR pathway restored the sensitivity of the cells to infigratinib and other FGFR inhibitors.

"Overall, our findings suggest that an mTOR inhibitor administered at the time of progression may re-sensitize tumor cells to an FGFR inhibitor in patients who develop resistance to these agents," Roychowdhury says.

More information: Melanie A. Krook et al. Efficacy of FGFR inhibitors and combination therapies for acquired resistance in FGFR2-fusion cholangiocarcinoma, *Molecular Cancer Therapeutics* (2020). DOI: 10.1158/1535-7163.MCT-19-0631

Provided by Ohio State University Medical Center