Novel gene mutations associated with bile duct cancer

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Investigators at the Massachusetts General Hospital (MGH) Cancer Center have identified a new genetic signature associated with bile duct cancer, a usually deadly tumor for which effective treatment currently is limited. Their report, which has been published online in *The Oncologist*, finds that growth-enhancing mutations in two related genes may account for nearly a quarter of bile duct tumors arising within the liver, presenting the possibility that drugs targeting this mutation could represent a new strategy to control tumor growth.

"Patients with bile duct cancer have a generally poor prognosis. Most of them are diagnosed with advanced or metastatic disease, so surgical resection is not feasible," says co-senior author Andrew Zhu, MD, PhD, director of Liver Cancer Research at the MGH Cancer Center. "Identifying this new and relatively common mutation in intrahepatic bile duct cancer may have significant implications for the diagnosis, prognosis and therapy of patients whose tumors harbor this mutation."

Cancers of the gallbladder and bile duct are diagnosed in 12,000 patients in the U.S. each year, the authors note; but only 10 percent are discovered early enough to allow successful surgical treatment. Chemotherapy is modestly effective, leading to an average survival time of less than one year.

The MGH Translational Research Laboratory was jointly established by the MGH Department of Pathology and the MGH Cancer Center to screen patient tumor samples for mutations known to drive tumor growth, identifying those that may be treatable with targeted therapies. As part of this project, the MGH team screened samples from 287 patients with gastrointestinal tumors for 130 known cancer-associated mutations and were surprised to find that 3 out of 12 biliary tract cancer tumors had mutations in a gene called IDH1. To confirm this finding, they ran a more detailed screen in additional samples, for a total of 62 bile duct tumors and 25 gallbladder tumors. Mutations in IDH1 were found in 13 percent of all bile duct tumors and in 23 percent of those located within the liver itself. Less commonly, mutations were identified in a similar gene IDH2.

"Mutations in these genes are rare examples of abnormalities that profoundly affect the normal function of a metabolic enzyme," says lead author Darrell Borger, PhD, co-director of the Translational Research Laboratory. "Our co-investigators previously found that, in other types of cancer, mutations in these genes cause overproduction and dramatic accumulation of the metabolite 2-hydroxyglutarate. How this causes tumor development is being actively investigated, and it is now emerging that 2-hydroxyglutarate can disrupt the activity of a family of proteins important in signal transduction and regulation of gene expression."

Although no approved drugs are currently available that target IDH mutations, extensive efforts are underway to develop such drugs, Zhu notes. "Identifying these mutations in bile duct cancer raises many questions, including whether mutational status can distinguish various types of bile duct tumors and help predict prognosis. Also of interest is determining whether high blood levels of 2-hydroxyglutarate could serve as a biomarker for IDH1/2 status, which could provide a minimally invasive way to monitor the effects of new IDH inhibitors that may become available," he says. Zhu is an associate professor, and Borger an instructor in Medicine at Harvard Medical School.

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