Discovery of a new approach to inhibiting a highly treatment-refractory liver cancer

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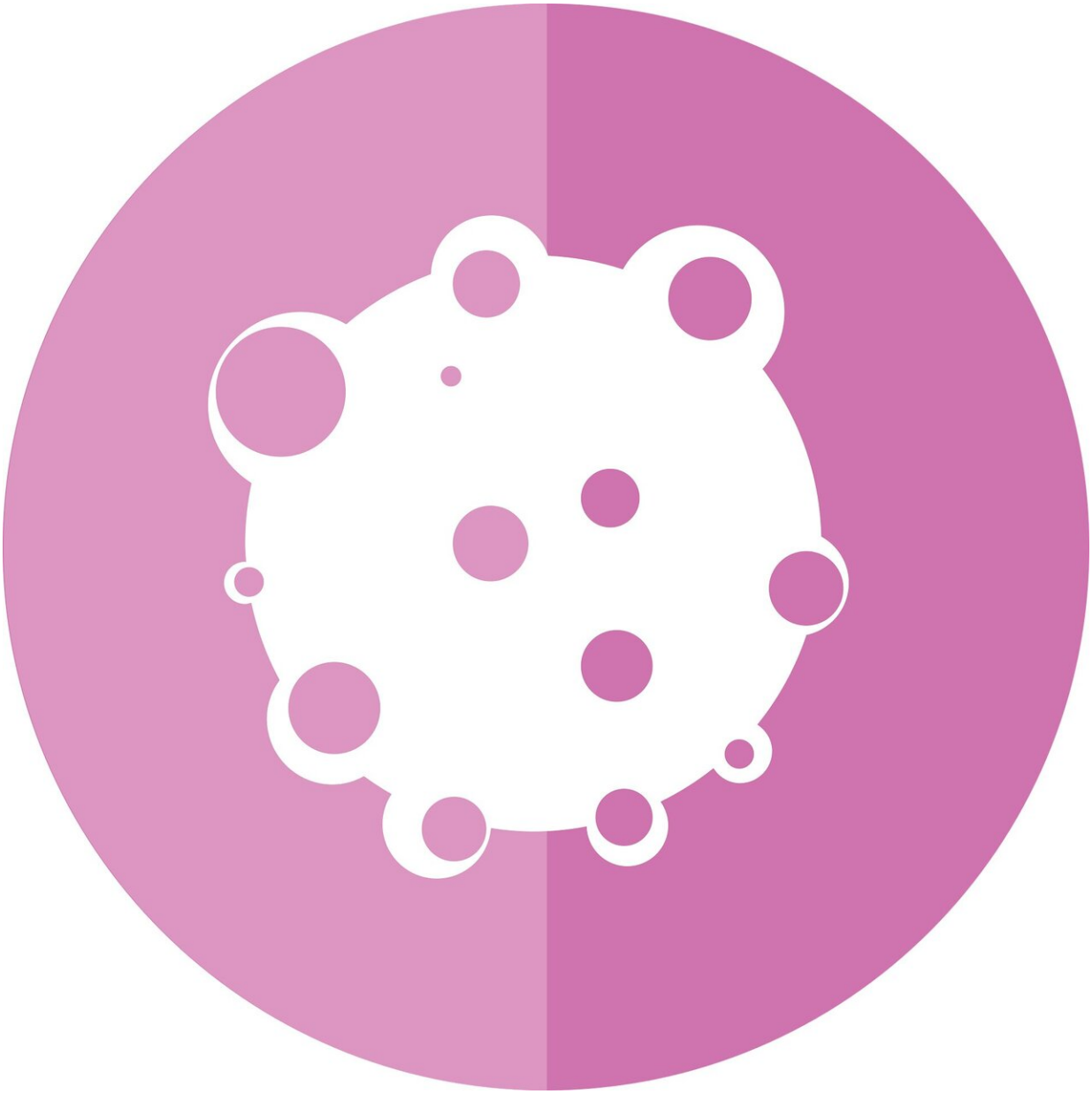

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Reprogramming the rich connective tissue microenvironment of a liver cancer known as intrahepatic cholangiocarcinoma (ICC) inhibits its progression and resistance to standard chemotherapy in animal models, researchers from Massachusetts General Hospital (MGH) have found. This new treatment for a disease with extremely poor outcomes uses antibodies to block placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family, which has been widely studied for its role in new vessel formation in cancers. PlGF is highly expressed in ICC compared to normal liver tissue, and blocking it reduces the production of connective tissue while increasing the efficacy of chemotherapy and survival in mice with ICC. These findings were reported in *Gut*, the journal of the British Society of Gastroenterology.

"We were able to demonstrate that PlGF is a mediator of ICC progression, and that antibody blockade of PlGF in ICC models inhibited the activity of cancer-associated fibroblasts (CAFs), which produce connective tissue and also provide ICC cells with pro-survival and pro-invasion signals," says Dan G. Duda, DMD, Ph.D., director of Translational Research in GI Radiation Oncology at MGH, and senior author of the study. "Our findings suggest that PlGF inhibition is a potential therapeutic target that could have implications for other emerging combination therapies that have shown promise against ICC, a largely intractable disease with a dismal prognosis."

ICC is an aggressive cancer of the liver with a five-year survival rate of 15% for patients with early-stage disease, and 6% for those with metastases to regional lymph nodes. The cancer is characterized by vascular abnormalities, abundant connective tissue (known as desmoplasia) produced by activated CAFs, and few therapeutic options.

Systemic chemotherapy using gemcitabine and cisplatin remains the standard of care for patients with advanced ICC, but the benefits are limited. "New therapies are urgently needed as incidence of ICC grows at 3% a year in the U.S. and worldwide," emphasizes Duda.

The MGH study was inspired by previous research by Duda and Rakesh K. Jain, Ph.D., director of the Edwin L. Steele Laboratories for Tumor Biology at MGH, and a pioneer in the fields of tumor microenvironment and cancer therapy, that identified PlGF as a potential target to inhibit the growth and spread of medulloblastoma, the most common pediatric malignant brain tumor. Their groundbreaking research demonstrated high expression of the PlGF receptor neuropilin 1 (Nrp1) in medulloblastoma and found that PlGF/Nrp1 blockade resulted in tumor regression, decreased metastasis, and increased survival in mice. PlGF blockade using antibodies has been tested in a phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT02748135) with final results to be reported later this year.

"Our prior work led us to study other cancers where PlGF might play a pivotal role," notes Duda. "We found that PlGF levels were also elevated in CAFs and circulating blood plasma in ICC patients, and were associated with disease progression." Investigation in mouse models further revealed that PlGF blockade reduced desmoplasia and tissue stiffness, which are determinants of tumor aggressiveness and resistance to treatment. Consequently, the antibody blockade re-opened collapsed tumor vessels and improved blood perfusion and chemotherapy efficacy, while reducing ICC cell invasion and increasing survival in mice. "In effect, we reprogrammed the hypoxic tumor microenvironment, which could have major implications for novel combination therapies targeting ICC or other highly desmoplastic tumors, such as pancreatic cancer," explains Jain, co-author of the latest study.

Such a systemic approach could enhance the efficacy of standard

chemotherapy but also radiation therapy or immune checkpoint inhibitors, including programmed cell death 1 (PD-1) blockade—all of which have shown promise against ICC. "Our results indicate that PlGF blockade can provide a clinical strategy for growing numbers of ICC patients who have failed to see any significant improvements in treatment over the years," says Duda.

More information: Shuichi Aoki et al. Placental growth factor promotes tumour desmoplasia and treatment resistance in intrahepatic cholangiocarcinoma. *Gut* dx.doi.org/10.1136/gutjnl-2020-322493

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