New research identifies a potential treatment target for hepatoblastoma, the most common liver cancer in children

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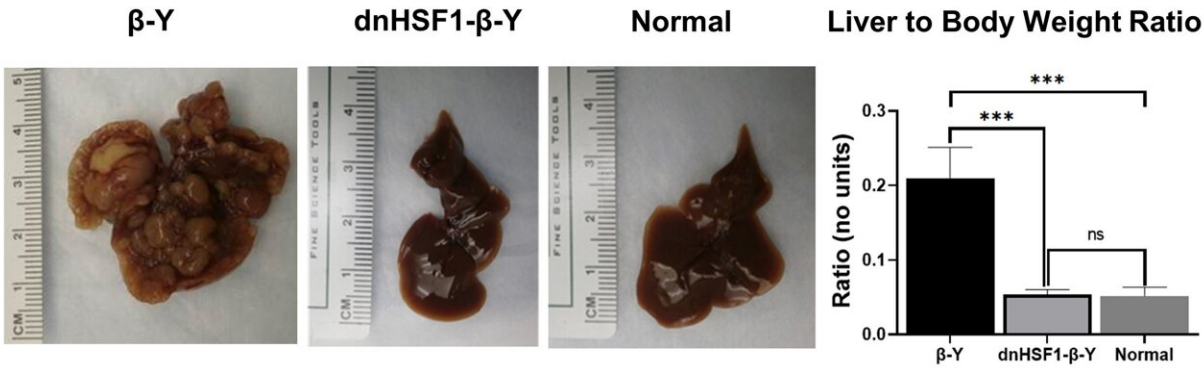

Left: Gross images of livers from mice transfected with β-catenin and YAP1(β-Y), β-catenin and YAP1 plus dominant negative HSF1 (dnHSF1-β-Y) and normal (control). Right: Liver to body weight ratios for three groups of mice. Credit: Monga Laboratory

Although rare compared to adult liver cancers, hepatoblastoma is the most common pediatric liver malignancy, and its incidence is increasing. In a novel study appearing in *The American Journal of Pathology*, investigators studying a mouse model of hepatoblastoma report that the protein heat shock transcription factor 1 (HSF1) is needed for aggressive tumor growth and may be a viable pharmacologic target for hepatoblastoma treatment.

"This study grew out of my long-standing interest in fetal and perinatal fetal liver development," explained lead investigator Edward H. Hurley, MD, Department of Pediatrics and the Pittsburgh Liver Research Center, University of Pittsburgh School of Medicine. "Premature and growth-restricted babies are at increased risk for hepatoblastoma for reasons currently unknown."

"The fact that liver transplantation with its associated lifelong immunotherapy and risk for secondary malignancies is considered a viable option for severe hepatoblastoma speaks to the critical clinical need for more effective therapeutic options for hepatoblastoma-specific therapies that are more effective but with fewer side effects," said Dr. Hurley. "However, the effort to develop more targeted hepatoblastoma-specific therapies has been stymied by the lack of fundamental knowledge about hepatoblastoma biology."

HSF1 is a transcription factor that is a canonical inducer of heat shock proteins (HSPs), which act as chaperone proteins to prevent or undo protein misfolding. Over the last 20 years there has been a growing appreciation for the role of HSF1 in cancer pathophysiology. Recent work has shown a role for HSF1 in cancer beyond the canonical heat shock response. However, its role in hepatoblastoma remained elusive.

Researchers working at the laboratory of Dr. Satdarshan P. Monga at the University of Pittsburgh School of Medicine developed a mouse model of hepatoblastoma based on transfecting mice with constitutively active beta-catenin and yes-associated protein 1 (YAP1) using hydrodynamic tail vein injection. They found increased HSF1 signaling in hepatoblastoma versus normal liver. Also, less differentiated, more embryonic tumors had higher levels of HSF1 than more differentiated, more fetal-appearing tumors.

The research group used the mouse model to test how inhibiting HSF1

early in tumor development would impact cancer growth. They found fewer and smaller tumors when HSF1 was inhibited suggesting HSF1 is needed for aggressive tumor growth. Moreover, increased apoptosis (cell death) in tumor foci was noted when HSF1 is inhibited. This work provides evidence that HSF1 may be a novel biomarker and pharmacologic target for hepatoblastoma.

"We were not surprised by the association of HSF1 signaling and hepatoblastoma given its role in multiple other cancers," commented Dr. Hurley.

"We were intrigued to find that less differentiated and more embryonic tumors had higher HSV1 expression levels than fetal-like, more differentiated tumors. However, we were surprised to find the association between HSF1 expression levels and mortality. In in vivo experiments, we anticipated that HSF1 inhibition would slow tumor formation and growth, but we were surprised by the near total prevention of tumor development.

"This work has established the importance of HSF1 in hepatoblastoma development and suggests HSF1 may be a viable pharmacologic target for hepatoblastoma treatment. Currently, HSF1 inhibitors are being developed for other cancers. We can foresee the potential of testing these agents in hepatoblastoma," he concluded.

Hepatoblastoma treatment was developed decades ago for treatment of adult cancers and currently includes surgical resection with or without chemotherapy, but in severe cases children require liver transplantation if the tumor cannot be successfully resected. All of the treatments have significant side effects including impacting hearing and growth.

Historically, patients with resectable tumors have a 10-year survival rate of 86% versus only 39% for nonresectable tumors. Between the late

1990s and late 2010s, the percentage of patients receiving liver transplants increased from 8% to nearly 20%.

More information: Edward H. Hurley et al, Inhibition of Heat Shock Factor 1 Signaling Decreases Hepatoblastoma Growth via Induction of Apoptosis, *The American Journal of Pathology* (2022). DOI: 10.1016/j.ajpath.2022.10.006