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High Levels of Protein p62 Predict Liver Cancer Recurrence

Study in mice and human tissues suggest new prognostic and therapeutic approach

Researchers at University of California San Diego School of Medicine and Sanford Burnham Prebys Medical Discovery Institute have discovered that high levels of the protein p62 in human liver samples are strongly associated with cancer recurrence and reduced patient survival. In mice, they also found that p62 is required for liver cancer to form.

The study, published May 19 in *Cancer Cell*, suggests p62 could be used as a prognostic marker and potential therapeutic target for liver cancer.

“By defining factors that allow liver cells to progress from pre-cancer to cancer, we were able to find one — p62 — that we can also use to predict a liver cancer patient’s outcome following full removal of a previous liver tumor,” said co-senior author Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology and Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases at UC San Diego School of Medicine.

Karin led the study with co-senior author Jorge Moscat, PhD, deputy director of the Cancer Center at Sanford Burnham Prebys Medical Discovery Institute, and first author Atsushi Umemura, PhD, a postdoctoral fellow in Karin’s lab.

Protein p62 normally acts as the cell’s trash collector, delivering specially tagged proteins to the cell’s degradation machinery. P62 also acts as a communication hub — it binds many different proteins to regulate important cellular functions, like growth and survival. Amounts of p62 are known to be elevated in many different cancers, including liver, and in pre-cancerous liver diseases.

In this study, Karin’s team looked at non-cancerous liver samples collected from people who had undergone previous treatment to completely destroy their liver cancers. They graded the livers from 0 to 3 based on the average number of p62-positive aggregates detected. Seventy-

nine of 121 specimens were p62 positive. Using the medical records corresponding to each liver sample, the team also noted the number of years each patient survived disease-free.

The researchers found that people with high-grade p62 were significantly more likely to see their cancer return and less likely to survive cancer-free than people with low or no p62. They found the same correlation when they looked at the link between the p62 gene and survival outcomes for an additional 450 liver cancer patients whose genomic data and clinical records are available in national research databases.

Work in mice led the researchers to attribute protein p62's pro-cancer effect to its ability to activate other proteins (NRF2, mTORC1 and c-Myc) and genes that help stressed cells survive. This extended lifespan allows liver cells to accumulate cancer-causing mutations and ultimately form malignant tumors. The researchers found that p62 alone was enough to induce liver cancer in several mouse models of the disease. Liver tumors couldn't form without the protein.

The specific type of liver cancer analyzed in this study was hepatocellular carcinoma, the most common form of adult liver cancer. While years of further testing are necessary before doctors might be able to use p62 information to make treatment decisions, new liver cancer detection and prevention methods are sorely needed. Liver cancer doesn't usually cause symptoms until later stages, contributing to its low survival rate. According to the American Cancer Society, just 17 percent of patients with all types of liver and bile duct cancer survive five years cancer-free.

"Our new study illustrates that p62 is necessary and sufficient to induce liver cancer in mice, and that its high expression level in liver tissue surrounding a tumor predicts recurrence of the disease after tumors are removed," said Moscat. "We believe that small molecules that interfere with p62 may be useful for preventing the progression of chronic liver disease to liver cancer."

Study co-authors include: Feng He, UC San Diego; Koji Taniguchi, Shinichiro Yamachika, Joan Font-Burgada, Zhenyu Zhong, Shankar Subramaniam, Sindhu Raghunandan, Mark A. Valasek, UC San Diego, Kyushu University and Keio University School of Medicine; Hayato Nakagawa, UC San Diego and University of Tokyo; Angeles Duran, Juan F. Linares, Miguel Reina-Campos, Maria T. Diaz-Meco, Sanford Burnham Prebys Medical Discovery Institute; Shiori Umemura, UC San Diego and Kyoto Prefectural University of Medicine; Ekihiro Seki, UC San Diego and Cedars-Sinai Medical Center; Kanji Yamaguchi, Yoshito Itoh, Kyoto Prefectural University of Medicine; and Kazuhiko Koike, University of Tokyo.

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Diseases/American Liver Foundation.

MEDIA CONTACT

Heather Buschman, 858-249-0456, hbuschman@ucsd.edu

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