# Cycles of Cell Death, Proliferation Key to Liver Cancer

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Research at the University of California, San Diego (UCSD) School of Medicine shows that liver cancer is likely caused by cycles of liver cell death and renewal.

The research, appearing online the week of June 19 in advance of publication in the journal *Proceedings of the National Academy of Sciences*, underscores the importance of JNK1-mediated cell death and compensatory proliferation. The findings by Michael Karin, Ph.D., professor pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, and colleagues strongly suggest that the control of tissue renewal through the IKK and JNK pathways plays a key role in liver cancer in mouse models.

One link between inflammation and cancer is known to involve the NF-kB pathway, which regulates gene expression. In research published in the journal *Cell* in 2005, Karin and his colleagues at UCSD implicated the pathway's activator, IKK, in chemically induced liver cancer. However, the surprising outcome of those studies was the finding that while NF-kB activation in hepatocytes (liver cells) prevents liver cancer, its activation in inflammatory cells, such as tissue macrophages, promotes tumor development.

In their latest work, the research team studied what precedes inflammation – the injury of hepatocytes caused by toxic chemicals, which sets in motion the inflammation process.

Their research showed that the absence of IKKb in hepatocytes led to increased c-Jun N-terminal kinase (JNK) activation after exposure to a chemical carcinogen used to elicit liver cancer in mice. Importantly, deletion of the gene that codes for the major isoform of JNK in liver cells, JNK1, prevented the development of liver cancer and reversed the tumor-enhancing effect caused by ablation of IKKb.

"We found that long-term JNK activation leads to cell death; if activated briefly, it stimulates proliferation of pre-malignant and cancerous tumor cells," said Karin. Blocking JNK prevents liver injury but also inhibits liver regeneration, so the timing and context of activation are very important, he added.

"In this research, we set out to identify what causes inflammation in response to liver injury, as well as what stimulates the proliferation of surviving hepatocytes," said Karin. "Since we

previously knew that JNK activity is required for normal liver cell proliferation, we wondered if the same activity is required for production of liver cancer in carcinogen-exposed mice. The results were clear – JNK1 is critical for tumor development."

The scientists genetically removed JNK1 to test if its increased activation, caused by the absence of IKKb, was responsible for accelerated tumor development. When JNK1 was removed, the number and size of cancerous liver tumors decreased, and the tumors grew more slowly. Increased JNK1 activation was found in diseased liver and tumors when compared to normal tissue.

Hepatocellular carcinoma (HCC), the most common form of liver cancer, is the third leading cause of cancer deaths worldwide. Its major risk factors are persistent infection with hepatitis B and C viruses, and exposure to toxic chemicals, including alcohol – all of which cause chronic liver injury and inflammation. Although not common in the United States., the incidence of HCC is on an upward trajectory, with little hope for treatment or cure through chemotherapy, radiation or other traditional cancer treatments.

"We now understand development of liver cancer in mice. Since inflammation drives both damage and regeneration in liver tissue, it is the repeating cycle of damage, inflammation and regeneration that leads to liver cancer," said Karin. "However, this knowledge is not satisfactory until we find out if it applies to humans."

Contributors to the paper include Toshiharu Sakurai, UCSD Laboratory of Gene Regulation and Signal Transduction and Kyoto University, Japan; Shin Maeda, UCSD and the Asahi Life Foundation, Tokyo; and Lufen Chang, UCSD and the Beckman Research Institute at City of Hope National Medical Center, Duarte, CA.

The research was supported by the National Institutes of Health and the Superfund Basic Research Program. Karin is an American Cancer Society Research Professor.

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