Scientists Uncover Protective Mechanism Against Liver Cancer

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A team of scientists from the UC San Diego School of Medicine and Osaka University in Japan have identified a protein switch that helps prevent liver damage, including inflammation, fibrosis and cancer. The findings suggest that a better understanding of how the protein, TAK1, works could lead to new insights into the development of liver disease and cancer.

"TAK1 appears to be a master regulator of liver function," said David A. Brenner, MD, professor of medicine and Dean of the UC San Diego School of Medicine. He and Ekihiro Seki, MD, PhD, assistant research scientist in the Department of Medicine, led the work. "Understanding its role in liver disease and cancer may eventually enable us to devise new therapeutic strategies." Their study appears on line the week of December 14 in advance of publication in the journal *Proceedings of the National Academy of Sciences*.

TAK1 is a kinase, a type of signaling protein involved in regulating various cell activities, including cell growth. Researchers have known that TAK1 activates two specific proteins, NF-kappaB and JNK, which are both involved in immunity, inflammation, programmed cell death and cancer. But NF-kappaB helps protect liver cells from dying and protects against cancer development. In contrast, JNK promotes cell death and cancer.

However, it has been unclear whether TAK1 promotes or prevents the development of liver cancer. To find out, Seki, Brenner and their group created a mouse model in which liver cells lacked the gene *Tak1*, which makes the TAK1 protein. In a series of experiments, they found a high rate of liver cell death in young animals lacking TAK1. The animals' livers then went into overdrive, producing too many liver cells to make up for the loss and causing liver damage, including inflammation and fibrosis – liver scarring – and eventually, cancer.

According to Seki, the study is the first to demonstrate the role of TAK1 in cancer development, and strongly suggests that the protein also contributes to cancer development in other organs. In addition, the liver cancer mouse model that the team developed is associated with sustained liver

inflammation and fibrosis – key features of human liver cancer – and should be useful in investigating whether fibrosis influences liver cancer development.

"We can also use the model to test whether a potential cancer drug or therapy affects both fibrosis and cancer, or either one," Seki said. "This study will open a new therapeutic potential targeting the expression of TAK1 for liver cancer."

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