To protect against liver disease, body puts cells 'under arrest'

August 21 2008

A stable form of cell-cycle arrest known to offer potent protection against cancer also limits liver fibrosis, a condition characterized by an excess of fibrous tissue, according to a new report in the August 22nd *Cell,* a Cell Press publication. Triggered by chronic liver damage produced by hepatitis infection, alcohol abuse, or fatty liver disease, liver fibrosis can lead to cirrhosis, a major health problem worldwide and the 12th most common cause of death in the United States.

The new findings may have important implications for treating cirrhosis, a disease now considered to be irreversible. It could offer new insight into other disease states as well.

" Fibrosis is a disease of many organs—lungs, kidneys, pancreas, prostate, skin," said Valery Krizhanovsky of Cold Spring Harbor Laboratory. "It's possible this mechanism in the liver is relevant to fibrotic situations in other tissues."

The state of cell-cycle arrest known as senescence was first described decades ago, but the phenomenon was thought to occur only in cultured cells in the laboratory, Krizhanovsky explained. More recent studies found that cellular senescence helps protect against the formation of tumors and aids in the response to certain anticancer agents.

Interestingly, the researchers said, senescent cells had also been observed in some aged or damaged tissues, including the cirrhotic livers of human patients. However, the functional contribution of cellular senescence to

diseases other than cancer hadn't been examined.

To study the potential role of senescence in liver cirrhosis, the researchers examined mice treated with a liver-damaging agent. They found that senescent cells accumulated in the livers of the mice, derived primarily from activated stellate cells. Stellate cells are those that initially proliferate in response to liver damage and are responsible for producing the extracellular matrix—a kind of structural support for cells—that is the hallmark of fibrotic scars.

" Once a lot of extracellular matrix has formed, it's very hard to clear," Krizhanovsky explained. "The material just sits there and creates an inflammatory environment."

Their new findings offer some hope, however. The senescent stellate cells showed signs of reduced secretion of extracellular matrix components, enhanced secretion of enzymes that degrade extracellular matrix, and enhanced immune surveillance. Accordingly natural killer cells preferentially target senescent-activated stellate cells both in cell culture and in living animals, they found, helping to resolve fibrosis. On the other hand, stellate cells continued to divide in mice lacking key components of the senescence program, leading to excessive liver fibrosis.

The results suggest that immunostimulatory therapies might enhance senescent cell clearance and should be tested for the potential treatment of patients with liver fibrosis, especially in its early stages or following short-term exposure to liver toxins.

"We suggest that, following tissue damage, hepatic stellate cells become activated and proliferate intensely, senesce, and are eventually cleared to protect the liver from an excessive fibrogenic response to acute injury," the researchers concluded. "However, in response to chronic tissue

damage, for example, as produced by viral hepatitis or fatty liver disease, continual rounds of hepatocyte [i.e. liver cell] death and stellate cell proliferation allow the production of senescent cells to outpace their clearance, contributing to persistent inflammation and advancing fibrosis. Such a state, while initially beneficial, may eventually trigger the aberrant proliferation and transformation of damaged hepatocytes, leading to cancer. "

In fact, Krizhanovsky noted, cirrhosis is the main risk factor for developing an often fatal form of liver cancer known as hepatocellular carcinoma

Source: Cell Press

Citation: To protect against liver disease, body puts cells 'under arrest' (2008, August 21) retrieved 19 April 2024 from https://medicalxpress.com/news/2008-08-liver-disease-body-cells.html

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