MedicalXpress

New study upends thinking about how liver disease develops

December 20 2010

In the latest of a series of related papers, researchers at the University of California, San Diego School of Medicine, with colleagues in Austria and elsewhere, present a new and more definitive explanation of how fibrotic cells form, multiply and eventually destroy the human liver, resulting in cirrhosis. In doing so, the findings upend the standing of a long-presumed marker for multiple fibrotic diseases and reveal the existence of a previously unknown kind of inflammatory white blood cell.

The results are published in this week's early online edition of the Proceedings of the National Academy of Sciences.

In all types of chronic diseases, healthy, functioning tissues are progressively replaced by fibrous scarring, which renders the tissues or larger organ increasingly dysfunctional until, eventually, it fails. The process is called fibrosis. In the human liver, the end result is cirrhosis, the 12th leading cause of death by disease in the United States with roughly 27,000 deaths annually. Fibrosis occurs in other organs as well, such as the heart, kidneys and lungs, with comparable deadly effect.

Scientists do not fully understand the process of fibrosis, particularly how problematic fibroblast cells are created. For years, conventional wisdom has posited that fibroblasts are likely to be transformed epithelial cells, a conversion called "epithelial to mesenchymal transition" or EMT. A protein called fibroblast-specific protein 1 (FSP1) has long been considered to be a reliable indicator of fibroblasts in

injured organs undergoing tissue remodeling and has been broadly used to identify the presence of fibrotic disease.

The new research undermines the validity of prevailing assumptions about EMT and FSP1, but also opens the door to new avenues of investigation that could ultimately lead to improved detection and treatment of cirrhosis and similar conditions.

"This work, along with earlier papers, puts into question a whole area of research - at least in terms of the liver" said David Brenner, MD, Vice Chancellor for Health Sciences, dean of the UC San Diego School of Medicine and co-author of the paper. "The old evidence and assumptions about the source of fibroblasts and the role of FSP1 as a marker are not valid."

Specifically, in experiments using cell cultures, human liver samples and mouse models, the researchers found no evidence of EMT - that transformed epithelial cells became liver fibroblasts. Rather, endogenous stellate cells appear to be the culprit, though the scientists note many types of cells seem to contribute, directly or indirectly, to liver fibrosis.

Likewise, experiments proved FSP1 to be an unreliable marker for fibrosis. Cells containing FSP1 increased in human and experimental liver disease and in liver cancer, but researchers found that liver fibroblasts do not express the protein, nor do hepatic stellate cells - a major cell type involved in liver fibrosis. Similarly, FSP1 was determined not to be a marker for myofibroblasts (a fibroblast with some properties of a smooth muscle cell) or any precursors of myofibroblasts.

"There have been hundreds of papers based on FSP1 as a marker," said Brenner. "That thinking now seems to have been a mistake. One of the take-home messages of this paper is that FSP1 clearly can't be reliably

used as a marker."

On the other hand, the scientists discovered that FSP1 is a consistent marker for a previously unknown subset of inflammatory white blood cells or macrophages found in injured livers. The protein appears to also perform biological functions in the macrophages, though these remain to be determined.

"It's a whole new class of monocytes," said Brenner. "We don't know what they do, but they're worth investigating."

Provided by University of California - San Diego

Citation: New study upends thinking about how liver disease develops (2010, December 20) retrieved 4 July 2023 from https://medicalxpress.com/news/2010-12-upends-liver-disease.html