Liver fibrosis 'off switch' discovered in mice

January 23 2020

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Chronic alcohol abuse and hepatitis can injure the liver, often leading to a buildup of collagen and scar tissue. Understanding this process, known as liver fibrosis, could help researchers develop new ways to prevent or treat conditions such as alcoholic liver disease, non-alcoholic steatohepatitis (NASH) and nonalcoholic flatty liver disease (NAFLD).

In a study published January 23, 2020 by *Gastroenterology*, researchers at University of California San Diego School of Medicine demonstrated for the first time that liver fibrosis progression could potentially be addressed by manipulating a special population of liver cells called hepatic stellate cells (HSCs).

In the liver, HSCs are found in three forms: naïve in healthy people, activated in people with liver disease and inactivated in people who have recovered from liver fibrosis. In both mouse and human liver tissue, the researchers discovered they can control this cellular switch by activating or inhibiting specific transcription factors, molecules that turn genes "on" or "off."

"We are excited to discover that HSCs have this flexibility, and that we can change their type by manipulating the molecules involved," said Tatiana Kisseleva, MD, Ph.D., associate professor of surgery at UC San Diego School of Medicine. "These insights may allow us to develop new ways to stop the progression of liver fibrosis." Kisseleva led the study with first author Xiao Liu, a researcher in her lab.

In healthy people, naïve HSCs store vitamin A and support normal liver function—filtering blood, metabolizing drugs and producing bile acids to aid digestion. But in alcoholic liver disease or hepatitis, HSCs become activated and start producing collagen, a hallmark of fibrosis.

The goals of the study, Kisseleva said, were to 1) understand the mechanism that switches HSCs from their naïve to their active state and 2) find ways to stop the process and inactivate collagen-producing HSCs.

Kisseleva and her team identified several transcription factors that distinguish active HSCs from naïve HSCs, and studied them in human liver samples and mouse models. Some of the transcription factors they

found prevent activation of HSCs or inactivate them. When the levels of each of these naïve-associated transcription factors were reduced in mouse HSCs, the cells became activated, increased their collagen production and promoted fibrosis. Liver fibrosis was more severe in mice lacking these transcription factors.

The researchers also took the opposite approach, stimulating one of these transcription factors, PPARγ, with a chemical called rosiglitazone. In mice treated with rosiglitazone, the researchers observed liver fibrosis regression and faster resolution of fibrous scars than in untreated mice.

"We essentially found that we can help PPARγ put a stop to collagen production by activated HSCs," Kisseleva said.

New therapeutic targets are urgently needed for liver fibrosis, she said. According to the US National Institutes of Health, weight loss is the only known method for reducing liver fibrosis associated with NAFLD and NASH. Therapeutic drugs to slow the progression of disease are only available in advanced stages, where NASH has led to liver cirrhosis. Alcoholic liver disease is most commonly treated with corticosteroids, but they are not highly effective. Early liver transplantation is the only proven cure, but is offered only at select medical centers to a limited number of patients.

To further their efforts, Kisseleva and team are now exploring the role of other transcription factors involved in maintaining HSC naïveté, and searching for activators and inhibitors. They also plan to take a closer look at the genes these transcription factors are regulating, and determine if they can be directly targeted to inactivate HSCs.

More information: Xiao Liu et al, Identification of Lineage-specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution, *Gastroenterology* (2020). DOI:

10.1053/j.gastro.2020.01.027