UC San Diego Health

Researchers Illuminate Key Role of NOX Proteins in Liver Disease

Study adds credence to new treatment approach now in clinical trials

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Researchers at the University of California, San Diego School of Medicine have demonstrated a direct connection between two signaling proteins and liver fibrosis, a scarring process underlying chronic liver disease, the 12th leading cause of death in the United States.

The finding adds further credence to a current pharmaceutical effort to create new treatments for diabetic nephropathy, liver fibrosis and other progressive fibrotic and inflammatory diseases, based on blocking these two molecules, both members of the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase (NOX) family of proteins.

The study published online July 29 in the journal *PLOS ONE*.

David Brenner, MD, vice chancellor of health sciences and dean, UC San Diego School of Medicine

"The research community has been committed to identifying core mediators of fibrosis as potential drug targets," said David A. Brenner, MD, vice chancellor for health sciences, dean of UC San Diego School of Medicine and senior author of the paper. "With this study, we have validated both NOX1 and NOX4 as core mediators of liver fibrosis and laid out the step-by-step cellular pathways that lead to this disease."

Liver fibrosis kills thousands of Americans each year and is the result of chronic liver injury caused by such agents as the hepatitis B and C viruses, alcoholic liver disease and non-alcoholic fatty liver

disease. The condition is manifested by extensive scarring of liver tissue and the organ's progressive inability to carry out its functions. These include filtering toxins from the blood, aiding in food digestion and other critical body activities. Liver fibrosis can lead to the development of liver cancer. Often, the only treatment for end-stage liver fibrosis is an organ transplant.

In their study, the researchers explored the possible connection between NOX1 and NOX4 and the activation of hepatic stellate cells (HSCs), which are known to be key players in liver scarring.

"We wanted to determine whether NOX1 and NOX4 signaling is directly involved in triggering the activation of the HSCs," said Brenner.

HSCs normally act as quiescent storage units for vitamin A in the liver. However, once activated, the HSCs acquire characteristics of another cell type called myofibroblasts, which are characterized by their abundant production of extracellular matrix proteins such as collagen. These proteins accumulate as scar tissue, rendering the organ progressively dysfunctional.

Brenner said the NOX family are transmembrane proteins that generate reactive oxygen species (ROS) from oxygen. This is part of normal cellular signaling and plays a role in various physiological functions. However, in some diseases, NOX activity goes into overdrive, leading to high levels of ROS production and oxidative stress, which can drive disease processes. In liver disease, excessive ROS triggers the activation of HSCs that, in turn, cause damage to liver tissues.

To test the importance of NOX in this process, the researchers worked in mice specially bred to lack the NOX1 and NOX4 proteins. When researchers used a hepatotoxin, known to induce liver fibrosis in mice, they found that mice deficient in NOX1 or NOX4 had significantly decreased liver injury, inflammation and scarring – the key characteristics of liver fibrosis. The researchers compared this result to normal mice, with both NOX proteins, and found that these mice did develop liver fibrosis after receiving the hepatotoxin.

The researchers also demonstrated NOX's involvement by showing that mice lacking the NOX proteins had fewer HSCs in the liver after hepatotoxin exposure. In addition, they found that cirrhotic human livers had much greater numbers of the NOX1 and NOX4 proteins than normal livers.

"By using various approaches, we validated that NOX1 and NOX4 have a key mediation role in liver fibrosis, including the direct activation of HSCs," said Brenner.

The finding is in keeping with a 2012 study by Brenner and his lab, which assessed the effectiveness of treating liver fibrosis with GKT137831 – a NOX1/4 inhibitor developed by Genkyotex SA of Geneva, Switzerland. The compound is now in phase II clinical trials for diabetic nephropathy and is being explored in other fibrotic diseases. Brenner's 2012 study, in mouse models of liver fibrosis, found that treatment with the GKT137831 NOX inhibitor suppressed ROS production and HSC activation and reduced fibrotic gene expression. "It showed the strong

potential of using a NOX inhibitor as an effective treatment for this devastating disease," said Brenner.

Coauthors of the study include: Tian Lan, UCSD and Guangdong Pharmaceutical University, Guangzhou, China; and Tatiana Kisseleva, UCSD.

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