

# Modified protein reverses cirrhosis in lab rats

March 3 2016

---

A protein modified to increase the amount of time it circulates in the bloodstream appears to reverse liver fibrosis and cirrhosis in rats, according to results of a study led by Johns Hopkins researchers.

The investigators say the findings, reported ahead of print in the March 3 early view edition of *Hepatology*, advance the search for a potential cure for the thousands of patients worldwide living with these incurable diseases. At present, there is little effective treatment and no cure other than [liver transplantation](#), which carries its own risks and often fails.

"Our findings demonstrate that the damaging effects of [liver cirrhosis](#) in laboratory rats can be effectively treated, and perhaps even reversed, using a protein therapeutic that has been modified to enhance its activity through site-specific conjugation of a polymer that greatly enhances its residence time in the body," says senior author Justin Hanes, Ph.D., director of the Center for Nanomedicine at the Wilmer Eye Institute at Johns Hopkins. "This approach has tremendous potential to help people with this devastating condition and may also be helpful to the millions of patients with other diseases where fibrosis plays an important role."

Liver fibrosis and its more severe form, cirrhosis, are caused by scar tissue that forms in the liver that is usually induced by chronic alcohol abuse, infections and autoimmune diseases. The progressive stiffening of the liver, a hallmark of the disorders, occurs when a type of liver cell known as the hepatic stellate cell is "activated" and overproduces the stringy network of proteins called the extracellular matrix that binds cells

together.

Being able to turn cirrhosis around, especially in its late stages, would be a great boon, says Seulki Lee, Ph.D., assistant professor in the Department of Radiology and Radiological Science at the Johns Hopkins University School of Medicine. "That's because liver fibrosis and cirrhosis can be asymptomatic for decades," Lee says. "Many patients only seek treatment when their disease becomes very advanced, at which point liver transplant is their only option."

Lee cautions, however, that his team's work is years from any possible application to patients.

Scientists have known for more than a decade that a protein called tumor necrosis factor-related apoptosis-inducing ligand—TRAIL, for short—can specifically kill activated hepatic stellate cells that overproduce the extracellular matrix, sparing healthy cells in the liver. However, Lee explains, TRAIL has thus far proven unsuccessful for clinical use because in animal studies, enzymes in the bloodstream quickly degrade it before it has time to work.

Seeking a way to extend TRAIL's half-life, or the time that it remains intact in the bloodstream, Lee and his colleagues coated TRAIL with polyethylene glycol (PEG), a synthetic polymer that's widely used as a preservative, lubricant and ingredient in skin creams, and is already being used to extend the bloodstream life of a handful of drugs that treat neutropenia, hemophilia and rheumatoid arthritis.

Lee says initial experiments showed that this "PEGylated" TRAIL had a half-life of between eight and nine hours in monkeys, compared to less than 30 minutes for the unmodified protein. When the scientists intravenously dosed rats that had [liver fibrosis](#) with the modified TRAIL for 10 days, the animals' activated hepatic stellate cells died off. By

fighting these bad cells, signs of fibrosis began to diminish. Further investigation showed that multiple genes associated with fibrosis had reduced activity, and the proteins produced by these genes faded away.

Findings were similar in rats with advanced cirrhosis, Lee says. Additionally, when the researchers examined the rodents' liver tissue under a microscope, they found that animals treated with PEGylated TRAIL had fewer deposits of collagen and other extracellular matrix proteins, offering some evidence that the disease had actually been reversed.

Further experiments showed that PEGylated TRAIL selectively killed human-activated hepatic stellate cells growing in petri dishes while leaving normal [liver](#) cells unharmed, suggesting that findings in these animal models could apply to damaged human livers with limited toxicity concerns.

Lee says the research team hopes to develop PEGylated TRAIL for clinical trials in human patients in the next two years. He adds that some preliminary data suggest that the modified protein could also treat other fibrotic diseases as well, such as pancreatic or lung fibrosis, which also have no effective treatment.

"Eventually," Lee says, "we might be able to develop PEGylated TRAIL into a universal anti-fibrotic agent that can treat many different conditions."

Provided by Johns Hopkins University School of Medicine

Citation: Modified protein reverses cirrhosis in lab rats (2016, March 3) retrieved 23 April 2024 from <https://medicalxpress.com/news/2016-03-protein-reverses-cirrhosis-lab-rats.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.