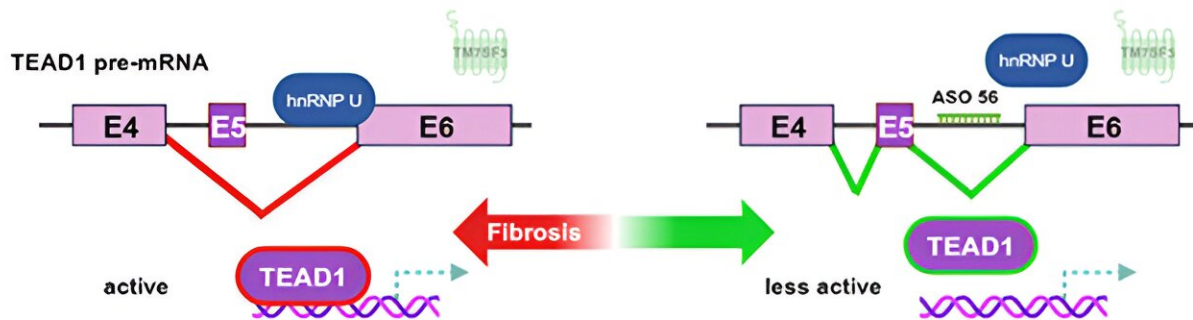


Scientists discover a new signaling pathway and design a novel drug for liver fibrosis

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Schematic of the TEAD 1 signaling module that drives liver fibrosis. Credit: UC San Diego Health Sciences

A healthy liver filters all the blood in your body, breaks down toxins and digests fats. It produces collagen to repair damaged cells when the liver is injured. However, a liver can produce too much collagen when an

excess accumulation of fat causes chronic inflammation, a condition called metabolic dysfunction-associated steatohepatitis (MASH). In an advanced state, MASH can lead to cirrhosis, liver cancer and liver-related death.

The cells that produce [collagen](#) in livers are called hepatic stellate cells (HSC). In a [paper published](#) in *Cell Metabolism*, scientists from the University of California San Diego investigated how these cells are activated. They found a three-component [signaling pathway](#) in the nucleus that functions according to a sort of police-controlling-the-police model.

In healthy livers, the first molecule in the pathway inhibits a second molecule, which inhibits the molecule that stimulates collagen-producing genes. MASH scales down the first molecule, so that inhibition is lifted on the second and third molecules, leading to stimulation of collagen production.

After discovering the signaling pathway, the scientists designed a short piece of RNA to prove the pathway behaved the way they thought it did. This RNA, called an antisense oligonucleotide (ASO), was so effective that it not only proved the viability of the pathway but also prevented liver fibrosis—too much collagen in the liver—without causing any side effects.

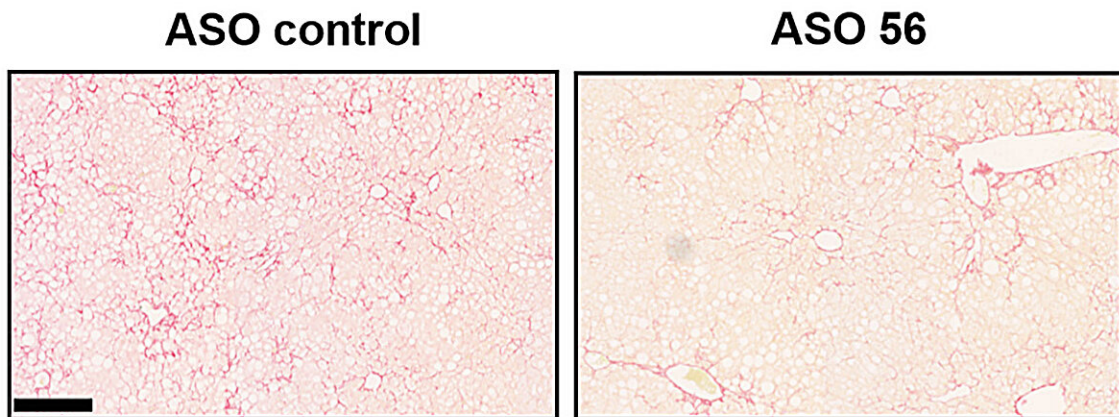
The scientists are currently discussing licensing the ASO as a therapeutic with various pharmaceutical and biotech companies.

"All the molecules in the pathway were known, but no one knew if or how they interacted. We put the pathway together, showing each step in this intracellular signaling module. That was the science of the research. The clinical message is this ASO, which can actually block liver fibrosis," said Jerrold Olefsky, a professor of medicine and assistant vice

chancellor for integrative research at UC San Diego Health Sciences, and senior author on the paper.

The scientists carried out their investigations in organoids—tiny little livers in a dish made from three types of liver cells fed a MASH cocktail of fatty acids, fructose and sugars.

They found that in normal livers, the first component of the pathway, a nuclear seven-transmembrane protein called TM7SF3, inhibits a splicing factor called hnRNPU. hnRNPU refrains from splicing out an inhibitory exon in the messenger RNA (mRNA) of TEAD1, a transcription factor that controls the genes that produce collagen. The inhibitory exon, exon 5, keeps TEAD1 from turning on the collagen-producing genes.



Fibrosis as measured by Sirius red staining in untreated and ASO 56 treated MASH mice. Credit: UC San Diego Health Sciences

In the MASH-fed organoids, TM7SF3 is reduced and does not inhibit the splicing factor. The active splicing factor splices out the inhibitory exon in the transcription factor, which turns on the genes that produce collagen. This is called alternative splicing.

Furthering their investigations, they designed an ASO to keep hnRNPU from splicing out exon 5. "It had the sequence that would put it just upstream of exon 5 where hnRPU binds. The ASO prevented the splicing factor from binding to the TEAD mRNA, so it couldn't ultimately splice it out. We got pretty much only inactive TEAD when we treated MASH mice with the ASO," said Olefsky. With TEAD inactivated, collagen wasn't produced. Neither was fibrosis.

"These findings show the key role of [alternative splicing](#) in shaping progression of fibrotic liver disease," said Roi Isaac, Ph.D., assistant project scientist, Medicine, and first author on the paper.

When ASOs are administered intravenously, they enter every cell in the body, not just the target cells. Serendipitously, the scientists found that within the liver, this hnRNPU mechanism only operated in stellate cells. That made their ASO both highly effective and highly specific—the epitome of good drug design.

According to Olefsky, a quarter of the U.S. population has MASH. While the scientists' ASO may well be an effective treatment, getting FDA approval for it would necessitate enormous clinical studies and could cost up to a billion dollars.

Olefsky and his team identified a much less common disease called primary sclerosing cholangitis, or PSC. It's relatively rare, often fatal, and until now there were no good treatments. When the scientists tested their ASO on a mouse model of PSC, they found that their ASO almost completely blocked the development of the disease.

"Getting FDA approval for PSC would be easier than getting it for MASH," said Olefsky, "so we're currently talking to biotech and pharma partners about licensing the ASO for PSC."

More information: Roi Isaac et al, TM7SF3 controls TEAD1 splicing to prevent MASH-induced liver fibrosis, *Cell Metabolism* (2024). [DOI: 10.1016/j.cmet.2024.04.003](https://doi.org/10.1016/j.cmet.2024.04.003)

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