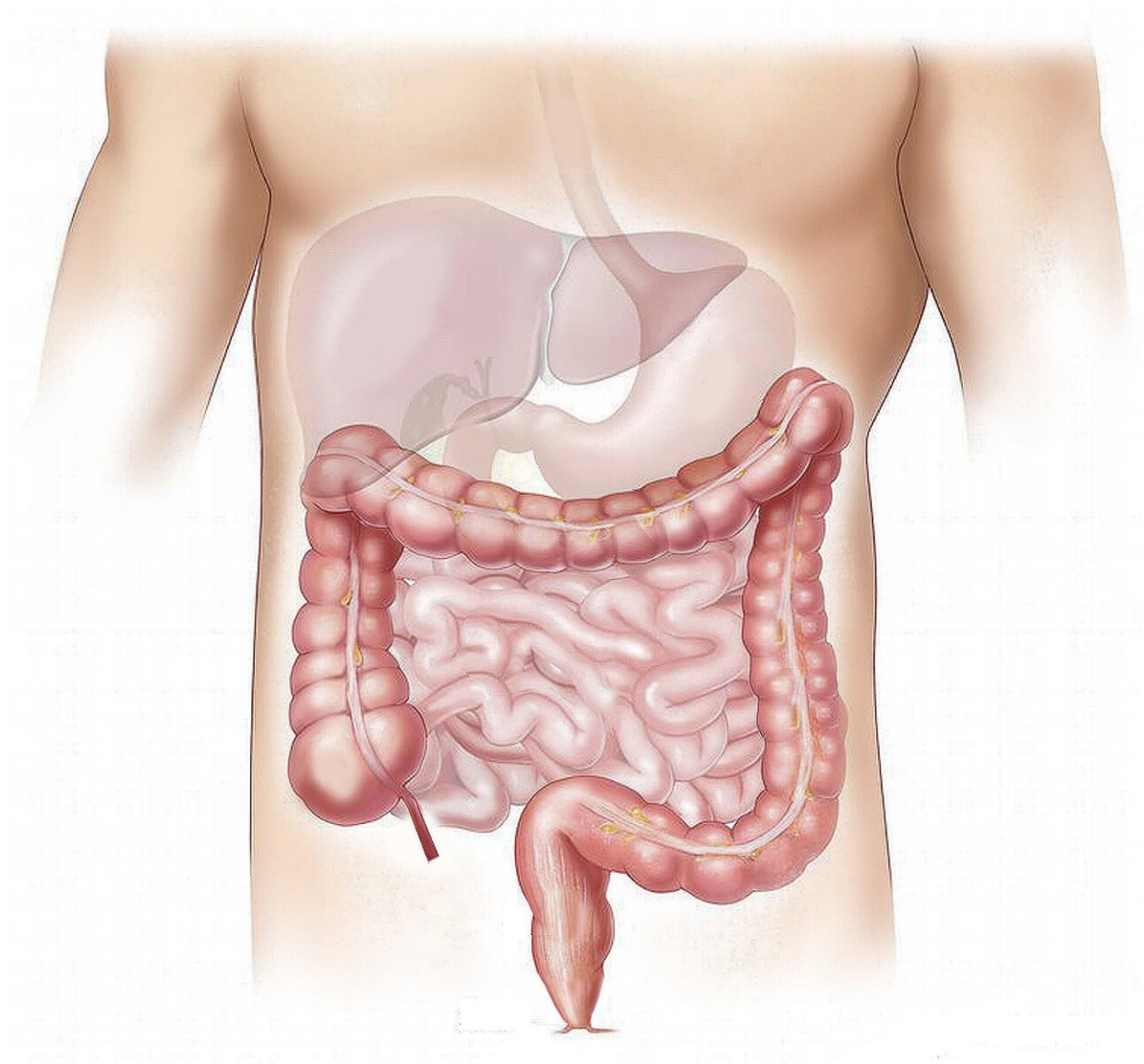
Studies suggest new path for reversing type-2 diabetes and liver fibrosis

February 4 2020



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In a pair of related studies, a team of Yale researchers has found a way to reverse type-2 diabetes and liver fibrosis in mice, and has shown that the underlying processes are conserved in humans.

The studies appear in the Feb. 4 edition of *Cell Reports* and in the Jan. 17 edition of *Nature Communications*.

In the earlier study, researchers found an important connection between how the body responds to fasting and type-2 diabetes. Fasting "switches on" a process in the body in which two particular proteins, TET3 and HNF4α increase in the liver, driving up production of blood glucose. In type-2 diabetes, this "switch" fails to turn off when fasting ends, as it would in a non-diabetic person.

Researchers hypothesized that if they could "knock down" the levels of these two proteins, they could stop diabetes from developing. Huang and team injected mice with genetic material known as small interfering RNAs (siRNAs) packaged inside viruses that targeted TET3 or HNF4β. They found that blood glucose and insulin dropped significantly—effectively stopping diabetes in its tracks.

In the Feb. 4 *Cell Reports* study, researchers looked at how TET3 contributed to the development of fibrosis in the liver, and found that the protein was involved in fibrosis on multiple levels. Almost all fibrosis, regardless of the organ involved, starts from abnormal protein signaling, Huang said.

She and colleagues discovered that TET3 plays a role in the fibrosis signaling pathway in three different locations—and acts as an important regulator in fibrosis development. This means there are likely opportunities to develop drugs that inhibit TET3 to slow or reverse

fibrosis, said Da Li, associate research scientist in genetics and co-author on both studies.

Both diseases—type-2 diabetes and fibrosis of the liver and other organs—are common, but have few treatment options. Around 28 million people in the U.S. have type-2 diabetes, characterized by high blood sugar levels, a condition that can lead to many other health problems, including heart disease, stroke, and kidney failure.

Cirrhosis is one of the leading causes of death worldwide and is marked by liver fibrosis—a buildup of scar tissue on the liver, said co-author James Boyer, M.D., professor and emeritus director of the Yale Liver Center.

Researchers noted that several drugs, such as metformin, are currently available to control blood sugar levels in patients with diabetes. But these have a range of unpleasant side effects, and patients can develop resistance to these drugs.

And there is little medical relief for fibrosis sufferers.

"Right now, there are no effective drugs for the treatment of fibrosis," said Xuchen Zhang, M.D., associate professor in pathology and co-author on the fibrosis study.

Huang has filed for a patent related to her discoveries with support from the Yale Office of Cooperative Research.

The next step, she said, will be to identify where to best target TET3 and HNF4α and to develop the most effective siRNAs or small molecules to treat type-2 diabetes or fibrosis.

More information: Yetao Xu et al. A Positive Feedback Loop of

TET3 and TGF-β1 Promotes Liver Fibrosis. *Cell Reports* VOLUME 30, ISSUE 5, P1310-1318.E5, FEBRUARY 04, 2020. DOI: doi.org/10.1016/j.celrep.2019.12.092

Da Li et al. Hepatic TET3 contributes to type-2 diabetes by inducing the HNF4α fetal isoform, *Nature Communications* (2020). DOI: 10.1038/s41467-019-14185-z