Lower protein activity after hepatitis C therapy may signal path to healing scarred liver

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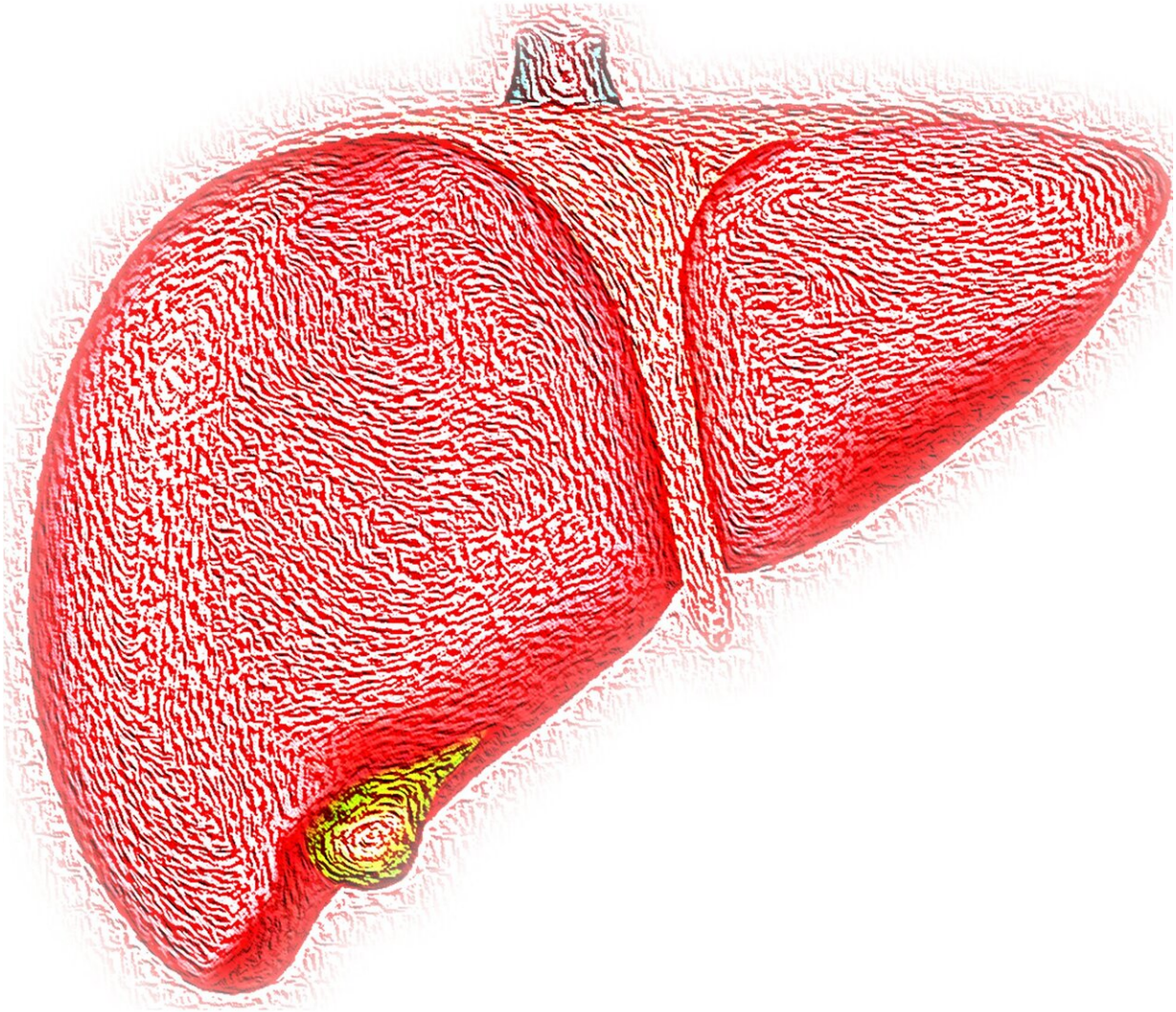

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Researchers at the Medical University of South Carolina (MUSC) report in the *Journal of Viral Hepatitis* that the activity levels of the proteins involved in liver scarring, or cirrhosis, begin to decrease immediately after treatment for the hepatitis C virus (HCV), suggesting the possibility of early healing. Understanding these changes could shed light on whether the treatment, which is curative of HCV, sets the body on a course to reverse the damage done by long-term infection. It could also inform novel therapeutic interventions for cirrhosis caused by hepatitis C.

Hepatitis C is a viral infection of the liver that over time can cause scarring, increasing the risk of organ failure and cancer. Fortunately, a curative treatment is already available.

"The great news about HCV treatment these days is that almost everybody who knows they have hepatitis C infection, and who seeks treatment, is cured," said Eric Meissner, M.D., Ph.D., senior author of the *Journal of Viral Hepatitis* article and an associate professor in the Division of Infectious Diseases at MUSC. "The cure rates of current therapies are in the ballpark of 95% to 98%. It's one of the most successful stories in infectious diseases. It has really been nothing short of revolutionary with respect to drug discovery."

Although the treatment is curative, in the sense that it rids the body of the virus, the extent to which the body can reverse existing damage caused by long-term infection and how this process might differ in different people is not well-understood.

Some patients do not know they are infected and harbor the virus for many years, making them vulnerable to cirrhosis caused by long-term infection and inflammation.

"Hepatitis C is a common infection, but not everybody knows that they have it," explained Meissner. "Most people don't know that it's recommended for every adult to get tested for hepatitis C at least once, whether or not they have obvious risk factors. Hepatitis C is easy to cure. The earlier it is treated, the less liver scarring you'll develop."

Although expanded testing and earlier treatment for HCV infection could prevent liver scarring and its adverse consequences in many people, Meissner's team wanted to examine, in this study, how the treatment affected already scarred liver.

"The purpose of this investigation was to gain a deeper understanding of the fate of the liver after hepatitis C has been eliminated," explained Meissner.

Meissner teamed up with Lauren Ball, Ph.D., director of the Mass Spectrometry Facility at the MUSC Proteomics Center, to design and interpret an in-depth analysis of the proteins in liver biopsy specimens from eight HCV patients collected before and after their curative treatments. Given the small amount of tissue available for the study, the samples were analyzed using state-of-the-art phosphoproteomics technology pioneered at Harvard Medical School to measure changes in protein modification.

"Analysis of the changes in protein abundance and modification following therapy revealed a robust anti-viral response to treatment," said Ball.

This research was substantially facilitated by MUSC's new Digestive

Disease Research Core Center(DDRCC), funded by the National Institute of Diabetes and Digestive and Kidney Diseases, which supports investigators performing digestive and liver disease research. The center also helps to fund the MUSC Proteomics Center, which was instrumental in carrying out this research and now provides this technology at MUSC for investigators.

"This work is extremely important as we work to improve noninvasive assessment not only of liver fibrosis but of those likely to have reversal of fibrosis after HCV eradication," said Don Rockey, M.D., director of the DDRCC.

As expected, the activity of proteins involved in fighting off the virus and causing liver inflammation decreased when the virus was treated. This expected finding gave the team confidence in their analysis and lent credence to an unanticipated finding: While levels of proteins involved in cirrhotic pathways did not change, their activity levels as reflected by the protein modifications were reduced.

"This decreased activity could be an early sign or window into how the liver might recover after the virus has been eliminated," said Meissner. "We think eliminating the virus sets the liver and its proteins on a course to healing."

Meissner believes that seeing changes in the levels of proteins could take longer.

"We didn't see any change in the actual proteins that represent scarred or damaged liver, but these changes in proteins may take a longer amount of time to see," said Meissner.

Although these findings are preliminary, Meissner is intrigued about what they suggest concerning the impact of HCV treatment on scarred

liver tissue.

"While the decreased activity of fibrotic proteins that we observed has to be researched further to understand fully any link to liver healing, it could offer new insight into how the liver healing process might be proceeding," speculated Meissner. "Seeing these changes so early after hepatitis treatment suggests that the healing process could begin as soon as the treatments end and the virus is eliminated. This finding highlights the importance for every patient with HCV infection to receive curative therapy as soon as they can."

More information: Lauren E. Ball et al, Hepatitis C virus treatment with direct-acting antivirals induces rapid changes in the hepatic proteome, *Journal of Viral Hepatitis* (2021). DOI: 10.1111/jvh.13593

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