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Protein may improve liver regeneration

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Researchers at UC Davis have illuminated an important distinction between mice and humans: how human livers heal. The difference centers on a protein called PPARα, which activates liver regeneration. Normally, mouse PPARα is far more active and efficient than the human form, allowing mice to quickly regenerate damaged livers. However, the research shows that protein fibroblast growth factor 21 (FGF21) can boost the regenerative effects of human PPARα. The findings suggest that the molecule could offer significant therapeutic benefits for patients who have had a liver transplant or suffer from liver disease. The study was published in the journal *Oncotarget*.

"We found that FGF21 is a good rescuing molecule that facilitates liver regeneration and perhaps tissue repair," said Yu-Jui Yvonne Wan, vice chair for research in the Department of Pathology and Laboratory Medicine at UC Davis and senior author on the paper. "Our data suggests that FGF21 could help with liver regeneration, either after removal or after damage caused by alcohol or a virus."

In the study, human and mouse PPARα showed different capacities for liver regeneration after surgery. Even after having two-thirds of their livers removed, normal mice regained their original liver mass within seven to 10 days. By contrast, mice with human PPARα never fully regenerated, even after three months. However, by increasing FGF21, the team boosted human PPARα's ability to regenerate and heal mouse livers.

While mouse PPARα has regenerative advantages over the human

version, there is also a downside, as this ability can lead to cancer. Human PPARα does not cause cancer; however, as noted, it cannot match the mouse protein's regenerative capacity. This trade-off provides a number of advantages on the human side. For example, several popular drugs target PPARα to treat high cholesterol and triglycerides.

Still, in the right context, a more active human PPARα could be a great boon for patients with liver conditions. Using FGF21 to boost this regenerative capacity is an important step in that direction.

These results also add another line to FGF21's impressive resume. In addition to boosting human PPARα's regenerative impact on the liver, the protein has been shown to alleviate insulin resistance, accelerate fat metabolism, and reduce fatty liver disease in animal models.

"FGF21 is a key molecule to regulate metabolism in the liver," said Wan. "There's research that shows that mice that overexpress FGF21 live 50 percent longer. Now we've shown that it can rescue human PPAR, allowing it to completely regenerate damaged livers in mice. This could provide significant therapeutic benefits for people after transplants or other liver injury."

Other authors included Hui-Xin Liu and Ying Hu at UC Davis, Samuel W. French at Harbor-UCLA Medical Center and Frank J. Gonzalez at the National Cancer Institute.

Provided by UC Davis