New genetic screen paves the way for long-sought treatments for liver disease

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Chronic liver failure is a major health problem that causes about one million deaths around the world each year. A study published April 11th by Cell Press in the journal *Cell* reveals a new type of screen for identifying genes that promote liver repair in mouse models of both acute and chronic liver disease. The study shows that the MKK4 gene could be a promising therapeutic target to enhance liver regeneration and provides a blueprint for future studies aimed at discovering new therapies for liver disease.

"It is now conceivable to develop specific pharmacological inhibitors of MKK4 in order to treat patients with liver disease," says senior study author Lars Zender of University Hospital Tuebingen. "Such treatment strategies are urgently needed in the clinic, as currently the only curative treatment option for patients with end-stage liver disease is liver transplantation, and the number of donors is limited."

Chronic liver disease is caused by infections with hepatitis B or C virus, as well as alcohol abuse and malnutrition. Typically, the liver can repair itself after injury by increasing the production of cells called hepatocytes, but serious disease can interfere with this process and ultimately result in liver failure.

To identify potential targets for treating liver disease, Zender and his team developed an unbiased screen to search for genes that regulate liver regeneration in animal disease models. After interfering with the expression of hundreds of genes in mouse livers, they found that MKK4

inhibition increased the production and survival of hepatocytes after acute and chronic liver damage, resulting in healthier livers and an increase in the long-term survival of mice. Moreover, MKK4 inhibition increased the survival and long-term viability of hepatocytes in culture, offering a much-needed strategy for improving cell transplantation in patients with liver disease.

"Based on previous studies, we would not have guessed that MKK4 would strongly influence liver regeneration," Zender says. "Our study shows that genetic screens are a powerful way to search for genes, without any preconceived notions, to identify therapeutic targets that can be used to enhance the regenerative capacity of tissues."

More information: Wuestefeld et al.: "A direct in vivo RNAi screen identifies MKK4 as a key regulator of liver regeneration." *Cell*, 2013. dx.doi.org/10.1016/j.cell.2013.03.026

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