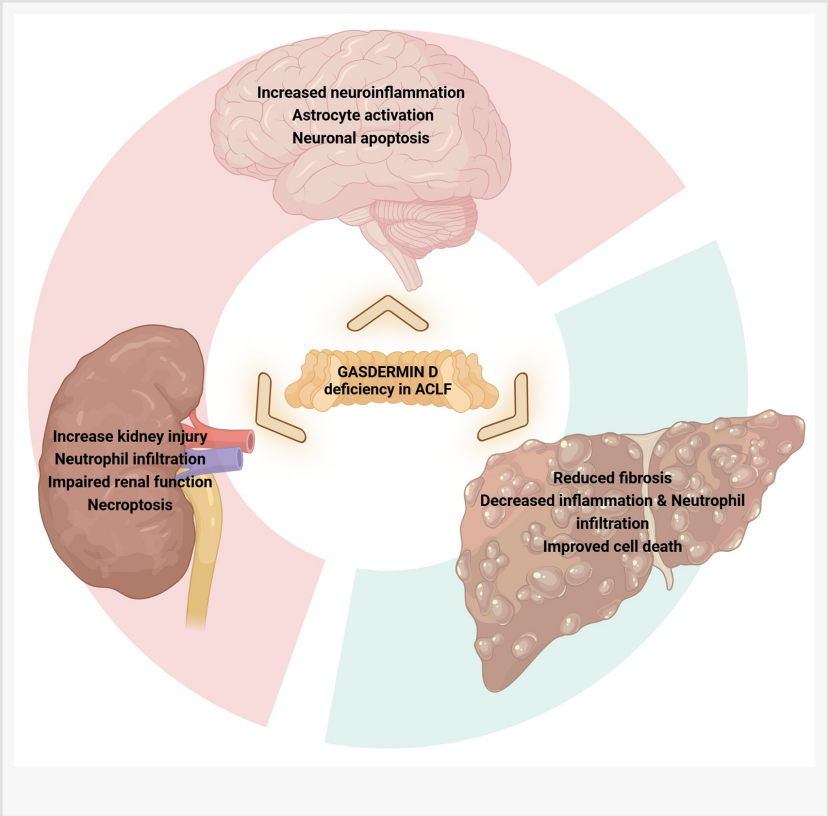
New Research Reveals Dual Impact of Liver Protein on Organ Function

Removing gasdermin D shields the liver in alcohol-induced ACLF but harms kidneys and brain, pointing to organ-specific therapies.



CHANGCHUN, CHINA, September 22, 2025 /EINPresswire.com/ -- In a twist that complicates the future of treatment for severe liver disease, scientists have discovered that blocking a key inflammatory protein in the liver may save one organ while damaging others. The new research centers on gasdermin D, a molecule best known for its role in pyroptosis, a type of cell death that acts as a biological alarm system, triggering inflammation in response to injury or infection. Until now, its role in acute-on-chronic liver failure (ACLF) has not been thoroughly explored.

ACLF is a dangerous condition that strikes patients with chronic liver disease. It occurs when a sudden insult, such as an alcohol misuse, pushes the liver past its limits, often causing a cascade of systemic inflammation and failure in other organs like the kidneys and brain. With few treatment options besides liver transplantation, researchers have been racing to understand the molecular drivers behind the syndrome.

The study, led by a team at Beth Israel Deaconess Medical Center and Harvard Medical School, used a mouse model to explore what happens when gasdermin D is genetically deleted. Mice lacking this protein experienced much less liver inflammation, fibrosis, and cell death after being subjected to the conditions that typically induce ACLF. Blood tests and liver tissue analyses confirmed these protective effects. Compared to normal mice, the gasdermin D-deficient group showed lower levels of pro-inflammatory molecules, decreased liver fibrosis and less infiltration of neutrophils, the immune cells that can worsen liver injury.

At first glance, the results seemed promising. Targeting gasdermin D appeared to spare the liver from the worst consequences of ACLF. But the story took a darker turn when researchers examined other organs. In the kidneys, damage actually worsened. Tissue samples revealed greater signs of injury, including tubular dilation and immune cell infiltration. Key markers of necroptosis—another form of programmed cell death—were elevated. Kidney function also declined, as measured by blood urea nitrogen levels.

The brain, particularly the cerebellum, also showed signs of distress in gasdermin D-deficient mice. Markers of neuroinflammation were increased, along with genes linked to astrocyte activation and neuronal apoptosis. These changes mirror aspects of hepatic encephalopathy, a severe complication of liver failure where toxic substances affect brain function.

Why would deleting a single protein improve liver health while damaging other organs? The answer likely lies in the complexity of pyroptosis. While often harmful to the liver during ACLF, pyroptosis may serve a protective role elsewhere. The loss of gasdermin D appears to shift the balance toward other, possibly more destructive, forms of cell death like necroptosis and apoptosis. These shifts seem to be organ specific. In the liver, avoiding pyroptosis reduced inflammation and allowed for more controlled tissue repair. However, pyroptosis might be a more tolerable alternative in the kidney and brain to the pathways that take over in its absence.

The findings offer a cautionary tale for researchers and drug developers. While blocking inflammation in ACLF is appealing, this study suggests that bluntly suppressing pyroptosis could backfire, especially if gasdermin D plays different roles in different tissues. Future therapies may need to target this pathway in a more nuanced way—perhaps selectively blocking gasdermin D in the liver while leaving it intact in other organs.

Interestingly, gasdermin D has already been linked to other liver diseases, including alcohol-associated hepatitis and metabolic dysfunction-associated steatohepatitis. This study adds ACLF to the list, highlighting the protein's growing importance as a therapeutic target. Yet the dual nature of its effects underscores the risks of broad inhibition.

The researchers acknowledge that their mouse model recapitulates molecular pathways from human ACLF but, like all the animal models, it cannot capture every aspect of the human ACLF pathophysiology. Mice used in the study had genetic backgrounds that may respond differently to alcohol-induced injury. Still, the results provide a compelling starting point for developing more targeted strategies.

As the next step, the team plans to explore whether gasdermin D inhibitors can be delivered selectively to the liver or if other parts of the pyroptosis pathway can be manipulated to preserve liver protection without triggering off-target damage. They are also interested in identifying biomarkers that predict which patients might benefit from such therapies based on their risk of extrahepatic complications.

For now, the research presents both promise and complexity. Gasdermin D may one day become a therapeutic bullseye for liver disease, but only if science finds a way to thread the needle—preserving its helpful roles while silencing the harmful ones.

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See the article:
Ortega-Ribera M, Zhuang Y, Brezani V, et al. Gasdermin D deletion prevents liver injury and exacerbates extrahepatic damage in a murine model of alcohol-induced ACLF. eGastroenterology 2025;3:e100151. doi:10.1136/egastro-2024-100151

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Dr. Gyongyi Szabo is a Professor of Medicine and Faculty Dean for Academic Affairs of Harvard Medical School, also the Chief Academic Officer of Beth Israel Deaconess Medical Center. A physician scientist gastroenterologist and an internationally known expert in liver diseases, Dr.

Szabo investigates the complex role of chronic inflammation in progression of liver diseases and focuses on molecular pathways to identify potential new therapeutic targets. Her investigations revealed the importance of micro-RNAs and extracellular vesicles in inter-cellular and inter-organ communication in liver diseases. Dr. Szabo conducted over 40 clinical trials in liver diseases and she serves on scientific advisory boards of numerous pharmaceutical industry partners. She is elected member of the Hungarian Academy of Sciences and fellow of the AASLD, AGA and the American College of Physicians (ACP). Dr. Szabo has chaired the NIAAA Board of Advisors and was member of the AASLD Governing Board and President in 2015.

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