



Editorial

Discovery of FOCAD: An Important Gene in Liver Cirrhosis

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Liver cirrhosis is the 11th most common cause of death, causing more than 1 million deaths globally each year, and together with liver cancer, it accounts for 3.5% of all deaths worldwide.¹ Cirrhosis develops due to long-term chronic liver inflammation, with the replacement of healthy liver parenchyma with diffuse liver fibrosis and regenerative nodules, leading to portal hypertension and various complications and even hepatocellular carcinoma.^{2–4} The management of cirrhosis is mainly based on the treatment of cause and complications including comprehensive supportive care. However, there are currently no effective drug therapies to cure the disease, and liver transplantation remains the gold standard treatment for cirrhosis.^{5,6} Given that cirrhosis has brought heavy health and economic burden to many countries, there is an urgent need for in-depth study of the pathogenesis and key factors of cirrhosis to find feasible intervention strategies.

Cirrhosis is traditionally considered a late-onset disease that appears in adults following environmental factors, such as viral infection, a high-fat diet, or chronic alcoholism.^{7,8} Thus, cirrhosis caused by genetic factors appears to have received less attention than environmental factors, and the etiology in infants and young children is far less understood. In a recent study published in *Nature Genetics*, titled “Loss of FOCAD, manipulated through the SKI messenger RNA surveillance pathway, leads to a pediatric syndrome with cirrhosis,” Traspas and colleagues uncovered the essentiality of the FOCAD gene in maintaining liver health and provided evidence that loss-of-function mutations in FOCAD may contribute to cirrhosis in children.⁹

The authors reported 14 children from 10 unrelated families in seven countries presenting with a multisystem syndrome characterized by severe neonatal cirrhosis. By combing genome/exome sequencing, a novel animal model of the human disease, and in vitro biological systems, the team identify that the FOCAD gene is indispensable for maintaining human liver health. Mutations in this gene cause a form of early-onset cirrhosis that has not been

documented before. Using CRISPR-Cas9 technology, they established in vitro and in vivo FOCAD knockout models to further study the cellular and molecular mechanisms of pediatric cirrhosis. Phenotypic replication of human disease in FOCAD-deficient zebrafish reveals features of altered messenger RNA degradation processes in the liver. FOCAD deficiency in patient primary cells and human liver cell lines impairs the SKI mRNA surveillance pathway by reducing levels of the RNA helicase SKIC2 and its cofactor SKIC3. Compared with other cell types, hepatocytes rely heavily on this mechanism. Hepatocytes exhibited a decrease in albumin expression and overproduction of the cytokine CCL2 following FOCAD knockout, which may play a key role in the progression of cirrhosis. These findings reveal the importance of FOCAD in maintaining liver homeostasis and the potential for therapeutic intervention by inhibiting the CCL2/CCR2 signaling axis.

There are few reports on the biological function of FOCAD, mainly involving focal adhesions, microtubule dynamics, cell cycle regulation, and cancer susceptibility.^{10,11} The authors found the novel function that the presence of FOCAD is critical for maintaining the protein half-life of SKIC2 and SKIC3, two important components of the super-killer (SKI) complex. The SKI complex is a cytoplasmic cofactor and regulator of RNA-degrading exosomes. In human cells, the SKI complex functions primarily in the cotranslational surveillance decay pathway, but the mechanism by which damaged SKI complex destroys hepatocytes remains unclear. RNA degradation is involved in the processing, turnover, and monitoring of almost all RNAs in eukaryotic cells and is therefore a central process in gene expression. The authors speculate that certain transcripts that are normally degraded by the SKI mRNA monitoring pathway may accumulate and cause specific toxicity to hepatocytes. One example is the cytokine CCL2, which attracts immune cells and promotes liver inflammation, possibly a key driver of disease progression.

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Monocyte chemoattractant protein 1 (MCP-1, CCL2) is the major ligand for the chemokine receptor C-C chemokine receptor 2 (CCR2) and is involved in a variety of diseases, including autoimmune diseases, viral infections, and cancer. During liver injury, CCL2 and CCR2 promote liver fibrosis by activating inflammatory signaling and immune cell infiltration. CCL2 is a potential therapeutic intervention point for patients with cirrhosis.^{12–14} At present, drug development targeting this pathway is in full swing, and most of the research has focused on small molecules and monoclonal antibodies targeting CCR2. Cenicriviroc (CVC) is a first-in-class oral dual CCR2/CCR5 antagonist developed by Tobira Therapeutics. CVC has potent anti-inflammatory and anti-fibrotic activities and is currently in clinical development for the treatment of liver fibrosis.^{12,15} According to the results of its 2-year Phase 2b clinical study (CENTAUR study), CVC is well tolerated and has antifibrotic activity in adult patients with nonalcoholic steatohepatitis and fibrosis.¹⁶ The present study further showed the overproduction of CCL2 in FOCAD-deficient patients and provided novel theoretical support for targeting the CCL2–CCR2 signaling axis as a potential target for liver disease patients.

Overall, this study confirms the clinical impact of recessive loss-of-function variants in the FOCAD gene and highlights the importance of the SKI mRNA surveillance pathway for liver homeostasis, and discloses a possible therapeutic intervention point via inhibition of the CCL2/CCR2 signaling axis. Although this study aimed to identify the underlying genetic causes of hepatic syndrome in children, it also has profound implications for the exploration of the pathogenesis of cirrhosis in adults. The relationship between abnormal FOCAD function and the susceptibility and severity of cirrhosis in adults remains to be further explored. In addition, further analysis of cirrhosis cases in different environmental backgrounds is promising to elucidate the genetic component of cirrhosis and its dependence on the environment. Furthermore, the knowledge and tools generated from this study have the potential to help discover and validate innovative targets for other common liver diseases such as fatty liver and hepatocellular carcinoma.

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Conflict of Interest

None declared.

Author's Contribution

The author read and approved the final manuscript.

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