pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0128
Clinical and Molecular Hepatology 2024;30:166-167

Editorial

JCAD, a new potential therapeutic target in cholestatic liver disease

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Keywords: Cholestatic liver disease; Primary biliary cholangitis; Junctional protein associated with coronary artery disease; Hepatic stellate cell

See Article on Page 206

Primary biliary cholangitis (PBC) is a chronic cholestatic immune liver disease characterized by persistent cholestasis due to damage to small bile ducts within the liver. Inflammation and destruction of the interlobular bile ducts and inflammation of the portal area of the liver are common pathological features.[1-3] This process can cause persistent liver damage, leading to liver fibrosis and cirrhosis. For the development of PBC, there is a complex interaction of various molecular and pathological mechanisms involved in the progressive destruction of intrahepatic bile ducts and the development of liver fibrosis. The main mechanism is an autoimmune attack on the small bile ducts in the liver.[4,5] Autoantibodies, such as anti-mitochondrial antibodies, target mitochondrial antigens on bile duct epithelial cells, triggering an immune response and promoting bile duct damage.[1,4] Immune-mediated inflammatory responses also play an important role, leading to an influx of lymphocytes and other immune cells into the bile ducts. Damage to the bile duct epithelial cell (BEC) caused by an immune-mediated attack disrupts bile flow, impairs bile acid metabolism, and accumulates toxic bile acids in the liver, worsening liver damage.[4,5] In addition, dysregulation of bile acid metabolism, epigenetic changes, and genetic susceptibility also contribute to the pathogenesis of PBC. Chronic inflammation and BEC damage due to various mechanisms stimulate the activation of hepatic stellate cells (HSCs) and the deposition of extracellular matrix proteins, leading to hepatic fibrosis.[4,5]

Junctional Protein Associated With Coronary Artery Disease (JCAD), also known as KIAA1462, junctional cadherin 5 associated or junctional protein associated with coronary artery disease is a gene identified as a risk locus for cardiovascular diseases (CVD) through genome-wide association studies.[6] JCAD plays a crucial role in the development of CVD by regulating various molecular mechanisms involved in endothelial dysfunction, atherosclerosis, inflammation, and thrombosis. It interacts with large tumor suppressor kinase 2 (LATS2) and negatively regulates the Hippo signaling pathway. This interaction leads to increased activity of yes-associated protein (YAP), the transcriptional effector of the Hippo pathway.[6,7]

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Editor: Yuri Cho, National Cancer Center, Korea

Received : Feb. 19, 2024 / **Revised :** Mar. 5, 2024 / **Accepted :** Mar. 6, 2024

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Dysregulation of Hippo signaling is associated with various cardiovascular diseases, including atherosclerosis and thrombosis. JCAD has also been reported to be associated with the development of hepatocellular carcinoma in nonalcoholic steatohepatitis by inhibiting LATS2 kinase activity. These results suggest that JCAD may affect metabolic and inflammatory pathways, contributing to both hepatic and CVD.[8]

In the current Clinical and Molecular Hepatology issue, Xie et al.[9] conducted a study on the effects of JCAD on HSCs and hepatic fibrosis in PBC, a cholestatic liver disease. This study confirmed that JCAD is an important regulator of HSC activation in cholestatic liver disease. JCAD deficiency has been shown to promote HSC activation through the Hippo-YAP signaling axis. JCAD binds to LATS, inhibits its kinase activity, and reduces the phosphorylation level of YAP. Subsequently, unphosphorylated YAP translocates to the nucleus and transactivates downstream target genes such as connective tissue growth factor (CTGF) and cyclin D1, resulting in HSC proliferation and activation. These findings demonstrate several potential clinical applications for treating cholestatic liver diseases. Approximately 40% of patients with PBC do not achieve adequate biochemical response or disease control with standard treatment with ursodeoxycholic acid.[1,2,10] While obeticholic acid, a new therapeutic agent, provides additional biochemical improvement in some patients, it may not be tolerated in individuals with advanced disease or severe pruritus symptoms.[1,2] These limitations suggest that JCAD may be a potential therapeutic target for cholestatic liver diseases, including PBC. Inhibiting JCAD expression or activity may attenuate HSC activation and reduce liver fibrosis progression. These findings suggest that the Hippo-YAP signaling pathway may be a promising target for treating cholestatic liver disease. Reducing HSC activation and fibrosis progression may be possible by inhibiting YAP nuclear translocation or downstream target genes such as CTGF and cyclin D1. However, this study showed the role of JCAD only in HSCs, which play the most critical role in fibrosis. However, it is known that BECs, hepatocytes, and inflammatory cells are closely related to the occurrence and progression of PBC, but, unfortunately, there are no results on the effect of JCAD expression on these cells.

In conclusion, this study provided a new understanding of the molecular pathways of cholestatic fibrosis and also identified potential therapeutic targets to treat this condition. Additional research is needed to verify the results of this study and develop effective treatments for cholestatic liver disease in the future.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

BEC, bile duct epithelial cell; CTGF, connective tissue growth factor; CVD, cardiovascular diseases; JCAD, junctional protein associated with coronary artery disease; LATS2, large tumor suppressor kinase 2; PBC, primary biliary cholangitis; YAP, yes-associated protein