No. 202431

Role of Sodium Channels in Hepatic Stellate Cells in Liver Fibrosis

Rubii Kondo

Department of Molecular and Cellular Pharmacology, Graduate School of Pharmaceutical Sciences, Nagoya City University

Summary

Liver fibrosis is a pathological condition characterized by excessive deposition of extracellular matrix (ECM). Its progression is a major determinant of prognosis in patients with chronic liver disease. Hepatic stellate cells (HSCs), when activated by liver injury, differentiate into myofibroblast-like cells and are widely recognized as the primary source of ECM.

While excessive dietary salt intake has recently been associated with increased risk of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis, the molecular mechanisms by which sodium affects HSC activation remain unclear.

This study aimed to investigate the role of SCN7A, also known as the NaX channel, a non-voltage-dependent sodium channel that senses extracellular sodium, in HSC activation and the progression of liver fibrosis. Although SCN7A has been characterized as a sodium sensor in the central nervous system, its function in peripheral tissues such as the liver remains unelucidated.

In vitro analyses using the human hepatic stellate cell line LX-2 and primary mouse HSCs revealed that SCN7A expression was significantly upregulated following TGF-β1 stimulation or long-term culture. Knockdown of SCN7A by siRNA in LX-2 cells suppressed the TGF-β1 induced expression of fibrosis-related genes - including COL1A1, α-SMA, and TGF-β1 - at the mRNA level, and also reduced COL1A1 protein expression.

In vivo, SCN7A expression was markedly increased in a NASH mouse model induced by a choline-deficient, L-amino acid-defined high-fat diet (CDAHFD), which also exhibited significant hepatic fibrosis. In contrast, no fibrosis or SCN7A induction was observed in mice given 4% NaCl in drinking water for 8 weeks.

These findings suggest that SCN7A is up-regulated during HSC activation and contributes to the fibrogenic phenotype. This study provides new insight into sodium-sensing pathways in liver fibrosis and highlights SCN7A as a potential therapeutic target.