論　文　要　旨

Hepatic expression of the SPTLC3 subunit of serine palmitoyltransferase is Associated with development of hepatocellular carcinoma in a mouse model of nonalcoholic steatohepatitis

Yozo Yoshimine

The molecular mechanisms underlying progression of nonalcoholic steatohepatitis (NASH) have not been fully elucidated. The aim of this study was to identify factors involved in NASH progression by analysis of pathophysiological features and gene-expression profiles in livers of STAM mice, a model of NASH-related hepatocarcinogenesis. C57BL/6N (B6N) mice were injected with streptozotocin to generate STAM mice. Four-week-old male STAM and B6N mice were fed either a high-fat diet (HFD) (STAM-F, B6N-F) or a conventional diet (STAM-C, B6N-C) until they were 10, 14, or 18 weeks old. Blood glucose and nonalcoholic fatty liver disease (NAFLD) activity scores of STAM-F were higher than those of STAM-C during all observation periods. STAM-F had more severe hepatic fibrosis at 14 weeks, and also exhibited higher levels of α-fetoprotein–positive hepatic tumor formation with multiplication than STAM-C at 18 weeks. At 14 weeks, cDNA microarray analysis revealed that hepatic expression of eight mRNAs was ≥30-fold higher in STAM-F than B6N-F. Expression of another four genes was increased ≥5-fold in STAM-F than B6N-F, and ≥5-fold in B6N-F relative to B6N-C. Among these 12 genes, the difference in Sptlc3 mRNA expression was most pronounced, and gradually increased over time, as determined by quantitative RT-PCR in STAM-F. In addition, Sptlc3 mRNA expression in STAM-F was higher than that in db/db mice that received HFD and in B6N fed a choline-deficient L-amino acid-defined diet. In conclusion, a high-fat diet aggravated pathophysiological findings in the liver in NASH mouse models, and hepatic expression of Sptlc3 mRNA is potentially associated with NASH progression.