論 文 要 旨

Serine palmitoyltransferase long chain subunit 3 is associated with hepatocellular carcinoma in patients with NAFLD

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The prevalence of non-alcoholic fatty liver disease (NAFLD) is continuously increasing, with the proportion of patients with liver carcinogenesis due to non-alcoholic steatohepatitis (NASH) rising accordingly. Although it is important to identify individuals with hepatic carcinogenesis among patients with NAFLD, useful biomarkers have not yet been established. Previously, in a mouse model of diabetes mellitus without genetic modifications, we reported that a high-fat diet increases serine palmitoyltransferase long chain subunit 3 (SPTLC3) expression in liver tissue, accompanied by high frequency of liver carcinogenesis. Serine palmitoyltransferase (SPT) catalyzes the metabolism of fatty acids, particularly sphingolipid synthesis, and SPTLC3 has been identified as its catalytic subunit, but its role in liver disease is unclear. In the present study, the importance of SPTLC3 in NAFLD development was investigated. *SPTLC3* mRNA expression was observed in a liver cancer cell line and in liver tissues from patients with NAFLD and liver cancer. In total, 99 patients with NAFLD (66 without hepatocellular carcinoma (HCC) and 33 with HCC were recruited, having been diagnosed by liver biopsy or imaging, along with 6 healthy volunteers (HVs). Serum was collected from patients and HVs, and SPTLC3 level was assessed by ELISA. *SPTLC3* expression was higher in non-cancerous compared with that in cancerous liver tissues. Serum SPTLC3 levels were negatively correlated with platelet count and positively correlated with hyaluronic acid levels, suggesting an association with liver fibrosis. Moreover, SPTLC3 levels were significantly higher in the HCC group than in the HV and NAFLD groups. Multivariate analysis of HCC-related factors identified platelets, alanine transferase, albumin and SPTLC3 as independent factors associated with HCC. Furthermore, in patients with other chronic liver diseases (hepatitis B and C, and alcoholic liver disease), no significant differences in serum SPTLC3 levels were observed between patients with or without HCC. Thus, SPTLC3 expression increases specifically with the progression of NAFLD. Overall, the present results indicate that SPTLC3 may be involved in the development of liver carcinogenesis during NAFLD.