論 文 の 内 容 の 要 旨

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論　文　題　目

A high-cholesterol diet promotes steatohepatitis and liver tumorigenesis
in HCV core gene transgenic mice
（高コレステロール食はHCVコア遺伝子トランスジェニックマウスにおける
脂肪性肝炎と肝腫瘍の発生を促進させる）

【Background and Aim】

Previous epidemiological studies have suggested a link between high-cholesterol intake and liver disease progression, including hepatocellular carcinoma (HCC). However, the precise mechanism of hepatotoxicity and hepatocarcinogenesis caused by excessive cholesterol consumption remains unclear.

【Methods】

We aimed to investigate the impact of dietary cholesterol using hepatitis C virus core gene transgenic (HCVcpTg) mice, which spontaneously developed HCC with age. Male HCVcpTg mice were treated for 15 months with either a control diet or an isocaloric diet containing 1.5% cholesterol, and liver phenotypes and tumor-associated signaling pathways were evaluated.

【Results】

The high-cholesterol diet-fed HCVcpTg mice exhibited a significantly higher incidence of liver tumors compared with the control diet mice (100% vs. 41%, $P < 0.001$). The diet induced steatohepatitis with pericellular fibrosis and evoked higher mRNA expression of pro-inflammatory and pro-fibrotic mediators along with greater oxidative and endoplasmic reticulum stress in the liver. Moreover, long-term consumption of cholesterol-rich diet activated nuclear factor-kappa B (NF-κB) and p62/sequestosome 1 (Sqstm1)-nuclear factor erythroid 2 (NRF2) axis, enhanced fibrogenesis, and consequently accelerated hepatic tumorigenesis.

【Conclusion】

These results demonstrate that dietary cholesterol facilitates liver tumorigenesis by inducing steatohepatitis and up-regulating cellular stress and pro-inflammatory NF-κB and detoxifying p62/Sqstm1-NRF2 signals. Therefore, high dietary cholesterol should be avoided for HCV-infected patients to prevent development of steatohepatitis, liver fibrosis, and HCC.