論 文 審 査 の 結 果 の 要 旨

報　告　番　号	甲　第　1185　号	氏　　名	王　暁　経
論 文 審 査 担 当 者	主　　査　　平塚　佐千枝 副　　査　　駒津　光久　・　菅野　祐幸		

(論文審査の結果の要旨)

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.

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.

その結果、「王　暁経」は以下の結論を得た。

1. The high-cholesterol diet-fed HCVcpTg mice exhibited a significantly higher incidence of liver tumors compared with the control diet mice.
2. The high-cholesterol 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.
3. 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.

The present results showed 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.

これらの結果は、高コレステロール食の長期摂取による肝腫瘍発生促進作用を明らかにし、その分子機構を理解するうえで重要な知見を提示していると考えられた。従って、主査、副査は一致して本論文を学位論文として価値があるものと認めた。