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Okayama University research: Lack of enzyme promotes fatty liver disease in thin patients

(Okayama, 07 March) **Researchers observe protection against obesity and insulin resistance but at the cost of prominent fatty liver disease in mice lacking the PEMT enzyme and patients with low levels of PEMT.**

Non-alcoholic fatty liver disease – steatohepatitis - is an increasingly common chronic form of hepatitis. As Jun Wada and colleagues at Okayama University Graduate School of Medicine, Shigei Medical Research Institute and Dainippon Sumitomo Pharma explain in a recent report, “Although obesity is undoubtedly one of the main risk factors for the development of non-alcoholic fatty liver disease, many clinical observations demonstrated the presence of lean NAFLD patients with normal body mass index (BMI).” The team’s latest work shows that absence of the enzyme phosphatidylethanolamine N-methyltransferase (PEMT), while protecting from diet-induced obesity and diabetes, leads to the prominent development of fatty liver disease and tumours in response to a high-fat high-sucrose diet.

PEMT catalyses methylation of phosphatidylethanolamine (PE) to phosphatidylcholine (PC) in liver cells using S-adenosyl methionine as a methyl donor. The ratio of PE to PC is known to be crucial to cell membrane integrity and resistance to endoplasmic reticulum stress and the infiltration of the liver with fat.

Wada and colleagues fed mice lacking the PEMT enzyme a high-fat high-sucrose diet for up to 90 weeks. They monitored the fat accumulation and insulin resistance before dissecting them to examine their livers. The researchers noted enhanced apoptosis and cell proliferation in the liver, which they explain through transactivation of the protein p53, which is inhibited in the presence of PEMT. The researchers also note a similarity in the response of the PEMT knock-out mice to that of lean human patients suffering from non-alcoholic steatohepatitis.

The researchers then performed genome-wide sequencing-based DNA methylation analysis. Further investigation revealed that PEMT mRNA expression in liver tissues of human non-alcoholic steatohepatitis patients was significantly lower than for simple steatosis, and as they add “lower quartiles of PEMT mRNA demonstrated lower BMI and platelet counts,

suggesting lower expression of PEMT is critically linked to the pathogenesis of lean non-alcoholic steatohepatitis."

Background

Non-alcoholic fatty liver disease (NAFLD)

Extensive build-up of fat in the liver is responsible for a range of diseases including simple steatosis and non-alcoholic steatohepatitis (NASH). The increased instances of NAFLD are linked with the rise in obesity and diabetes, which are now considered to have reached epidemic proportions. However, NASH has also been reported in patients with a normal body mass index (BMI), and the prevalence of "lean NAFLD" was recently reported at 12% in Greece, 20% in India and 15% in China.

Choline deficiency and lean NAFLD

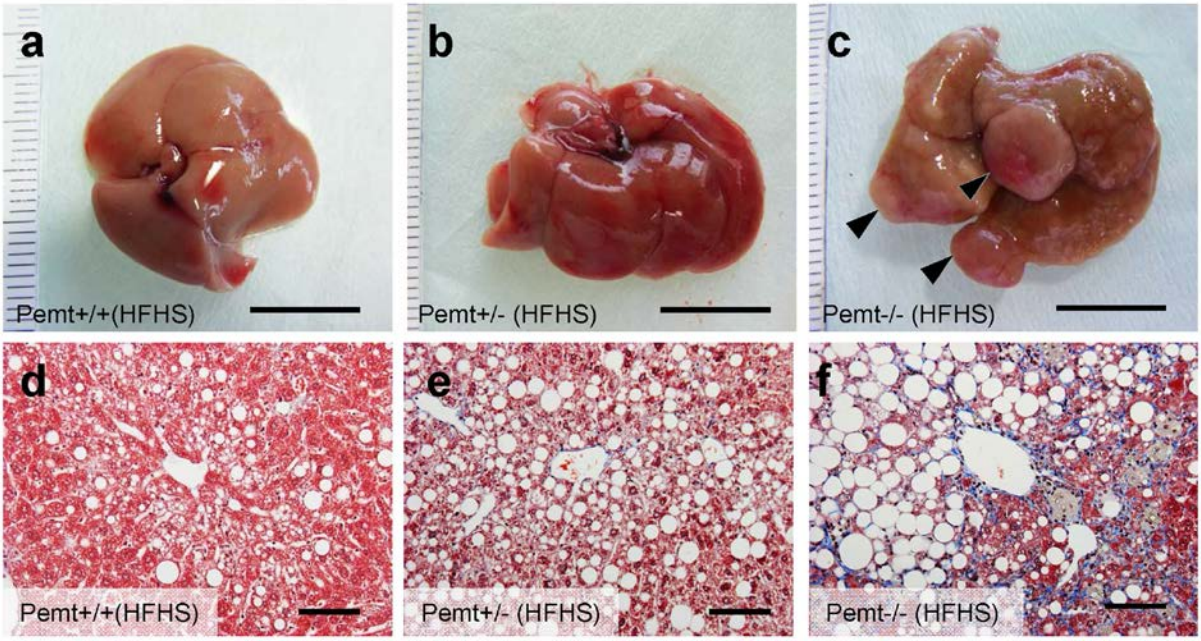
Mice fed a methionine- and choline-deficient diet (MCD) are a widely used mouse models for NASH research. An absence of obesity and insulin resistance has been observed in both MCD mice and PEMT knockout mice fed high-fat high-sucrose diets.

PC is synthesized from choline, and a balance in PE and PC levels is thought to be important for maintaining cell membrane integrity, stabilising lipid droplets and the normal distribution of fat. Disrupting this balance appears to cause accumulation of fat in the liver.

PEMT catalyses methylation of PE, which also produces PC. The similar effects – lack of obesity and prominent steatohepatitis – is also observed in PEMT knock-out mice and human NAFLD patients with low levels of PEMT.

DNA methylation analysis

The genome-wide sequencing-based DNA methylation analysis by the researchers revealed enhanced methylation of two genes associated with cyclin D1 degradation and negative regulation. These results implicate the upregulation of cyclin D1 in the development of liver disease and tumours in PEMT knock-out mice.



Caption

Phenotype of Pemt+/+, Pemt+/− and Pemt−/− mice under high fat-high sucrose (HFHS) diet at 60 weeks of age. (a–c) Gross appearance of liver. Bar = 1 cm. Regenerative nodules and adenoma are indicated by arrow heads (c). (d–f) Masson-Trichrome staining of liver tissues. Bar = 100 μ m.

Reference

Atsuko Nakatsuka, Makoto Matsuyama, Satoshi Yamaguchi, Akihiro Katayama, Jun Eguch, Kazutoshi Murakami, Sanae Teshigawara, Daisuke Ogawa, Nozomu Wada, Tetsuya Yasunaka, Fusao Ikeda, Akinobu Takaki, Eijiro Watanabe & Jun Wada. Insufficiency of phosphatidylethanolamine N-methyltransferase is risk for lean non-alcoholic steatohepatitis, *Scientific Reports* 6 21721 (2016).
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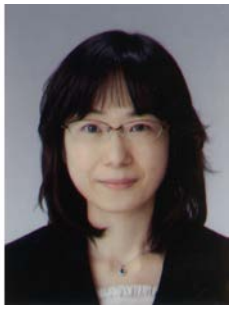
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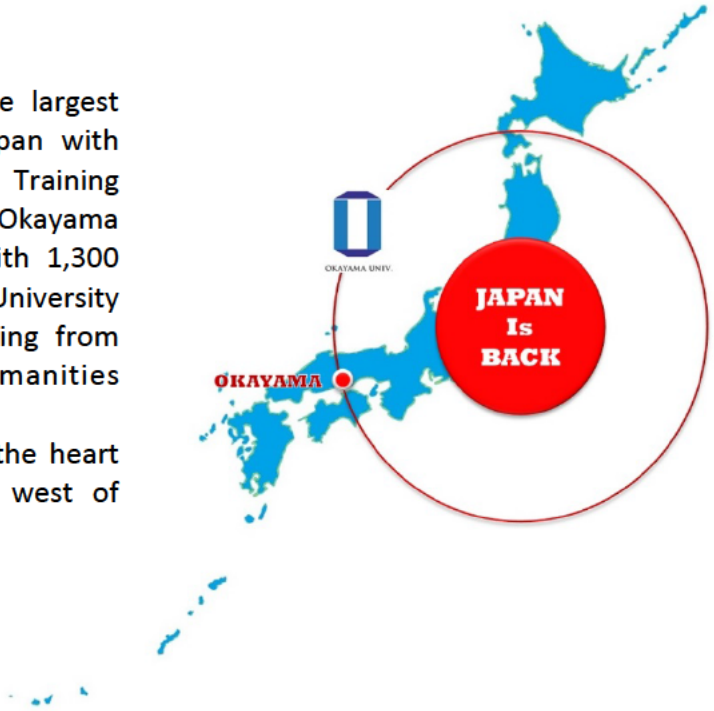
About Okayama University

Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 14,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.
Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.



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