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Animal models of non-alcoholic steatohepatitis

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The availability of reliable non-alcoholic steatohepatitis (NASH) is crucial for the elucidation of its pathogenesis and evaluation of therapeutic candidates. The widely used high-fat high-Calorie (HFC) diet induces obese and liver fat accumulation, and may lead to mild insulin resistance in rodents. Methionine/choline-deficient (MCD) diet feeding causes hepatosteatosis and body weight loss in rodents, but no insulin resistance develops in these mice. Genetic leptin receptor-deficient Ob/ob mice exhibit obese, high insulin levels and resistance, but no significant steatohepatitis. Other genetic deficient mice, such as KK-A (y) diabetic mice, do not develop steatohepatitis automatically, however are more susceptible to HFC or other diets than normal mice. Other models tending to develop hepatic steatosis and hepatocellular carcinoma (HCC) are available, but they often do not exhibit significant insulin resistance. Therefore, there is the lack of reliable animal models to reflect NASH with significant insulin resistance, which is the characteristic for those who suffer from diabetes and metabolic syndrome with a complication of steatohepatitis. It was developed a nutritional model of steatohepatitis in mice by feeding diet containing trans-10, cis-12 conjugated linoleic acid (CLA), and these mice show marked hepatic steatosis with focal cell death, enhanced Kupffer cell recruitment and activation of hepatic stellate cells (HSC). Striking characteristic of these mice is insulin resistance manifested as high insulinemia, abnormal insulin tolerant test, and insulin signaling defects with reduced Akt phosphorylation. The fatty accumulation in the liver was the result of an immortalization of body fat into the liver with increased total fatty acid content, saturated fatty acids and reduced polyunsaturated fatty acids. The enhanced fatty acid synthesis and reduced β-oxidation also contribute to the increased fat accumulation as indicated by high expression of rate-limit enzyme genes (such as stearoyl-CoA desaturase, acetyl CoA carboxylase and fatty acid synthase) in fatty synthesis and reduced expression of critical enzyme genes (carnitine palmitoyl transferase-1∝acyl-CoA oxidase 1) in fatty acid consumption. In conclusion, the model caused by feeding diet containing CLA is superior to existing NASH models when investigating the influence of insulin resistance and lipotoxicity on the progression of steatosis to steatohepatitis and fibrosis, and would be of significant value in evaluating potential therapeutics to improve the outcome of NASH treatment.

Biography

Jian Wu received his PhD degree from University of Umeå, Sweden, holds a Professor position in UC Davis since 2009. His research mainly focuses on the development of targeting approaches for drug and gene delivery in the treatment of liver diseases, including cancer. He has published more than 100 original papers, invited reviews and book chapters; authored 3 books, and owns two patents. He has received several research awards at national levels from Sweden, the US and China. As a Liver Scholar, he has been a well-known expert in the field of liver injury, fibrosis, transplant and stem cell research.

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