Abstract

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Chronic ethanol consumption plus dietary atherogenic diet intake created metabolic steatohepatitis with advanced liver fibrosis in apolipoprotein E/low-density lipoprotein receptor double-knockout mice

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Abstract

Background: Nonalcoholic steatohepatitis is the inflammatory subtype of nonalcoholic fatty liver disease with high-risk progress to liver fibrosis. We investigated metabolic steatohepatitis with advanced liver fibrosis in apolipoprotein E/low-density lipoprotein receptor double-knockout (AL) mice fed a co-diet of ethanol (Et) with atherogenic diet (AD; a low-carbohydrate–high-protein-high-fat diet) for 16 weeks. The underlying mechanisms, especially hepatic sympathetic activation, were examined.

Methods: We maintained 12-week-old male AL mice on AD and a standard chow diet (SCD) with or without Et treatment for 16 weeks. Age-matched male C57BL/6J mice on SCD without Et treatment served as controls. We conducted blood biochemical, histopathological, and fluorescence immunohistochemical examinations and PCR.

Results: AL mice showed significant hyperlipidemia. AD induced increased body weight, hepatic steatosis, and hepatic damage; Et and AD co-diet resulted in hepatic sympathetic activation accompanied by hepatic steatosis, lobular inflammation, bridging fibrosis, and hepatic damage. Hepatic Kupffer cells (KCs) and hepatic stellate cells (HSCs), which showed sympathetic activation, produced 4.4- to 9.4-fold more inflammation factors (KC and KC-derived tumor necrosis factor-α, and chemokine [C-C motif] ligand 2) and 2.0- to 32-fold more fibrosis factors (HSC and HSC-derived transforming growth factor β1 and collagen 1a1); all $p<0.05$ vs. controls.

Conclusions: We created a model of metabolic steatohepatitis with advanced liver fibrosis from coexisting hyperlipidemia and hepatic sympathetic activation in AL mice on a co-diet of Et and AD. KCs and HSCs became the cellular targets of hepatic sympathetic activation, which in turn could play a role in the initiation and progression of metabolic steatohepatitis with advanced liver fibrosis

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Biography

Jinyao Liu has his expertise in evaluation of alcohol- and nutritional imbalance diet-related health and wellbeing. He has created a mouse model that exhibits the features of metabolic steatohepatitis with advanced liver fibrosis observed in many NASH patients, with the coexistence of hyperlipidemia and hepatic sympathetic activation through alcohol consumption and dietary atherogenic diet (a low-carbohydrate–high-protein-high-fat diet) intake. Kupffer cells and hepatic stellate cells became the cellular targets of hepatic sympathetic activation, which in turn could play a role in the initiation and progression of steatohepatitis with advanced liver fibrosis. His findings might contribute to novel treatment strategies in NASH with hyperlipidemia.