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<th>CHOP deficiency attenuates steatohepatitis, fibrosis and carcinogenesis in mice fed an MCD diet</th>
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Abstract

**Background & Aims:** Hepatic steatosis is a metabolic liver disease with the potential to progress to steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC). The aim of this study was to investigate the impact of CCAAT/enhancer-binding protein homologous protein (CHOP) deficiency in the development of steatosis-associated progression of HCC. **Methods:**

Eight-week-old wild type (WT) and CHOP knockout (CHOP-/-) mice were fed a normal or methionine-choline deficient (MCD) diet. Mice were sacrificed after 3 weeks, and steatosis, inflammation, apoptosis, and liver damage were assessed. We also evaluated fibrosis after 8 weeks of nutrition intervention. To explore the role of CHOP in liver carcinogenesis, 25 mg/kg of diethylnitrosamine (DEN) was injected intraperitoneally into 2-week-old mice, which were then fed the aforementioned diets from 8 to 24 weeks of age. CHOP expression in HCC patient livers was also evaluated.

**Results:** CHOP deficiency did not affect steatosis but significantly reduced apoptotic cells, inflammation scores, and serum liver enzymes. It also significantly suppressed total serum bilirubin levels, fibrotic area size, and mRNA expression of profibrotic cytokines. DEN-initiated carcinogenesis was promoted
by the MCD diet, while CHOP deficiency significantly attenuated the total number and maximum diameter of tumors and the Ki-67 labeling index. In human livers, CHOP expression was enhanced in parallel with NASH-to-HCC progression.

**Conclusions:** CHOP deficiency attenuated apoptosis, inflammation, fibrosis, and tumorigenesis under fat-loading conditions, indicating that a therapeutic strategy targeting CHOP might be effective for fat induced-liver injury and protecting against promotion of carcinogenesis in patients with liver steatosis.
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