**The role of TCF7L2 in NAFLD**

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**Abstract**

Nonalcoholic fatty liver disease (NAFLD) associated with type 2 diabetes more easily progresses toward severe forms of nonalcoholic steatohepatitis (NASH) and fibrosis, and the underlying mechanism is under active investigation. Here, we established the role of transcription factor 7-like 2 (TCF7L2), the most significant T2D susceptibility gene, in NAFLD development and progression. We found decreased TCF7L2expressionin liver biopsies of patients with NAFLD. Based on the major risk factors for NAFLD development, liver-specific TCF7L2 knockout mice were subjected to a high-fat diet (HFD) providing fatty acids (FAs) and refeeding/high-carbohydrate diet (HCD) stimulating *de novo* lipogenesis. Hepatic TCF7L2 deficiency significantly increased the lipid biosynthetic pathways and hepatic TG accumulation by preferentially metabolizing carbohydrates than FAs. Mechanistically, TCF7L2 regulated miRNAs targeting SREBF1c and enhanced proteasome-mediated MLXIPL (ChREBP) degradation. Further, the absence of hepatic TCF7L2 aggravated hepatic steatosis induced by a chronic HCD, but not a chronic HFD; and restoration of hepatic TCF7L2 expression alleviated hepatic steatosis induced by both acute and chronic HCD conditions. Finally, TCF7L2 deficiency-induced hepatic steatosis progressed toward steatohepatitis with fibrosis. Our findings will deepen the pathophysiological mechanism of NAFLD associated with dietary carbohydrates and diabetes, and will provide a potential target for treatment of NAFLD and NASH.