# NME4 mediates metabolic reprogramming and promotes nonalcoholic fatty liver disease progression


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## Abstract

Nonalcoholic fatty liver disease (NAFLD) is mainly characterized by excessive fat accumulation in the liver, and it is associated with liver-related complications and adverse systemic diseases. NAFLD has become the most prevalent liver disease; however, effective therapeutic agents for NAFLD are still lacking. We combined clinical data with proteomics and metabolomics data, and found that the mitochondrial nucleoside diphosphate kinase NME4 plays a central role in mitochondrial lipid metabolism. Nme4 is markedly upregulated in mice fed with high-fat diet, and its expression is positively correlated with the level of steatosis. Hepatic deletion of Nme4 suppresses the progression of hepatic steatosis. Further studies demonstrated that NME4 interacts with several key enzymes in coenzyme A (CoA) metabolism and increases the level of acetyl-CoA and malonyl-CoA, which are the major lipid components of the liver in NAFLD. Increased level of acetyl-CoA and malonyl-CoA lead to increased triglyceride levels and lipid accumulation in the liver. Taken together, these findings reveal that NME4 is a critical regulator of NAFLD progression and a potential therapeutic target for NAFLD.