Mouse models of diet-induced nonalcoholic steatohepatitis reproduce the heterogeneity of the human disease

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BACKGROUND AND AIMS: Non-alcoholic steatohepatitis (NASH), the potentially progressive form of nonalcoholic fatty liver disease (NAFLD), is the pandemic liver disease of our time. Although there are several animal models of NASH, consensus regarding the optimal model is lacking. We aimed to compare features of NASH in the two most widely-used mouse models: methionine-choline deficient (MCD) diet and Western diet.
METHODS: Mice were fed standard chow, MCD diet for 8 weeks, or Western diet (45% energy from fat, predominantly saturated fat, with 0.2% cholesterol, plus drinking water supplemented with fructose and glucose) for 16 weeks. Liver pathology and metabolic profile were compared.
RESULTS: The metabolic profile associated with human NASH was better mimicked by Western diet. Although hepatic steatosis (i.e., triglyceride accumulation) was also more severe, liver non-esterified fatty acid content was lower than in the MCD diet group. NASH was also less severe and less reproducible in the Western diet model, as evidenced by less liver cell death/apoptosis, inflammation, ductular reaction, and fibrosis. Various mechanisms implicated in human NASH pathogenesis/progression were also less robust in the Western diet model, including oxidative stress, ER stress, autophagy deregulation, and hedgehog pathway activation.
CONCLUSION: Feeding mice a Western diet models metabolic perturbations that are common in humans with mild NASH, whereas administration of a MCD diet better models the pathobiological mechanisms that cause human NAFLD to progress to advanced NASH.

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