Reduced lipoapoptosis, hedgehog pathway activation and fibrosis in caspase-2 deficient mice with non-alcoholic steatohepatitis

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Résumé en anglais	**OBJECTIVE:** Caspase-2 is an initiator caspase involved in multiple apoptotic pathways, particularly in response to specific intracellular stressors (eg, DNA damage, ER stress). We recently reported that caspase-2 was pivotal for the induction of cell death triggered by excessive intracellular accumulation of long-chain fatty acids, a response known as lipoapoptosis. The liver is particularly susceptible to lipid-induced damage, explaining the pandemic status of non-alcoholic fatty liver disease (NAFLD). Progression from NAFLD to non-alcoholic steatohepatitis (NASH) results, in part, from hepatocyte apoptosis and consequential paracrine-mediated fibrogenesis. We evaluated the hypothesis that caspase-2 promotes NASH-related cirrhosis. **DESIGN:** Caspase-2 was localised in liver biopsies from patients with NASH. Its expression was evaluated in different mouse models of NASH, and outcomes of diet-induced NASH were compared in wild-type (WT) and caspase-2-deficient mice. Lipotoxicity was modelled in vitro using hepatocytes derived from WT and caspase-2-deficient mice. **RESULTS:** We showed that caspase-2 is integral to the pathogenesis of NASH-related cirrhosis. Caspase-2 is localised in injured hepatocytes and its expression was markedly upregulated in patients and animal models of NASH. During lipotoxic stress, caspase-2 deficiency reduced apoptosis, inhibited induction of profibrogenic hedgehog target genes in mice and blocked production of hedgehog ligands in cultured hepatocytes. **CONCLUSIONS:** These data point to a critical role for caspase-2 in lipid-induced hepatocyte apoptosis *in vivo* for the production of apoptosis-associated fibrogenic factors and in the progression of lipid-induced liver fibrosis. This raises the intriguing possibility that caspase-2 may be a promising therapeutic target to prevent progression to NASH.
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