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LIVER DISEASE

Conscious uncoupling in NASH

Non-alcoholic steatohepatitis (NASH) — an inflammatory disease that can progress to cirrhosis and end-stage liver disease — is becoming increasingly common, and there are no approved pharmacological therapies. Wang *et al.* have now identified that CASP8 and FADD-like apoptosis regulator (CFLAR) can suppress steatohepatitis by inhibiting dimerization of apoptosis signal-regulating kinase 1 (ASK1; also known as MAP3K5), which indicates a new approach to treat this disease.

Given the role of CFLAR in the regulation of apoptosis, inflammation and fibrosis — all of which are hallmarks of NASH — Wang *et al.* hypothesized that CFLAR could be involved in NASH pathogenesis. Indeed, levels of CFLAR protein expression were considerably lower in the livers of mice and patients with NASH than in those of healthy individuals, and CFLAR expression correlated negatively with the extent of NASH progression.

To further investigate the role of CFLAR in NASH, the authors generated hepatocyte-specific *Cflar*-knockout (*Cflar*-HepKO) mice as well as hepatocyte-specific *Cflar*-overexpressing transgenic (*Cflar*-HepTg) mice. *Cflar* knockout was associated with a high-fat diet (HFD)-induced increase in hepatic lipid accumulation, insulin resistance and inflammatory response, whereas overexpression of *Cflar* markedly improved these parameters.

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Next, the authors analysed the activation of the different components of the mitogen-activated protein kinase (MAPK) signalling pathway — a key pathway in the pathogenesis of NASH — in the livers of *Cflar*-HepKO and *Cflar*-HepTg mice. Levels of phosphorylated ASK1 in the liver were significantly increased by *Cflar* deletion and suppressed by *Cflar* overexpression, whereas the phosphorylated levels of other MAPK pathway kinases tested were not affected. Deletion of *Ask1* largely reversed the exacerbation of HFD-induced hepatic steatosis, insulin resistance and impaired glucose handling caused by *Cflar* ablation. The authors then found that ASK1 and CFLAR interact directly, and that one fragment of CFLAR (203–260; CFLAR(S1)) binds to the amino-terminal domain of ASK1, which impairs its dimerization and subsequent autophosphorylation and activation.

Interestingly, the amino acid sequence of the CFLAR(S1) fragment is highly conserved among mice, monkeys and humans, so the authors evaluated the potential of CFLAR(S1) to ameliorate HFD-induced steatohepatitis by expressing the sequence encoding CFLAR(S1) in the livers of mice and monkeys using adeno-associated virus 8 (AAV8), a liver-targeted gene therapy vector. AAV8-mediated expression of CFLAR(S1) decreased hepatic lipid accumulation, inflammation and fibrosis, and improved glucose metabolism and insulin resistance in mice that had been fed a HFD. Similar therapeutic effects were observed in monkeys that already had moderate steatosis, inflammation and fibrosis before receiving AAV8-CFLAR(S1) and being fed a HFD. Together, these results indicate that treatment with CFLAR(S1) can reverse NASH and metabolic syndrome progression.

This study confirms ASK1 as a key therapeutic target for NASH. Although gene therapy with CFLAR(S1) is not likely to be a practical approach in humans, the authors suggest that future efforts could focus on identifying small molecules that mimic CFLAR(S1) or block ASK1 dimerization. Another strategy could be to use selective ASK1 inhibitors, and one such compound, selonsertib, has recently been successful in a phase II clinical trial in patients with NASH (NCT02466516).

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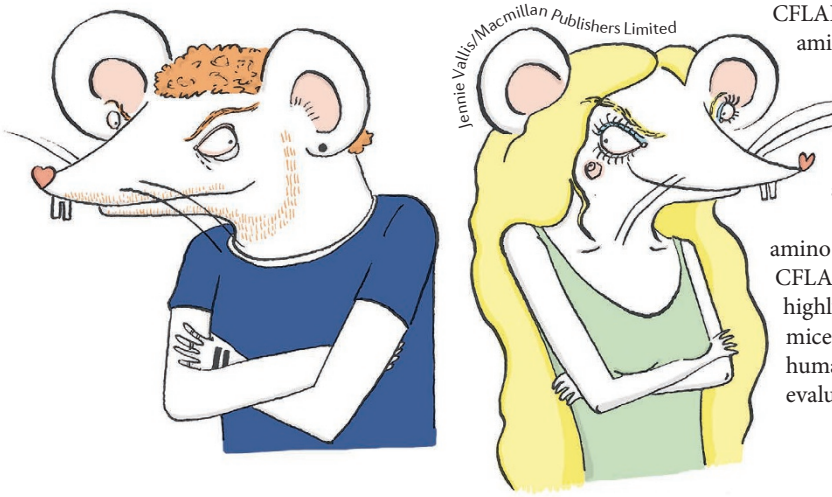

ORIGINAL ARTICLE Wang, P. -X. *et al.* Targeting CASP8 and FADD-like apoptosis regulator ameliorates nonalcoholic steatohepatitis in mice and nonhuman primates. *Nat. Med.* http://dx.doi.org/10.1038/nm.4290 (2017)

FURTHER READING Musso, G. *et al.* Non-alcoholic steatohepatitis: emerging molecular targets and therapeutic strategies. *Nat. Rev. Drug Discov.* **15**, 249–274 (2016)