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NASH

NASH and TLR9

New research shows that TLR9, an endosomal pattern-recognition receptor required for NASH development in mice, is activated by mitochondrial DNA (mtDNA) released from hepatocytes.

NAFLD is a leading cause of chronic liver disease in the developed world. NAFLD can progress to NASH in some individuals, although the mechanisms underlying this progression remain unclear.

"We have shown that TLR9 is required to elicit various types of liver injury in mice, including NASH, yet TLR9 is ubiquitously expressed. This made us consider if the difference between people who are obese with or without NASH is the presence of the ligand for TLR9," explains corresponding author Wajahat Mehal.

Because mtDNA is released by hepatocytes after liver injury, the researchers measured plasma mtDNA concentrations in patients who were obese, with or without NASH. Patients with NASH had higher levels of plasma mtDNA than patients without NASH. In addition, plasma from patients with NASH produced stronger activation of a TLR9 reporter cell line than plasma from patients without NASH.

Using a mouse model of NASH induced by high-fat diet feeding, the authors next investigated whether loss of TLR9 specifically in lysozyme-producing cells, which include liver-resident macrophages, could reduce liver inflammation and steatosis. Mice lacking *Tlr9* in these cells had less severe NASH and lower expression of pro-inflammatory genes than wild-type mice when both groups were fed a high-fat diet. Administration of a TLR7–TLR9 antagonist to wild-type mice with established NASH reduced the hepatic expression of inflammatory cytokines and markedly reduced NASH severity.

The authors plan to investigate the mechanisms of mtDNA release from hepatocytes in future work. "MtDNA from hepatocytes might be also responsible for activation of macrophages via TLR9 in other places such as adipose tissue or atheroma plaques," remarks Mehal.

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ORIGINAL ARTICLE Garcia-Martinez, I. *et al.* Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI83885