A positive feedback loop between RIP3 and JNK controls non-alcoholic steatohepatitis.

Non-alcoholic fatty liver disease (NAFLD) represents the most common liver disease in Western countries and often progresses to non-alcoholic steatohepatitis (NASH) leading ultimately to liver fibrosis and liver cancer. The occurrence of hepatocyte cell death—so far characterized as hepatocyte apoptosis—represents a fundamental step from benign steatosis toward progressive steatohepatitis. In contrast, the function of RIP3-dependent "necroptosis" in NASH and NASH-induced fibrosis is currently unknown. We show that RIP3 is upregulated in human NASH and in a dietary mouse model of steatohepatitis. RIP3 mediates liver injury, inflammation, induction of hepatic progenitor cells/activated cholangiocytes, and liver fibrosis through a pathway suppressed by Caspase-8. This function of RIP3 is mediated by a positive feedback loop involving activation of Jun-(N)-terminal Kinase (JNK). Furthermore, RIP3-dependent JNK activation promotes the release of pro-inflammatory mediators like MCP-1, thereby attracting macrophages to the injured liver and
further augmenting RIP3-dependent signaling, cell death, and liver fibrosis. Thus, RIP3-dependent necroptosis controls NASH-induced liver fibrosis. This pathway might represent a novel and specific target for pharmacological strategies in patients with NASH.