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STEATOHEPATITIS

PARP inhibition protective against alcoholic steatohepatitis and NASH

Inhibition of poly(ADP-ribose) polymerase (PARP) ameliorates alcoholic steatohepatitis and NASH in animal models, highlighting the therapeutic potential for PARP inhibitors as a treatment for steatohepatitis. Given that PARP inhibitors are already approved for other diseases (such as cancer), these agents could be repurposed for use in liver disease.

PARPs are key enzymes involved in DNA repair, but additional roles in oxidative stress, mitochondrial function and intermediary metabolism have been identified, all of which are key features in the development of steatohepatitis. As previous work described PARP activation in cirrhosis, as well as anti-inflammatory and anti-fibrotic effects of PARP inhibition in experimental models of liver fibrosis, the researchers explored whether PARP inhibition could have favourable effects on steatohepatitis.

Using a mouse model of alcoholic steatohepatitis (chronic and binge ethanol feeding), the investigators confirmed that excessive alcohol intake led to increased hepatic PARP activation, depleted NAD^+ levels and decreased sirtuin 1 levels. Conversely, pharmacological inhibition of PARP in the mouse models reversed the decrease in hepatic NAD^+ content and sirtuin 1 levels and led to beneficial effects on metabolic, inflammatory and oxidative stress changes induced by alcohol feeding as well as protected against hepatocellular injury. The same trend was also observed in *Parp1*$^{-/-}$ animals.

Switching to mouse models of NASH (high-fat diet or a diet deficient in methionine and choline), the study authors found that PARP inhibition was also beneficial in this context. Pharmacological treatment with PARP inhibitors attenuated liver injury, steatosis, metabolic disturbances, inflammation and fibrosis in NASH mouse models.

> “…therapeutic potential for PARP inhibitors as a treatment for steatohepatitis”

“These results demonstrate an important pathological role of PARP in development of alcoholic and nonalcoholic steatohepatitis or liver disease … by controlling oxidative or nitrative stress-induced hepatocellular injury or cell demise and consequent or preceding inflammatory processes, and also by facilitating pathological metabolic reprogramming leading to steatosis and steatohepatitis,” explains author Pal Pacher. The investigators are planning further research into the role of PARP inhibition in inflammation and metabolism in liver disease, as well as whether PARP inhibition might be beneficial for other alcohol-related pathologies.

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