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**The role of neutrophil extracellular traps (NET) and NLRP3 in alcohol- induced acceleration of MASH fibrosis**

*Babuta M, Morel C, de Carvalho Ribeiro M, et al. Neutrophil extracellular traps activate hepatic stellate cells and monocytes via NLRP3 sensing in alcohol- induced acceleration of MASH fibrosis. Gut 2024; 73: 1854–1869. doi: 10.1136/gutjnl-2023-331447.*

Excess alcohol use in patients with metabolic dysfunction- associated steatotic liver disease (MASLD) has been shown to be associated with an increased risk of hepatic fibrosis and hepatocellular carcinoma (HCC). In this study, Babuta et al. explored the mechanisms through which repeated alcohol binges exacerbate liver injury by using transcriptomic profiling and mechanistic approaches.

The investigators administered weekly alcohol binges in mice fed with a high fat-cholesterol-sugar diet (MASH (metabolic dysfunction-associated steatohepatitis) diet). It was demonstrated that the extent of liver fibrosis was increased in MASH plus alcohol- administered mice compared with the MASH-diet or alcohol-alone groups. Transcriptomic analysis also revealed differential expression of signalling pathways in combined MASH-alcohol group compared to MASH alone or alcohol alone groups. There was a significant increase in genes involved in neutrophil infiltration. Alcohol binges were found to promote neutrophil extracellular trap (NET) formation in the liver. NETs directly activated the hepatic stellate cells which is mediated by the NLRP3 (Nod-like receptor protein 3) inflammasome. NETs were also found to induce proinflammatory cytokine production in monocytes via NLRP3 sensing. The therapeutic role of neutrophil depletion and disruption of NETs was evaluated in vivo. Neutrophil depletion using anti-Ly6G antibody or NET disruption with deoxyribonuclease treatment attenuated liver damage and fibrosis. Additionally, inhibition of NLRP3 using MCC950 or NLRP3 deficiency attenuated NET formation, liver injury and fibrosis in MASH plus alcohol diet-fed mice.

This study highlighted how NET-induced activation of HSCs (hepatic stellate cells) and monocytes plays an important role in alcohol-induced acceleration of MASH fibrosis. Inhibition of NETs and/or NLRP3 could be used as novel therapeutic approaches to attenuate the profibrotic effects of alcohol in MASH.