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**Stressed hepatocyte sustains alcohol-associated hepatitis progression by producing leukocyte cell-derived chemotaxin 2**

Xu H, Wu Z, Qin J, *et al.* Stressed hepatocyte sustains alcohol-associated hepatitis progression by producing leukocyte cell-derived chemotaxin 2. Gut 2025; 74(8): 1321-1334. doi: 10.1136/gutjnl-2024-334318

Alcohol-associated hepatitis (AH) progression is driven by a deleterious interaction between hepatocytes and neutrophils mediated by hepatocyte-derived leucocyte cell–derived chemotaxin 2 (LECT2). Xu *et al.* analysed bulk and single-cell RNA sequencing data from AH patient liver tissues and demonstrated marked upregulation of LECT2, correlating strongly with disease severity. Clinical validation through serum measurements and biopsy assessments confirmed these findings. Further, Xu *et al.* found in ethanol-fed mouse models replicating human AH, hepatic LECT2 expression increased significantly, and pharmacological inhibition of endoplasmic reticulum stress abolished this induction. Genetic manipulations provided functional evidence: Lect2-deficient mice displayed markedly reduced liver injury following ethanol exposure, while hepatic overexpression of Lect2 exacerbated histological damage and biochemical markers of injury. Mechanistic studies demonstrated that LECT2 binds directly to prohibitin 2 (PHB2) on neutrophil membranes, destabilising PHB1/PHB2 heterodimers and triggering PHB2 degradation. This disruption promoted reactive oxygen species accumulation, neutrophil activation, and neutrophil extracellular trap formation, thereby perpetuating inflammatory damage. Therapeutic intervention using Lect2-targeted shRNA in vivo significantly ameliorated ethanol-induced liver injury, reducing neutrophil infiltration and inflammatory markers. Collectively, the findings reveal a pathogenic LECT2–PHB2 axis that establishes a self-perpetuating loop of hepatocyte–neutrophil crosstalk and sustained inflammation, driving AH progression. These findings may open new therapeutic avenue in AH by targeting LECT2, either by suppressing its expression through gene-silencing strategies, blocking its interaction with PHB2, or modulating upstream endoplasmic reticulum stress pathways.