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Single-Cell Multi-Omic Analysis Reveals a Transitional Hepatocyte State Driving Liver Regeneration After Acetaminophen-Induced Necrosis

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Abstract

The cellular heterogeneity underlying liver regeneration remains incompletely understood. Employing single-cell RNA-seq, ATAC-seq, and mitochondrial DNA mutational profiling of 45,000 cells from acetaminophen-overdosed murine livers, we identified a rare transitional hepatocyte population (tHeps) expressing both mature hepatocyte markers (*Alb*, *Ttr*) and biliary transcription factors (*Sox9*, *Opgn*). These tHeps emerged at 48 hours post-injury, exhibited enhanced proliferative capacity, and gave rise to regenerating hepatocyte clones. Lineage-tracing using *Sox9-CreER* mice confirmed their bipotent differentiation potential. Interleukin-6/STAT3 signaling was requisite for tHep emergence. Therapeutic enhancement of this transitional state may accelerate recovery in acute liver failure.

Keywords: single-cell multi-omics, liver regeneration, transitional hepatocytes, acetaminophen toxicity, lineage tracing, IL-6/STAT3 signaling