Integrated single-cell and epigenomic analysis reveals cellular specificity of CYP2E1 in human alcohol-related liver disease

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Abstract

Cytochrome P450 2E1 (CYP2E1) is a key hepatic xenobiotic metabolizing enzyme classically localized to pericentral hepatocytes. However, its cellular specificity and regulatory landscape in human alcohol-related liver disease (ALD) remain incompletely defined. We aimed to delineate the spatial, cellular, and epigenetic determinants of CYP2E1 expression in health and in ALD. We integrated cross-species immunohistochemistry (human, mouse, rat, pig) with bulk RNA sequencing (human), single-cell RNA sequencing, and paired single-nucleus RNA and ATAC sequencing. Healthy controls and patients with ALD, including alcoholic hepatitis and cirrhosis, were analyzed to define CYP2E1 localization, zonation, and regulatory features across hepatocyte and non-parenchymal cell (NPC) populations. In healthy liver, CYP2E1 protein and transcript expression were predominantly localized to zone 3 hepatocytes across species and platforms. Apparent CYP2E1 signals in NPC populations were not accompanied by CYP2E1-linked chromatin accessibility and were consistent with hepatocyte-derived ambient RNA or technical contamination rather than bona fide NPC expression. In human ALD, CYP2E1 expression is reduced in alcoholic hepatitis and cirrhosis, particularly in the pericentral compartment, and is associated with increased AST levels and impaired metabolic zonation. These findings contrast with ethanol-induced CYP2E1 upregulation during active exposure and suggest that advanced ALD is characterized by loss of CYP2E1 expression linked to hepatocyte dysfunction. CYP2E1 is a predominantly hepatocytic enzyme that, in the healthy liver, exhibits strong pericentral enrichment. In chronic ALD, CYP2E1 expression appears to reflect pericentral hepatocyte integrity rather than ethanol responsiveness, highlighting the importance of rigorous cell-type validation in liver disease studies.