MULTI-OMICS PROFILING OF BALLOONED HEPATOCYTES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IDENTIFIES A DIAGNOSTIC HISTOPATHOLOGICAL PANEL

Olivier Govaere

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Spatial multi-omics profiling of MASH liver biopsies identifies a spectrum of hepatocyte ballooning phenotypes and a panel of molecular markers with potential diagnostic utility for grading and staging MASLD.

KEY POINTS

- Comparison of regions with and without ballooning in 8 MASH F3 patient biopsies identified 194 differentially expressed genes in epithelial cells, including upregulation of stress-response markers SQSTM1/p62 and UBD, cell remodelling marker Annexin 2, and retinol metabolism markers AKR1B15 and AKR1B10.
- Expression of AKR1B10, AKR1B15, and UBD was linearly correlated with hepatocyte ballooning scores, lobular inflammation scores, and fibrosis stage in bulk RNA sequencing data from 206 MASLD patients.
- Immunohistochemistry validation in 20 MASLD biopsies showed nuclear and cytoplasmic expression of AKR1B10 and SHH in classical ballooned hepatocytes and intermediate periportal hepatocytes, while UBD/UBB and p62 expression was detected in smaller subsets of ballooned hepatocytes with Mallory-Denk-Bodies.
- Proteome multiplexing revealed cellular heterogeneity within ballooned hepatocytes, reflecting diverse cellular stress responses and pathological adaptations across a spectrum of ballooning phenotypes.
- This work addresses the urgent need for reliable markers to diagnose MASH given reported interobserver variability in H&E staining assessment of hepatocyte ballooning.

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