

Alcohol Reshapes Liver Zonal Plasticity and Immune-Metabolic Reprogramming in Metabolic-Syndrome Associated Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) commonly arises in metabolic dysfunction-associated steatohepatitis (MASH), alcohol-related liver disease (ALD), and metabolic dysfunction-associated ALD (MetALD), yet how zonal metabolic programs govern tumor lineage and immune responses remains unclear.

Methods: The study utilized complementary murine models of steatohepatitis-associated hepatocarcinogenesis. Additionally, experimental interventions included pharmacologic AhR inhibition and hepatocyte-specific β -catenin deletion to evaluate tumor burden and immune therapy response.

Results: We show that CTNNB1-mutant MASH-HCC originates from periportal and midlobular hepatocytes through perivenous reprogramming. This transition is characterized by β -catenin activation, loss of periportal metabolic functions, and induction of the immunosuppressive IDO1-kynurenine-AhR axis. In contrast, ethanol exposure suppresses perivenous xenobiotic programs, destabilizes the β -catenin/AhR/CAR axis, and increases tumor heterogeneity by generating both progenitor/biliary- and hepatocyte-derived MetALD-HCC that remain sensitive to anti-programmed death-1 (aPD1) therapy. Furthermore, pharmacologic AhR inhibition or hepatocyte-specific β -catenin deletion reduces MASH-HCC burden and restores sensitivity to aPD1 treatment.

Conclusions: Together, these findings identify AhR as a central mediator of β -catenin-driven tumor immunosuppression and a potential therapeutic target in CTNNB1-mutant HCC, highlighting context-dependent mechanisms of immune escape in alcohol-associated HCC.