Retinoic acid generates a beneficial microenvironment for liver progenitor cell activation in acute liver failure.

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Abstract

BACKGROUND: When massive necrosis occurs in acute liver failure (ALF), rapid expansion of HSCs called liver progenitor cells (LPCs) in a process called ductular reaction is required for survival. The underlying mechanisms governing this process are not entirely known to date. In ALF, high levels of retinoic acid (RA), a molecule known for its pleiotropic roles in embryonic development, are secreted by activated HSCs. We hypothesized that RA plays a key role in ductular reaction during ALF. METHODS: RNAseq was performed to identify molecular signaling pathways affected by all-trans retinoid acid (atRA) treatment in HepaRG LPCs. Functional assays were performed in HepaRG cells treated with atRA or cocultured with LX-2 cells and in the liver tissue of patients suffering from ALF. RESULTS: Under ALF conditions, activated HSCs secreted RA, inducing RARalpha nuclear translocation in LPCs. RNAseq data and investigations in HepaRG cells revealed that atRA treatment activated the WNT-beta-Catenin pathway, enhanced stemness genes (SOX9, AFP, and others), increased energy storage, and elevated the expression of ATP-binding cassette transporters in a RARalpha nuclear translocation-dependent manner. Further, atRA treatment-induced pathways were confirmed in a coculture system of HepaRG with LX-2 cells. Patients suffering from ALF who displayed RARalpha nuclear translocation in the LPCs had significantly better MELD scores than those without. CONCLUSIONS: During ALF, RA secreted by activated HSCs promotes LPC activation, a prerequisite for subsequent LPC-mediated liver regeneration.