

PISA 2026 Abstract

Title: Investigating the Mechanisms of Retinoic Acid Signaling in Liver and Hepatic Stellate Cell Development

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Introduction: Retinoic acid (RA) signaling is key to several developmental and pathologic processes, acting as a mediator of target gene expression. Hepatic stellate cells (HSCs) are the primary storage site for retinoids. In mice, loss of HSC retinoid storage leads to increased RA signaling in the liver and decreased hepatocellular carcinoma (HCC) incidence (Shirakami Y, 2012, *Carcinogenesis*, 33:268-274). We hypothesize that RAR signaling is essential for normal liver development and for reducing a proliferative phenotype that is a frequent hallmark of precancerous cells.

Methods: This project is investigating the RA signaling pathway in larval zebrafish by pharmacologically modulating RA activity in the period when HSCs are entering the liver (56-80 hours post fertilization (hpf)). We treat larval zebrafish with RA pathway agonists and inhibitors, then evaluate HSCs and liver phenotype by confocal imaging and gene expression by in situ stains and qPCR. The resulting proliferative state and gene expression expose the involvement of the targeted RA components in late-stage liver development.

Results: Treatment of larval zebrafish with the retinoic acid receptor- α (RAR α) agonist AM580 decreases the number of HSCs in the larval liver at (hpf), while treatment with the retinoid X receptor (RXR) agonist methoprene acid (MA) increases HSC number (Yin C, Evason KJ, 2012, *Hepatology*, 56:1958–70). I confirmed that MA increases HSC number at 80 hpf and extended these findings, showing that liver volume was not affected by MA at 80 hpf but was increased at 144 hpf. Treatment with DEAB, a drug which inhibits ALDH from synthesizing RA, results in a higher number of HSCs at 80 hpf. Dissimilar to the effect of MA on liver volume, DEAB treatment did not significantly impact liver size. Together, these findings suggest that HSC and hepatocyte proliferation may not be controlled by the same RA factors, but still the modulation of RA signaling results in abnormal HSC and liver development.

Conclusions: During early embryonic stages of development, RA plays an important role in embryo patterning, hepatic fate specification, and liver budding. Despite the mature liver being the primary site of retinoid storage, hepatic RA signaling mechanisms are poorly understood after the liver bud formation stage. This project aims to fill that gap by modulating RA signaling during the developmental stage during which HSCs are entering the liver.