

Targeting De Novo Pyrimidine Synthesis via CAD Inhibition Suppresses Hepatic Stellate Cell Activation and Liver Fibrosis

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Background

Chronic liver injury leads to fibrosis and cirrhosis, a leading cause of death worldwide, and is driven by hepatic stellate cell (HSC) activation, characterized by proliferation and collagen deposition. HSC activation, when stimulated by platelet-derived growth factor (PDGF), has been shown to involve increased glycolysis, but the involvement of other metabolic pathways remains elusive. Pyrimidine metabolism from glutamine (de novo) or recycled nucleic bases (salvage) (Thymine, Cytosine, and Uracil) generates nitrogenous bases required for DNA/RNA synthesis. How de novo drives HSC activation and subsequent liver fibrosis remains unknown, which is the focus of the study.

Methods

We pharmacologically inhibited the Carbamoyl-phosphate synthetase 2, Aspartate transcarbamoylase, and Dihydroorotase complex (CAD) in primary human HSCs *in vitro* and patient-derived precision-cut liver slices *ex vivo*.

Results

In vitro, PDGF increased HSC proliferation compared to vehicle as measured by uptake of 5-Ethynyl-2'-deoxyuridine, which was abrogated by sparfosic acid, a CAD inhibitor. *Ex vivo*, PDGF increased collagen deposition compared to vehicle in human PCLS, which was attenuated by sparfosic acid. Collagen deposition was assessed by total collagen staining via picrosirius red and collagen 1 expression via western blot.

Conclusion

Collectively, these findings demonstrate that pyrimidine from de novo synthesis promotes HSC proliferation and fibrosis, presenting a novel therapeutic target.