PPI-4050 Inhibits Hepatic Stellate Cell Proliferation and Activation Via AMPK, and Improves Hepatic Fibrosis in CCL4-Induced Liver Injury Model

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Rationale
Hepatic stellate cells (HSC) are considered a key player in the fibrogenic process of the liver. In response to liver injury, HSCs become activated and transdifferentiate into myofibroblast-like cells which display increased proliferation and collagen synthesis. Recent studies have shown that the activation of AMPK modulates HSCs activation and inhibits transforming growth factor (TGF-β) induced fibrogenic property of HSC. In the present study, we investigated whether treatment with PPI-4050 could decrease in vitro HSC activation and in vivo liver fibrosis in mice. PPI-4050 is a first-in-class antifibrotic compound presently in clinical phase II trial in metabolic syndrome associated with diabetes and in idiopathic pulmonary fibrosis.

Methods
In vitro human HSC activation: Serum-starved HSC cells were treated with or without PPI-4050 (500 µM and 250 µM) and TGF-β1 (10 ng/ml) for 24 h. Cells proliferation was assessed with resazurin cell viability assay and cell cycle was analyzed by flow cytometry. Protein were quantified by western blot performed with TaqMan Gene Expression Assay.

Results
- PPI-4050 reduces HSC proliferation
- PPI-4050 treatment inhibits α-SMA
- PPI-4050 induces G0-G1 cell cycle arrest
- PPI-4050 activates AMPK
- Hydroxyproline Content
- Histomorphometry
- mRNA Expression

Conclusions
This study demonstrates that PPI-4050:
- Reduces HSC activation via AMPK
- Reduces liver fibrosis by decreasing overexpression/overproduction of:
  - profibrotic/EMT markers
  - remodeling markers
  - collagen deposition

These results suggest that PPI-4050 offers the potential as a novel therapy for hepatic fibrosis.