Metformin and Mannose Inhibit Human Hepatic Stellate Cell Activation and Proliferation: Implications for Anti-Fibrotic Therapies in Patients with MPI Deficiency and Chronic Liver Disease

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Introduction: Children with mutations in mannose phosphate isomerase (MPI) develop early liver fibrosis that can progress to require liver transplantation. We have previously shown that MPI loss in hepatic stellate cells (HSCs) promotes HSC activation and mannose can decrease HSC activation and expression of PDGFR a potent cytokine that promotes HSC proliferation. Metformin can decrease HSC activation and proliferation and promote mannose uptake in dermal fibroblasts. Therefore, we hypothesized that mannose supplementation would decrease HSC proliferation and have synergistic anti-proliferative and anti-fibrotic effects when combined with metformin. Methods: LX2 and primary human HSCs were treated with increasing concentrations of mannose +/- metformin for 24-72 hours and HSC proliferation assessed by MTT assays. Metformin effects on HSC activation were assessed by qPCR. A stable model of MPI loss was created using CRISPR-Cas9 lentiviral infection to study impact of mannose and metformin in a more physiologically relevant in vitro model of MPI deficiency. Results: 1) Mannose supplementation (25mM) alone reduced HSC proliferation and metformin significantly decreased HSC proliferation, though synergistic effects were not yet observed. 2) Metformin decreased markers of HSC activation and MPI expression, the latter which may reflect feedback inhibition resulting from increased endogenous intracellular mannose. 3) Decreased MPI activity and HSC activation was seen in CRISPR MPI cells and will serve as a tool for additional studies. Conclusion: Mannose and metformin can dampen HSC activation and proliferation. Future work focuses on impact of mannose metabolism on receptor signaling important for HSC biology and interplay with metformin.

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