Poster

Tumor microenvironment modulation in hepatocarcinoma

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ABSTRACT

Motivation: Hepatocellular carcinoma, one of the most aggressive malignancies with the lowest survival rates, has a complex tumor microenvironment containing immune cells, tumor cells, HSCs, and other cancer-associated cells. The tumor microenvironment signals tumoral cells to become more tumorigenic. In liver fibrosis and HCC, HSCs transdifferentiate and become active, expressing a-SMA and producing ECM proteins. Energy-intensive HSC activation needs glycolysis, mitochondrial respiration, and glutaminolysis. Targeting HSC activation in HCC is a possible therapy for this prevalent disease. Previous research from our group has demonstrated that GATA4 modulates HSC, leading it to switch from active to inactive state. This work investigates the effect of GATA4 on the metabolism of active HSCS and the efficacy of pharmacological treatments to increase endogenous GATA4 expression in active HSCs to inactivate them.

Methods: Activated human-derived activated hepatic stellate cell line, LX2, was used to determine the effect of GATA4 overexpression in cellular respiration. Previously identified putative activators of GATA4 endogenous expression were interrogated for their potential to inactivate HSCs.

Results: GATA4 overexpression in activated HSCs induces decreased in mitochondrial respiration and metabolomic analysis showed a decreased in a-cetoglutarate. The addition of Dimetil a-cetoglutarate, DMKG, did not restored the inactivation of HSCs promoted by GATA4. Two different molecules with potential of activated the endogenous expression of GATA4 were not able to revert the active phenotype of HSCs.

Conclusions: : The decrease of mitochondrial respiration induced by GATA4 to revert the active phenotype of HSCs is independent of a-cetoglutarate. The potential activators of GATA4 expression identified in a previous screening from a repurposing library were not able to induce the reversion of the activate state, as measured by a-SMA expression and ECM proteins.

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