AMPK/PGC-1α-mediated metabolic reprogramming of hepatic stellate cells promotes stemness of hepatocellular carcinoma via metabolite lactate shuttle

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INTRODUCTION

Hepatic stellate cells (HSCs), as important interstitial cells in liver **tumor microenvironment (TME)**, play an important role in the malignant process of liver tumor. We previously found that the metabolic shifts of mitochondria drove the malignant transformation of tumors, suggesting that the **mitochondrial metabolism mode** might affect the cell fates in the tumor microenvironment.

AIM

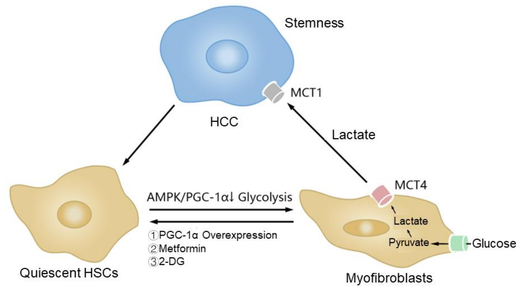
We aim to explore the roles of HSCs in **hepatocellular carcinoma (HCC) stem cell pool** and its regulatory mechanisms.

METHOD

- Glucose uptake ability, oxygen consumption rate (OCR) and lactate accumulation, as well as AMPK activity, PGC-1α expression of HSCs were measured in a co-culture system with HCC cells.
- The expression of MCT1, the abilities of side population, sphere formation and tumor incidence and metastasis were detected to explore the stemness of HCC cells after co-culture.
- The glycolytic phenotype and pro-fibrotic capacity of HSCs, as well as stemness of HCC cells, were determined using AMPK agonists metformin or inhibitors of lactate accumulation.

RESULTS

- After co-culture with HCC cells, HSCs were activated with the **metabolic phenotype switch from oxidative phosphorylation to glycolysis** mediated by the **AMPK/PGC-1α signaling inactivation**, characterized by increased glucose uptake, oxygen consumption rate and lactate production **(Figure 1)**.
- The metabolic intermediate **lactate** transferred to and took up by HCC cells via the lactate transporter MCT1, promoted the stemness of HCC cells **(Figure 2)**.
- **Overexpression of PGC-1α or inhibitors of lactate accumulation** administrated in HSCs not only converted myofibroblasts to quiescent HSCs, but also reduced the side population, sphere formation and inhibited tumor incidence of HCC in an in vivo tumor model **(Figure 3)**.



Graphic Abstract: Metabolic coupling between HCC and HSC in TME.

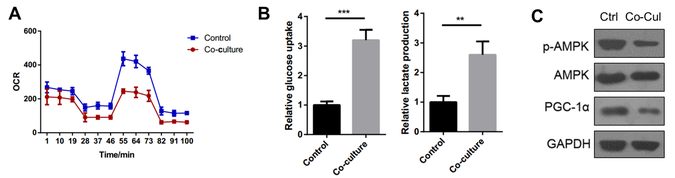


Figure 1. Metabolic phenotype switch of HSCs after co-culture with HCC.

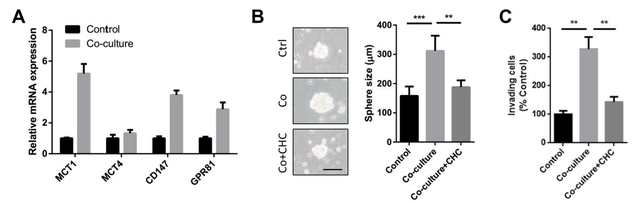


Figure 2. Lactate secreted by HSCs promoted the stemness of HCC.

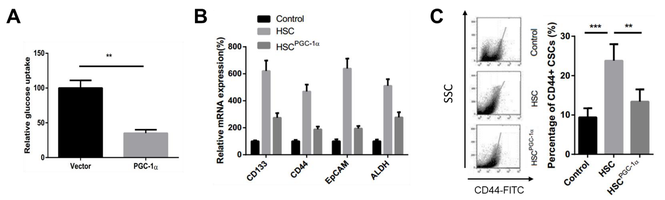


Figure 3. Overexpression of PGC-1α reduced the side population of HCC.

CONCLUSIONS

In this study, we explored the mechanisms of **AMPK/PGC-1α signaling pathway in HSCs mitochondrial metabolic shifts** and demonstrated **a reciprocal metabolic interplay** between HSCs and cancer cells through **metabolite lactate shuttle** in HCC TME **(Graphic Abstract)**, providing a novel cue of metabolism-based approaches to enhance the efficacy of cancer therapy.

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