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A HIF1α-GPD1 feedforward loop inhibits the progression of renal clear cell carcinoma via mitochondrial function and lipid metabolism

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Abstract

Background: Hypoxia signaling, especially the hypoxia inducible factor (HIF) pathway, is a major player in clear cell renal cell carcinoma (ccRCC), which is characterized by disorders in lipid and glycogen metabolism. However, the interaction between hypoxia and lipid metabolism in ccRCC progression is still poorly understood.

Methods: We used bioinformatic analysis and discovered that glycerol-3-phosphate dehydrogenase 1 (GPD1) may play a key role in hypoxia and lipid metabolism pathways in ccRCC. Tissue microarray, IHC staining, and survival analysis were performed to evaluate clinical function. In vitro and in vivo assays showed the biological effects of GPD1 in ccRCC progression.

Results: We found that the expression of GPD1 was downregulated in ccRCC tissues, and overexpression of GPD1 inhibited the progression of ccRCC both in vivo and in vitro. Furthermore, we demonstrated that hypoxia inducible factor-1α (HIF1α) directly regulates GPD1 at the transcriptional level, which leads to the inhibition of mitochondrial function and lipid metabolism. Additionally, GPD1 was shown to inhibit prolyl hydroxylase 3 (PHD3), which blocks prolyl-hydroxylation of HIF1α and subsequent proteasomal degradation, and thus reinforces the inhibition of mitochondrial function and phosphorylation of AMPK via suppressing glycerol-3-phosphate dehydrogenase 2 (GPD2).

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