


RESEARCH

Open Access

A HIF1 α -GPD1 feedforward loop inhibits the progression of renal clear cell carcinoma via mitochondrial function and lipid metabolism



Ren Liu^{1†}, Yuanfa Feng^{2,3†}, Yulin Deng^{1†}, Zhihao Zou², Jianheng Ye², Zhiduan Cai⁴, Xuejin Zhu^{2,3}, Yingke Liang², Jianming Lu², Hui Zhang², Yong Luo⁵, Zhaodong Han², Yangjia Zhuo², Qingling Xie^{1,4}, Chi Tin Hon⁶, Yuxiang Liang^{2*}, Chin-lee Wu^{7,8*} and Weide Zhong^{1,2,3,6,7,8*} 

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-1 α (HIF1 α) 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 HIF1 α and subsequent proteasomal degradation, and thus reinforces the inhibition of mitochondrial function and phosphorylation of AMPK via suppressing glycerol-3-phosphate dehydrogenase 2 (GPD2).

* Correspondence: doctorbaby@126.com; cwu2@mg.harvard.edu; zhongwd2009@live.cn

[†]Ren Liu, Yuanfa Feng and Yulin Deng contributed equally to this work.

²Department of Urology, Guangdong Key Laboratory of Clinical Molecular Medicine and Diagnostics, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou 510180, China

⁷Departments of Urology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA

¹Guangdong Provincial Institute of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

Full list of author information is available at the end of the article



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.