ARTICLE OPEN

Metformin escape in prostate cancer by activating the PTGR1 transcriptional program through a novel super-enhancer

Jianheng Ye[1], Shanghua Cai[1,2,3], Yuanfa Feng[1,2], Jinchuang Li[1], Zhiduan Cai[1], Yulin Deng[2], Ren Liu[1], Xuejin Zhu[1], Jianming Lu[1], Yangjia Zhuo[1], Yingke Liang[1], Jianjiang Xie[1], Yanqiong Zhang[4], Huichan He[2], Zhaodong Han[1]✉, Zhenyu Jia[5,6]✉ and Weide Zhong[1,2,3,7]✉

The therapeutic efficacy of metformin in prostate cancer (PCa) appears uncertain based on various clinical trials. Metformin treatment failure may be attributed to the high frequency of transcriptional dysregulation, which leads to drug resistance. However, the underlying mechanism is still unclear. In this study, we found evidences that metformin resistance in PCa cells may be linked to cell cycle reactivation. Super-enhancers (SEs), crucial regulatory elements, have been shown to be associated with drug resistance in various cancers. Our analysis of SEs in metformin-resistant (MetR) PCa cells revealed a correlation with Prostaglandin Reductase 1 (PTGR1) expression, which was identified as significantly increased in a cluster of cells with metformin resistance through single-cell transcriptome sequencing. Our functional experiments showed that PTGR1 overexpression accelerated cell cycle progression by promoting progression from the G0/G1 to the S and G2/M phases, resulting in reduced sensitivity to metformin. Additionally, we identified key transcription factors that significantly increase PTGR1 expression, such as SRF and RUNX3, providing potential new targets to address metformin resistance in PCa. In conclusion, our study sheds new light on the cellular mechanism underlying metformin resistance and the regulation of the SE-TFs-PTGR1 axis, offering potential avenues to enhance metformin's therapeutic efficacy in PCa.

Signal Transduction and Targeted Therapy (2023)8:303 ; https://doi.org/10.1038/s41392-023-01516-2

INTRODUCTION

Prostate cancer (PCa) is the most common male malignant tumor and the second leading cause of cancer death in the United States.[1] To date, PCa therapy still faces great challenges due to the heterogeneous nature of the disease. Although PCa patients receiving androgen deprivation therapy (ADT), surgery, radiation and chemotherapy tend to have a lower risk of recurrence and better survival outcomes,[2] manifestations of metabolic syndrome, such as obesity, insulin resistance and impaired glucose tolerance, often occur following treatment which eventually causes drug resistance and distal metastasis.[3] To maintain a sufficient energy supply for PCa cells, alterations in cellular metabolism continue to occur during the progression from prostate intraepithelial neoplasia to metastasis. For example, healthy prostate cells utilize citrate to synthesize prostatic fluid so that the tricarboxylic acid (TCA) cycle is largely inhibited.[4] In contrast, the energy production in aggressive PCa cells is accomplished mainly through the TCA cycle and oxidative phosphorylation (OXPHOS).[4] However, OXPHOS level has been reported to be decreased while glycolytic activity is compensatorily increased in metastatic PCa cells.[5] Taken together, the previous studies indicated that PCa may rely on distinct metabolic pathways for energy production at various stages, providing potential targets for precision therapy.

Metformin is a first-line oral hypoglycemic drug derived from extracts of the herb *Galega officinalis*. Accumulating studies have indicated that metformin may be a potential candidate adjuvant therapeutic agent for PCa due to its multiple anticancer effects, satisfactory tolerance in humans, and low cost.[6–8] Metformin not only exerts excellent glucose-lowering effects, but also suppresses cancer growth by inducing G0/G1 arrest and decreasing OXPHOS level to modulate tumor cell metabolism.[7–9] Although accumulating clinical data have demonstrated the association between metformin treatment and favorable outcomes in PCa patients,[10–14] it has been reported that certain patients fail to respond to metformin.[15–18] This is consistent with a previous study that preliminary demonstrated resistance to metformin treatment in various cancers due to tumor heterogeneity.[19] Therefore, we hypothesized that a subpopulation of PCa patients may develop metformin resistance after a period of treatment and aimed to find insights into the underlying mechanism.

Specific phenotypes of a certain cancer, including acquired drug resistance stemming from gradual adaptation to extracellular stimulation, may be associated with unique genomic

[1]Department of Urology, Guangzhou First People's Hospital, South China University of Technology, 510180 Guangzhou, Guangdong, China; [2]Urology Key Laboratory of Guangdong Province, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, 510230 Guangzhou, Guangdong, China; [3]Guangzhou National Laboratory, No. 9 XingDaoHuanBei Road, Guangzhou International Bio Island, 510005 Guangzhou, Guangdong, China; [4]Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, 100700 Beijing, China; [5]Department of Botany and Plant Sciences, University of California, Riverside, CA 92507, USA; [6]Graduate Program in Genetics, Genomics & Bioinformatics, University of California, Riverside, CA 92507, USA and [7]State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Taipa, 999078 Macau, China
Correspondence: Zhaodong Han (75028579@qq.com) or Zhenyu Jia (zhenyuj@ucr.edu) or Weide Zhong (zhongwd2009@live.cn)
These authors contributed equally: Jianheng Ye, Shanghua Cai, Yuanfa Feng

Received: 2 September 2022 Revised: 25 May 2023 Accepted: 30 May 2023
Published online: 16 August 2023