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Metabolic epigenetic rewiring driven by MCT4 mediated lactate export contributes to resistance to PD-1 blockade in NSCLC

X. Niu¹, H. Wang², X. Zhang², J. Zhong³, H. Qin³, S.S. Hu²

¹Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai/CN.

²Zhejiang Key Laboratory of Multiomics and Molecular Enzymology, Yangtze Delta Region Institute of Tsinghua University, Zhejiang, 314006, China, Hangzhou/CN.

³Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, 241 Huaihai West Road, Xuhui District, Shanghai 200030, Shanghai/CN.

Correspondence: Xiaomin Niu, email: artey@sjtu.edu.cn



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INTRODUCTION

Resistance to PD-1 blockade remains a major obstacle in non-small cell lung cancer (NSCLC) treatment. To understand the molecular mechanisms underlying immunotherapy resistance, we performed integrative transcriptomic and proteomic analyses of clinical tumor samples from immunotherapy responders and nonresponders.

METHODS

Clinical samples from NSCLC patients who received PD-1/PD-L1 immunotherapy at Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, were collected between 2018 to 2024.

DISCUSSION AND CONCLUSION

These findings indicate that the lactate transporter MCT4 suppresses antitumor immunity and that targeting MCT4 represents a promising strategy to overcome immunotherapy resistance in patients with highly glycolytic NSCLC.

RESULTS

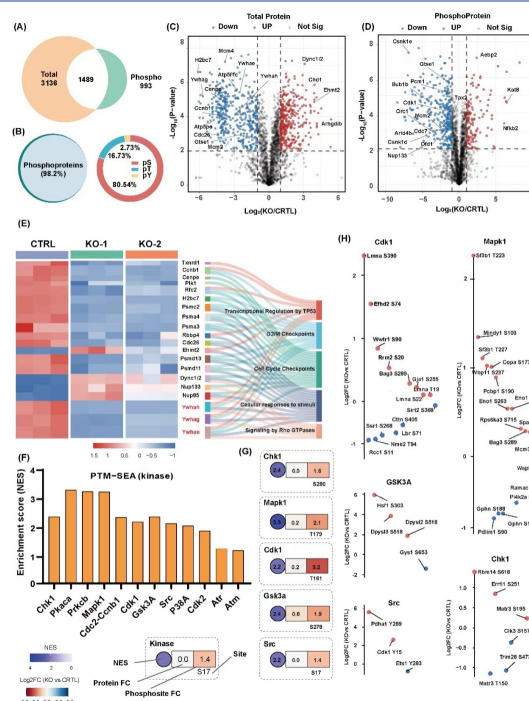


Figure: Effects of MCT4 knockout on total and phosphorylated protein levels. (A) Venn diagrams showing the identified total and phosphorylated proteins in LLC and LLC MCT4-ko cells. (B) Specificity of the phosphorylated proteins isolated by Ti4+-IMAC and the proportions of phosphoserine (pS), phosphothreonine (pT), and phosphotyrosine (pY) residues among the phosphosites. Volcano plot representing the results of the quantitative analysis of LLC MCT4-KO1/2 cells versus CTRL cells in terms of (C) total protein and (D) phosphoprotein levels. (E) Hierarchical clustering heatmap and functional enrichment analysis of differentially expressed proteins in MCT4-depleted LLC cells. (F) Kinase signatures were significantly (FDR < 0.05) different between MCT4-KO1/2 LLC cells and control LLC cells, as assessed by PTM signature enrichment analysis (PTM-SEA). (G) Diagram showing kinases with increased activity inferred from the phosphorylation levels of their substrates and the corresponding kinase-activating sites. (H) Dot plot showing the median log2-fold change in kinase substrate phosphorylation. Pink and blue indicate sites with increased and decreased phosphorylation, respectively, between LLC WT and MCT4-ko cells.

Tumors from nonresponders exhibited increased glycolytic activity and expression of the lactate transporter MCT4, which correlated with reduced CD8⁺T-cell infiltration and unfavorable clinical outcomes. In highly glycolytic NSCLC cell models, MCT4 deficiency not only restored CD8⁺T-cell proliferation and effector function but also induced tumor-intrinsic mitochondrial stress, characterized by increased reactive oxygen species levels, reduced ATP production, and loss of mitochondrial membrane potential, ultimately leading to G2/M cell cycle arrest. Mechanistically, MCT4 deficiency activated the EHMT2/H3K9me3 axis, resulting in the transcriptional repression of genes that govern cell cycle progression. Importantly, pharmacological inhibition of MCT4 produced comparable effects.