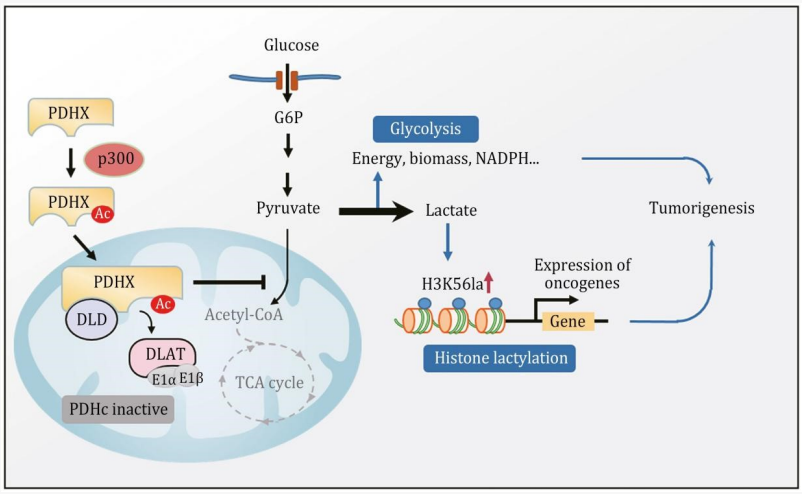
Metabolic shift in liver cancer: how PDHX acetylation drives tumor growth

GA, UNITED STATES, March 3, 2025 /EINPresswire.com/ -- A recent study has unveiled a new mechanism driving hepatocellular carcinoma (HCC) progression through the acetylation of pyruvate dehydrogenase complex (PDC) component X (PDHX), a critical component of the PDC. This modification disrupts PDC assembly, inhibits its function, and shifts metabolism towards aerobic glycolysis, promoting tumor growth. The findings highlight PDHX acetylation as both a potential biomarker and therapeutic target, offering new possibilities for liver cancer treatment and advancing our understanding of cancer cell metabolism.



Working model: PDHX acetylation promotes tumor progression by disrupting PDC assembly and activating lactylation-mediated gene expression.

Cancer cells are known to favor aerobic glycolysis for energy production, a phenomenon termed the Warburg effect. This metabolic shift is essential for tumor growth, supplying energy, metabolites, and maintaining redox balance. The pyruvate dehydrogenase complex (PDC) plays a pivotal role in linking glycolysis to the tricarboxylic acid (TCA) cycle, but the mechanisms regulating PDC activity—especially through post-translational modifications like acetylation—remain poorly understood. While previous research has focused on the phosphorylation of pyruvate dehydrogenase (PDH), acetylation has been largely overlooked, making it a critical area for further exploration.

In a study (DOI: 10.1093/procel/pwae052) published on September 23, 2024, in Protein & Cell, researchers from the University of Science and Technology of China revealed a novel regulatory mechanism by which pyruvate dehydrogenase complex component X (PDHX) acetylation accelerates hepatocellular carcinoma (HCC) progression. This research offers fresh insights into how metabolic alterations fuel cancer growth, uncovering a previously unappreciated role of acetylation in modulating PDC activity and its impact on liver cancer metabolism.

The study demonstrates that PDHX, a key component of the PDC, undergoes acetylation at lysine 488 by the acetyltransferase p300. This modification impedes the interaction between PDHX and dihydrolipoyl transacetylase (DLAT), disrupting PDC core assembly and reducing its activity. As a result, glucose metabolism is rerouted towards aerobic glycolysis, boosting lactate production. The elevated lactate levels then induce histone lactylation, especially at H3K56, triggering oncogene expression that drives tumor growth.

Significantly, the researchers found that PDHX acetylation is upregulated in HCC tissues and correlates with poor clinical prognosis. Inhibition of PDHX acetylation or restoration of PDC activity effectively suppresses tumor growth. For instance, treatment with dichloroacetate (DCA), a PDH kinase (PDK) inhibitor that restores PDC function, significantly targeted glycolysis-dependent tumors exhibiting high PDHX acetylation levels. These findings suggest that PDHX acetylation could serve as a diagnostic biomarker for HCC and offer a potential therapeutic target for intervention.

Dr. Huafeng Zhang, a senior author of the study, highlighted the significance of their discovery: Our research uncovers an entirely new aspect of cancer metabolism, where PDHX acetylation plays a crucial role in disrupting PDC activity and driving tumor progression. This finding not only broadens our understanding of liver cancer biology but also opens up promising new pathways for targeted therapeutic development.

The implications of this research are far-reaching for the diagnosis and treatment of liver cancer. PDHX Lys 488 acetylation could serve as a valuable biomarker for predicting tumor progression and assessing patient prognosis. Targeting PDHX acetylation or its downstream metabolic effects, such as lactate-driven gene expression, may offer new avenues for therapeutic intervention. Future research could focus on developing inhibitors that target the p300 acetyltransferase or explore the potential of existing drugs like DCA to restore PDC activity in cancer cells. These approaches could lead to more effective and personalized treatment strategies for liver cancer patients.

DOI
10.1093/procel/pwae052

Original Source URL
https://doi.org/10.1093/procel/pwae052

Funding information
This work is supported in part by National Natural Science Foundation of China (Grant Nos. 81930083, 82192893, 81821001, and 82303217), National Key R&D Program of China (2022YFA1304504), the Chinese Academy of Sciences (XDB39000000), the Global Select Project (DJK-LX-2022001) of the Institute of Health and Medicine, Hefei Comprehensive National Science Center and the Fundamental Research Funds for the Central Universities (WK9100000051).

Lucy Wang
BioDesign Research
email us here