

Article

Deciphering the Metabolic Basis and Molecular Circuitry of the Warburg Paradox in Lymphoma

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Simple Summary: This study explores Warburg's paradox, whereby cancer cells use both glucose and oxygen to survive, even though glucose is converted to lactate instead of being oxidized. By systematically investigating cellular metabolism during each phase of cell division and comparing the metabolic profiles of lymphoma cells and non-malignant lymphocytes, we discovered that pyruvate, the end-product of glucose metabolism, is converted into alanine. This conversion directs glutamine carbon, rather than glucose, into the TCA cycle. Furthermore, using fludarabine to selectively inhibit lymphoma cell proliferation, we showed that blocking the conversion of pyruvate to alanine disrupts the TCA cycle and interferes with the supply of nucleotides and the energy necessary for cancer cell growth. Our findings suggest that with the suppression of glucose oxidation, the conversion of pyruvate to alanine is the crucial metabolic link that connects glucose and oxygen metabolism and serves as a key component of Warburg's paradox.

Abstract: **Background/Objectives:** Warburg's metabolic paradox illustrates that malignant cells require both glucose and oxygen to survive, even after converting glucose into lactate. It remains unclear whether sparing glucose from oxidation intersects with TCA cycle continuity and if this confers any metabolic advantage in proliferating cancers. This study seeks to understand the mechanistic basis of Warburg's paradox and its overall implications for lymphomagenesis. **Methods:** Using metabolomics, we first examined the metabolomic profiles, glucose, and glutamine carbon labeling patterns in the metabolism during the cell cycle. We then investigated proliferation-specific metabolic features of malignant and nonmalignant cells. Finally, through bioinformatics and the identification of appropriate pharmacological targets, we established malignant-specific proliferative implications for the Warburg paradox associated with metabolic features in this study. **Results:** Our results indicate that pyruvate, lactate, and alanine levels surge during the S phase and are correlated with nucleotide synthesis. By using ¹³C_{1,2}-Glucose and ¹³C₆, ¹⁵N₂-Glutamine isotope tracers, we observed that the transamination of pyruvate to alanine is elevated in lymphoma and coincides with the entry of glutamine carbon into the TCA cycle. Finally, by using fludarabine as a strong inhibitor of lymphoma, we demonstrate that disrupting the transamination of pyruvate to alanine correlates with the simultaneous suppression of glucose-derived nucleotide biosynthesis and glutamine carbon entry into the TCA cycle. **Conclusions:** We conclude that the transamination of pyruvate to alanine intersects with reduced glucose oxidation and maintains the TCA cycle as a critical metabolic feature of Warburg's paradox and lymphomagenesis.

Keywords: Warburg effect; lymphoma; lactate; glucose; nucleotides; glutamine; targeted inhibitors; transaminase

1. Introduction

"At first glance, it appears paradoxical that a cell that can live by fermentation may die because it lacks oxygen". "But there is really no contradiction here" and "Providing



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Metabolic And Molecular Basis Of Acquired Disease

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