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AEROBIC GLYCOLYSIS IN CANCER CELLS (THE WARBURG EFFECT): BIOCHEMICAL MECHANISMS AND THERAPEUTIC IMPLICATIONS

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Annotation (Abstract) : Cancer cells exhibit a peculiar metabolic phenotype known as aerobic glycolysis or the Warburg effect, where they preferentially convert glucose to lactate even in the presence of sufficient oxygen. This review outlines the biochemical foundations of this phenomenon, contrasting it with normal oxidative phosphorylation. We discuss the key enzymatic shifts (e.g., increased hexokinase 2, pyruvate kinase M2, and LDHA), the role of oncogenes (c-Myc, HIF-1α) and tumor suppressors (p53), and the resulting metabolic advantage for rapid proliferation. Finally, we highlight potential therapeutic strategies targeting this pathway.

Keywords: Warburg effect, aerobic glycolysis, cancer metabolism, lactate, hexokinase 2, PKM2, HIF-1α, tumor microenvironment.

Introduction.

For nearly a century, the metabolic behavior of cancer cells has fascinated and perplexed biologists. In the 1920s, the German physiologist Otto Warburg made a groundbreaking observation: unlike normal tissues that primarily generate energy through mitochondrial oxidative phosphorylation (OXPHOS) in the presence of oxygen, tumor slices exhibited unusually high rates of glucose consumption and lactate production even under fully aerobic conditions. This phenomenon, later termed the Warburg effect or aerobic glycolysis, contradicted the long-held belief that cells with access to oxygen would suppress fermentation (the Pasteur effect).

At first glance, aerobic glycolysis appears biologically inefficient. Oxidative phosphorylation yields approximately 36 molecules of ATP per molecule of glucose, whereas aerobic glycolysis yields only 2 ATP per glucose. To compensate, cancer cells consume glucose at rates up to 200 times higher than their normal counterparts—a metabolic shift so consistent that it forms the basis for 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET), a cornerstone of clinical cancer imaging. Understanding the detailed biochemical mechanisms of the Warburg effect is not merely an academic exercise. It has direct translational implications. Metabolic enzymes such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), LDHA, and the pyruvate dehydrogenase kinases (PDKs) are emerging as druggable targets. Several small-molecule inhibitors have entered preclinical and clinical trials, offering hope for selective cancer therapy

Relevance. The Warburg effect is not merely an epiphenomenon but a central driver of malignancy, associated with tumor aggressiveness, metastasis, and therapy resistance. Since this metabolic phenotype is rare in normal adult tissues, it offers a promising target for diagnostic imaging (e.g., 18F-FDG PET) and selective anticancer therapies. Elucidating its molecular mechanisms remains highly relevant for improving patient outcomes.

Materials and Methods. This review synthesized peer-reviewed literature from PubMed and Scopus databases (2000–2024). Search terms included "Warburg effect," "aerobic glycolysis," "cancer metabolism," "HK2," "PKM2," "HIF-1α," and "lactate." Original research articles, reviews, and meta-analyses were selected based on relevance and mechanistic insight. Data on enzymatic activity, gene expression, and metabolic flux were compiled and analyzed qualitatively.

Results (Biochemical Basis)

· Hexokinase 2 (HK2): Overexpressed and bound to the mitochondrial outer membrane (via VDAC), giving it privileged access to ATP and avoiding product inhibition. This drives the first committed step of glycolysis.

· Phosphofructokinase-1 (PFK1): Activated by oncogenic signaling (e.g., Akt), while the liver-type PFK2 isoform (PFKFB3) produces fructose-2,6-bisphosphate, a potent allosteric activator of PFK1.

· Pyruvate Kinase M2 (PKM2): The embryonic isoform is re-expressed in tumors. It exists in a less active dimeric form, allowing accumulation of glycolytic intermediates that can be shunted into serine, glycine, and nucleotide synthesis.

· Lactate Dehydrogenase A (LDHA): Highly upregulated, rapidly converting pyruvate to lactate, regenerating NAD+ to sustain glycolysis and producing lactate that acidifies the tumor microenvironment.

Transcriptional and Oncogenic Regulation:

· HIF-1α (Hypoxia-inducible factor-1α): Even under normoxia, many cancers stabilize HIF-1α, which transactivates genes for GLUT1, HK2, LDHA, and PDK1 (pyruvate dehydrogenase kinase 1). PDK1 phosphorylates and inhibits PDH, blocking pyruvate entry into the mitochondria.

· c-Myc: Directly induces expression of glycolytic enzymes (HK2, PKM2, LDHA) and glutaminase, coupling glycolysis with glutaminolysis.

· p53: Normally suppresses glycolysis (e.g., by inducing TIGAR and SCO2). Loss of p53 function, common in cancer, removes this brake, further enhancing aerobic glycolysis.

Conclusion.

The Warburg effect represents one of the most consistent and robust metabolic hallmarks of cancer. Over the past century, our understanding has evolved from viewing it as a mysterious inefficiency to recognizing it as a sophisticated, evolutionarily conserved adaptation that supports rapid proliferation. The biochemical basis of aerobic glycolysis is now understood at multiple levels: enzymatic, transcriptional, and signaling. At the enzymatic level, cancer cells systematically upregulate rate-limiting glycolytic enzymes (HK2, PFKFB3, PKM2, LDHA) while suppressing pyruvate entry into mitochondria via PDK1. The re-expression of the PKM2 splice isoform and its predominantly dimeric, low-activity state allows the accumulation of glycolytic intermediates for biosynthetic side-branches—a concept that overturns the traditional view that maximum ATP yield is always advantageous.

At the transcriptional level, oncogenic activation of HIF-1α, c-Myc, and PI3K/Akt/mTOR pathways, combined with inactivation of p53, creates a transcriptional program that drives the expression of glucose transporters, glycolytic enzymes, and lactate exporters. Notably, HIF-1α stabilization can occur even in normoxic tumors through mechanisms such as loss of von Hippel-Lindau (VHL) tumor suppressor function or oncogene-induced ROS, explaining the "aerobic" nature of the Warburg effect.

In summary, the Warburg effect is a prime example of how cancer rewires fundamental cellular processes to meet the demands of uncontrolled growth. A detailed biochemical understanding has already translated into diagnostic tools and is now guiding the development of novel therapeutics. Future research should focus on identifying patient subsets most likely to respond to metabolic inhibitors, overcoming resistance mechanisms, and integrating metabolic targeting into multimodal cancer treatment. The Warburg effect, once a biochemical curiosity, has become a cornerstone of modern cancer biology and a promising frontier in oncology.

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