

Vithurshika S., Ashwinraj S.

TARGETING PKM2 TO REVERSE THE WARBURG EFFECT IN CANCER CELLS

Tutor: Ph.D, associate professor Tahanovich A.D.

*Department of Biological Chemistry
Belarusian State Medical University, Minsk*

Cancer is an uncontrollable growth and division of tumor cells. Cancer cells exhibit a distinct metabolic phenotype characterized by the **Warburg effect, which was discovered by renowned German biochemist Otto Warburg in the 1920s**, the Warburg effect preferentially utilize **aerobic glycolysis** over **oxidative phosphorylation**, even in the presence of sufficient amount of oxygen. This metabolic reprogramming not only supports cancer cell survival but also enables adaptation to hostile environments (adapting to Hypoxia) and highlighting crucial potential treatment targets within the metabolic pathways that sustain tumorigenesis.

This metabolic alteration is driven by various oncogenic pathways, including **HIF-1 α** , **PI3K/AKT/mTOR**, and the **suppression of p53**, which collectively facilitate rapid cell proliferation, maintain redox homeostasis, and promote immune evasion. A pivotal enzyme in this metabolic shift is **Pyruvate kinase M2 (PKM2)**, which catalyzes the final step of glycolysis. Unlike the high-activity tetrameric form of **PKM1**, **PKM2** predominantly exists as a low-activity dimer in cancer cells. This dimerization results in the accumulation of glycolytic intermediates that fuel biosynthetic pathways essential for tumor growth and survival.

Warburg Effect refers to the fact that, even when oxygen is present, cancer cells prefer glycolysis and lactic acid fermentation over normal cells, which mainly use oxidative phosphorylation to produce ATP. This predilection is partially caused by the hypoxic (low oxygen) environment that is frequently present in tumours because cancer cells have the ability to overrun their blood supply, which results in low oxygen levels. Glycolysis only produces two ATP per glucose, whereas oxidative phosphorylation can produce up to 32 ATP, this metabolic change causes cancer cells to use glucose far more and also glycolysis produces ATP faster than oxidative phosphorylation (Rapid reaction). This adaptation aids in the survival and proliferation of cancer cells in a low-oxygen environment.

This dependence on glycolysis allows tumour growth and metastasis by supplying vital building blocks for fast cell proliferation in addition to energy. Because the Warburg effect has the potential to act as a major source of energy for tumor cells with the aim to increase their viability should be avoided. Developing more potent cancer treatments may be possible by focussing on this particular metabolic pathway.

In our study, we conducted a comprehensive analysis based on scientific literature utilizing diverse research methodologies, focusing on several key aspects to reverse the Warburg effect by **inhibiting PKM2**: the **lactylation of PKM2** (Wang et al.), the impact of **celastrol** on the Warburg effect (Luo et al.), the role of **CHIP/STUB1** in regulating PKM2 through dephosphorylation (Shang et al.), and the suppression of the Warburg effect by **melittin** which directly targets PKM2 (Fan et al.). These research methodologies were rigorously evaluated using techniques in biochemical investigations: **LPS stimulation**, **animal models**, **Western blotting**, **immunofluorescence**, **SiLAD proteomics**, **binding assays** and **Glycolytic measurements** to assess PKM2 activity and its downstream effects.

According to the literature PKM2 inhibition significantly decreases aerobic glycolysis, stimulates oxidative phosphorylation, and reduces ATP levels in tumor cells. This metabolic shift diminishes glucose consumption and the fermentation of glucose to lactate, leading to a reconfiguration of metabolic pathways critical for cancer cell viability. Furthermore, **flow cytometry analysis** reveals a notable increase in necrosis, while metabolic