

THE INFLUENCE OF CALCITRIOL ON THE WARBURG EFFECT IN CANCER

Cojoc Daniela¹, Sardari Veronica¹, Munteanu Roman¹, Stratulat Silvia¹, Pantea Valeriana², Tagadiuc Olga¹

¹Department of Biochemistry and Clinical Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova.

²Laboratory of Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova.

Background. Cancer cells undergo changes in the tumorigenic process through the Warburg effect, also known as aerobic glycolysis. The Warburg effect ensures the conversion of glucose to pyruvate and subsequently to lactate by lactate dehydrogenase A (LDH A), leading to increased tumor microenvironment (TME) acidity (pH 6.0–6.5), which affects macrophage reprogramming and T cell functionality.

Objective of the study. To elucidate the mechanism of suppression of the Warburg effect by the biologically active form of vitamin D, calcitriol (1,25-dihydroxyvitamin D3).

Materials and methods. A review of the literature from 2019-2024 was performed, using 10 articles, including data from PubMed, Experimental and Molecular Medicine, Wiley Online Library, MDPI, Journal of Cancer Research.

Results. Physiologically, glucose metabolism occurs in mitochondria through oxidative phosphorylation in the presence of oxygen. Although the mitochondrial respiratory chain remains functional, cancer cells adopt the Warburg effect, excessively consuming glucose and converting it into lactate. Lactate is then transported to the TME by monocarboxylate transporters (MCTs) to supply energy to cancer-associated fibroblasts (CAFs) and stromal cells. Oxidative phosphorylation produces more energy than anaerobic glycolysis, but cancer cells compensate by increasing glucose uptake and accelerating glycolysis. Glycolytic enzymes are regulated by the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway through hexokinase 2 (HK2), which phosphorylates glucose. Consequently, cancer cells disrupt the normal function of these proteins. Vitamin D is a hormone responsible not only for calcium and phosphorus homeostasis, but also for extraskelatal functions. Its biological effects are mediated by the vitamin D receptor (VDR). Recent studies indicate that calcitriol inhibits key glycolytic enzymes of the Warburg effect, including HK2, LDHA, and glucose transporter GLUT1 reducing lactate production and tumor microenvironment acidity. In addition, calcitriol reduces TME acidification and increases the rate of oxygen consumption in cancer cells by altering aerobic glycolysis at the mitochondrial respiratory chain, thereby decreasing tumor volume and weight.

Conclusions. Cancer progression can be interrupted by calcitriol, which reduces cell proliferation, stimulates apoptosis and cell differentiation and has a protective role. According to studies, calcitriol inhibits cancer cell progression and has potential chemopreventive and anticancer capacity.

Keywords: cancer, Warburg effect, glycolytic enzymes, glycolysis, calcitriol.