

GLYCOGEN SYNTHASE KINASE 3B INDUCES WARBURG EFFECT IN GLIOMA CELLS

CHIH-HSUN WU, JING-HUEI LAI, HSUN-JIN JAN, HORNG-MO LEE

Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University

Cancer cells have the tendency to increase uptake of glucose, metabolize glucose to lactate, and is associated with decrease in mitochondrial respiration and adenosine triphosphate (ATP) production; a phenomenon first described by Otto Warburg in the 1920s and is termed the “Warburg effect.” Much attention has focused on the Warburg effect as a target for cancer therapy, including for glioblastomas. Glycogen synthase kinase 3 β (GSK3 β) is a serine/threonine kinase that participate in numerous signaling pathways involved in cellular and metabolic processes. The objective is to study the role of GSK3 β in Warburg effect, which has not been elucidated previously. Specifically, this study focuses on the metabolic roles of GSK3 β in glioblastomas; we studied Warburg effect in glioblastoma cells with and without treatment of a GSK3 β activation inhibitor. The inhibition of GSK3 β activation by 4-benzyl, 2-methyl, 1,2,4-thiadiazolidine, 3,5 dione (TDTZ-8) decreased hypoxia inducible factor-1 (HIF-1) and glucose transporter-1 (Glut-1) expressions and decreased pyruvate dehydrogenase (PDH) phosphorylation. HIF-1, Glut-1 and PDH are major regulators of cell metabolism and Warburg effect. Furthermore, the use of TDTZ-8 to inhibit GSK3 β activation decreased glucose uptake and lactate accumulation, but increased ATP production. The increase in ATP production together with the decrease in lactate accumulation suggests a change in cellular metabolism from anaerobic Warburg effect to aerobic usage of glucose. These results suggest that GSK3 β activation may induce the Warburg effect and its inhibition may decrease this metabolic phenomenon. Our findings support a novel role for GSK3 β in metabolism, GSK3 β may be a possible target for cancer therapy and TDTZ-8 which is the inhibitor of GSK3 β may reverse the Warburg effect.