ANAEROBIC METABOLISM: A HALLMARK OF CANCER CELL IMMORTALITY

Karam F. Soliman

College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, USA

Abstract: One factor involved in cancer cell immortality is the continuous activity of cell telomerase. In addition, activated oncogenes and the inhibited apoptosis significantly contribute to the immortality of the cancer cells. Most cancer cells exhibit increased glycolysis and use this metabolic pathway for generation of ATP as a main source of their energy supply. This metabolic change may be attributed to mitochondrial defects and malfunction, adaptation to hypoxic tumor microenvironment, oncogenic signaling, and abnormal expression of metabolic enzymes. Importantly, the increased dependence of cancer cells on glycolytic pathway for ATP generation provides another basis for immortality. In the current study, the neurotoxic 1-methyl-4-phenylpyridinium (MPP+) was used to inhibit mitochondrial function in murine Neuro-2A (N2-A) neuroblastoma cells. MPP+ exerts its lethal effect by inhibition of Complex I in the electron transport chain (ETC). MPP+ shuts down aerobic oxidative phosphorylation and ETC mediated ATP synthesis. The present investigation examines anaerobic survival during MPP+ toxicity in N2-A. Exposure to MPP+ resulted in the attenuation of cell viability, mitochondrial O2 consumption (MOC) and ATP concentration in a dose dependent manner. The addition of 10mM of D-(+)-glucose prevented MPP+ toxicity, attenuated the loss of ATP, but did not reverse the complete inhibition of MOC, indicating substrate level phosphorylation and explicit anaerobic survival. Additional glucose prevented the MPP+-mediated drop in ΔΨm, endoplasmic reticulum and intracellular organelle membrane potential tantamount to an increase of cell viability. We further investigated the ability of several compounds preferentially kill cancer cells by the pharmacological inhibition of glycolysis. Several small molecules have emerged that exhibit promising anticancer activity in vitro and in vivo. Because increased anaerobic glycolysis is commonly seen in a wide spectrum of human cancers and hypoxia is present in most tumor microenvironment, development of novel glycolytic inhibitors as a new class of anticancer agents is likely to have broad therapeutic applications. The results obtained suggest that cancer cell immortality and its anaerobic glycolytic ability are intimately linked and fully consonant phenomena.

Keywords: Immortality, cancer, anaerobic glycolysis, MPP+, mitochondria

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