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Regulation of pericellular pH homeostasis in the cancer cell

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Malignant tumor cells display an accelerated rate of glucose consumption with dominant reliance on substrate level phosphorylation (SLP) rather than oxidative phosphorylation (OXPHOS) to produce ATP. The heightened glycolytic activity is typically indicative of the metabolic response to the lack of oxygen. In the cancer cell, this pattern occurs in the presence or absence of O2 with accumulation of lactic acid (Warburg effect). Using whole-genome, proteomic MALDI-TOF-MS and metabolite analysis, we investigated the Warburg effect in malignant neuroblastoma N2A cells. The findings show that the Warburg effect serves a functional role in regulating acidic pericellular pH (pHe), which is mediated by metabolic inversion or a fluctuating dominance between glycolytic-rate substrate level phosphorylation (SLP) and mitochondrial (mt) oxidative phosphorylation (OXPHOS) to control lactic acid production. The results also show that an alkaline pHe caused an elevation in SLP/OXPHOS ratio of 98%, while the ratio was approximately 56% at neutral pHe and approximately 93% in acidic pHe. Acidic pHe paralleled greater expression of mitochondrial biogenesis and OXPHOS genes, such as complex III -V (Uqcr10, Atp5 and Cox7c), mt Fmc1, Romo1, Tmem 173, Tomm6, aldehyde dehydrogenase, mt Sod2 mt biogenesis component PPAR-c co-activator 1 adjunct to loss of mt fission (Mff). Moreover, acidic pHe corresponded to metabolic efficiency evidenced by a rise in mTOR nutrient sensor GbL, its downstream target (Eif4ebp1), insulin modulators (Trib3 and Fetub) and loss of catabolic (Hadhb, Bdh1 and Pygl)/glycolytic processes (aldolase C, pyruvate kinase, Nampt and aldose-reductase). In contrast, alkaline pHe initiated loss of mitofusin 2, complex II-IV (Sdhaf1, Uqcrq, Cox4i2 and Aldh1l2), aconitase, mitochondrial carrier triple repeat 1 and mt biosynthetic (Coq2, Coq5 and Coq9). It was concluded from this study that the Warburg effect might expand beyond its role in energy metabolism and could be the primary means by which tumor cells can regulate the rate of glycolysis (glucose/lactate conversion) to neutralize the microenvironment. The negative feedback system involves a rapid switch between acid-mediated mitochondrial OXPHOS (lactate production is halted) or excessive lactate produced by SLP, with a rise in alkalinity. These effects are independent of energy requirements and/or levels of O_2.

Biography

Karam F. A. Soliman has completed his Ph.D. at the University of Georgia in 1972. He currently serves as a Distinguished Professor of Basic Pharmaceutical Sciences, RCMI Program Director, Director of Center of Excellence for Cancer Research Training and Community Service at the College of Pharmacy & Pharmaceutical Sciences of Florida A&M University. He has published extensively in national and international refereed journals (146 publications). His research is focused on utilizing interdisciplinary approaches to investigate the metabolic pathways in the brain. He had continuous research support from the NIH for the past 35 years totaling over $64 million. During his academic career, he was actively involved in the mentoring and supervising 26 Ph.D. students in Pharmacology. He has had significant experience in research administration as he served as director of Pharmaceutical Research Center and Center of Excellence for Cancer Research Training and Community Service at the College of Pharmacy & Pharmaceutical Sciences Florida A&M University. He served on study sections for the NIH and on the editorial board of three Journals. He is an active member of American Physiology Society (APS), American Society for Pharmacology and Experimental Therapeutics (ASPET), Endocrine Society, and the Society for Neuroscience.

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