Modelling the role of Hypoxia Inducible Factor in the regulation of metabolic key genes Lactate Dehydrogenase and Pyruvate Dehydrogenase: Emergence of Warburg Phenotype.

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Abstract

Hypoxia Inducible Factor (HIF), the main actor in the cell response to hypoxia, represents a potential target in cancer therapy. HIF is involved in many biological processes such as cell proliferation, survival, apoptosis, angiogenesis, iron metabolism and glucose metabolism. This protein regulates the expressions of Lactate Dehydrogenase (LDH) and Pyruvate Dehydrogenase (PDH), both essential for the conversion of pyruvate to be used in aerobic and anaerobic pathways. HIF upregulates LDH, increasing the conversion of pyruvate into lactate which leads to higher secretion of lactic acid by the cell and reduced pH in the microenvironment. HIF indirectly downregulates PDH, decreasing the conversion of pyruvate into Acetyl Coenzyme A which leads to reduced usage of the Tricarboxylic Acid (TCA) cycle in aerobic pathways. Upregulation of HIF may promote the use of anaerobic pathways for energy production even in normal extracellular oxygen conditions. Higher use of glycolysis even in normal oxygen conditions is called the Warburg effect. In this paper, we focus on HIF variations during tumour growth and study, through a mathematical model, its impact on the two metabolic key genes PDH and LDH, to investigate its role in the emergence of the Warburg effect. Mathematical equations describing the enzymes regulation pathways were solved for each cell of the tumour represented in an agent-based model to best capture the spatio-temporal oxygen variations during tumour development caused by cell consumption and reduced diffusion inside the tumour. Simulation results show that reduced HIF degradation in normoxia can induce higher lactic acid production. The emergence of the Warburg effect appears after the first period of hypoxia before oxygen conditions return to a normal level. The results also show that targeting the upregulation of LDH and the downregulation of PDH could be relevant in therapy.