Transcriptional Reprogramming Underlying Warburg Effect in Glioblastoma

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Introduction Gliomas are highly aggressive brain tumors. The most aggressive form, Glioblastoma Multiform, has very poor prognosis, with average survival time around 18 months in treated patients. Metabolic alterations implying a higher glycolysis demand, known as the Warburg effect, occurs in gliomas as well as other solid tumors. The rearrangement of glucose metabolism machinery is pointed by several studies as being related to the aggressiveness of those tumors. Analyzing the transcriptional profile of genes encoding enzymes acting on glucose fate, the aim of the present study was to discuss how metabolic impairments leading to Warburg effect can improve the fitness of neoplastic cells in tumor micro-environment.

Material And Methods We accessed the expression rates of genes related to glucose metabolism, trans-membrane transporters (i.e. GLUT I – V), glycolytic, pentose-phosphate pathway, and oxidative phosphorylation enzymes in 120 glioma samples compared to 8 healthy control samples by analyzing gene expression microarrays retrieved from Genome Expression Omnibus online repository (GSE16011). Results And Discussion We found several alterations in enzymes transcriptional level. Key glycolytic (e.g. HK2, GLUT3) and pentose-phosphate pathway (e.g. G6PD) enzymes were up-regulated on glioma samples, while almost the entire set of genes encoding oxidative phosphorylation enzymes were down-regulated. If protein levels reflect this transcriptional pattern, the attenuation of oxidative phosphorylation activity and increase of pentose-phosphate pathway can contribute to divert glucose from its original aerobic fate. Conclusion Oxidative phosphorylation and pentose-phosphate pathways are both related to redox metabolism, but with counteracting roles. Attenuation of oxidative phosphorylation activity and increase of pentose-phosphate pathway are pointed by several studies as a strategy to cope with oxidative stress, also pointed as the main cause of glioblastoma cell death. While oxidative phosphorylation attenuation leads to less radicals yield, pentose-phosphate pathway provides molecules for reactive species detoxification.

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