Aerobic glycolysis

Aerobic glycolysis is a series of reactions wherein oxygen is required to reoxidize NADH to NAD+, hence the name. This ten-step process begins with a molecule of glucose and ends up with two molecules of pyruvate

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RNA-binding proteins (RBPs) and circular RNAs (circRNAs) play important roles in glioblastoma. Aerobic glycolysis is a metabolic characteristic of Glioblastoma. However, the roles of RBPs and circular RNAs in aerobic glycolysis in Glioblastoma remain unclear. The aim of this study is to explore the mechanisms by which RBPs and circRNAs regulate aerobic glycolysis in Glioblastoma cells.

RNA sequencing and circRNA microarray analysis were performed to identify RBPs and circRNAs for further study. Mass spectrometry validated the encoded protein and its interacting proteins. Quantitative reverse transcription PCR and western blot assays were used to determine the mRNA and protein expression, respectively. Furthermore, immunofluorescence and fluorescence in situ hybridization assays were used to determine the protein and RNA localization, respectively. Glucose and lactate measurement assays, Seahorse XF glycolysis stress assays and cell viability assays were conducted to investigate the effects on glycolysis and proliferation in Glioblastoma cells.

Results: We selected zinc finger CCHC-type and RNA-binding motif 1 (ZCRB1) and circRNA HEAT repeat containing 5B (circHEATR5B) as candidates for this study. These genes were expressed at low levels in Glioblastoma tissues and cells. Both ZCRB1 and circHEATR5B overexpression suppressed aerobic glycolysis and proliferation in Glioblastoma cells. ZCRB1 overexpression promoted the Alu element-mediated formation of circHEATR5B. In addition, circHEATR5B encoded a novel protein HEATR5B-881aa which interacted directly with Jumonji C-domain-containing 5 (JMJD5) and reduced its stability by phosphorylating S361. JMJD5 knockdown increased pyruvate kinase M2 (PKM2) enzymatic activity and suppressed glycolysis and proliferation in Glioblastoma cells. Finally, ZCRB1, circHEATR5B and HEATR5B-881aa overexpression inhibited Glioblastoma xenograft growth and prolonged the survival time of nude mice.

This study reveals a novel mechanism of regulating aerobic glycolysis and glioblastoma proliferation through the ZCRB1/circHEATR5B/HEATR5B-881aa/JMJD5/PKM2 pathway, which can provide novel strategies and potential targets for Glioblastoma treatment [1)]

Highly malignant brain tumors harbor the aberrant propensity for aerobic glycolysis, the excessive conversion of glucose to lactic acid even in the presence of ample tissue oxygen. Lactic acid is rapidly effluxed to the tumor microenvironment via a group of plasma-membrane transporters denoted monocarboxylate transporters (MCTs) to prevent “self-poisoning.” One isoform, MCT2, has the highest affinity for lactate and thus should have the ability to respond to microenvironment conditions such as hypoxia, lactate, and pH to help maintain high glycolytic flux in the tumor. Yet, MCT2 is considered to not respond to hypoxia, which is counterintuitive. Its response to tumor lactate has not been reported. In this report, we experimentally identify the transcription initiation site/s for MCT2 in astrocytes (normal) and glioma (tumor). We then use a BACmid library to isolate a 4.2-kbp MCT2 promoter-exon I region and examine promoter response to glycolysis-mediated stimuli in glioma cells. Reporter analysis of nested-promoter constructs indicated response of MCT2 to hypoxia, pH, lactate, and glucose, the major physiological “players” that facilitate a tumor's growth and proliferation.

Immunoblot analysis of native MCT2 expression under altered pH and hypoxia reflected the reporter data. The pH-mediated gene-regulation studies we describe are the first to record H+-based reporter studies for any mammalian system and demonstrate the exquisite response of the MCT2 gene to minute changes in tumor pH. Identical promoter usage also provides the first evidence of astrocytes harnessing the same gene regulatory regions to facilitate astrocyte-neuron lactate shuttling, a metabolic feature of normal brain [2].

The effectiveness of calorie restriction or a ketogenic diet can be understood through analysis of its biochemistry. A landmark study by Nobel laureate Otto Warburg demonstrated neoplastic metabolic dependence on aerobic glycolysis for energy production [3].

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