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 circRNAs 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)]

1)
Song J, Zheng J, Liu X, Dong W, Yang C, Wang D, Ruan X, Zhao Y, Liu L, Wang P, Zhang M, Liu Y. A novel protein encoded by ZCRB1-induced circHEATR5B suppresses aerobic glycolysis of Glioblastoma through phosphorylation of JMJD5. J Exp Clin Cancer Res. 2022 May 10;41(1):171. doi: 10.1186/s13046-022-02374-6. PMID: 35538499.