

Presenting Author Name

Helgi Kuzmychova

Phonetic spelling of your (full) name

hElgee kuzmychOva

Presenting Author Category

PhD Student

Supervisor Name

Tanveer Sharif

GBD Audio File

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Headshot

Helgi_2026.jpg

Short Bio (100 words)

Helgi Kuzmychova is a PhD student in the Department of Pathology and a member of Dr. Tanveer Sharif’s research team. She first joined the lab as an undergraduate student and has been part of the group for the past five years. Her research focuses on understanding and targeting metabolic processes that drive the aggressiveness in adult and pediatric brain cancers.

Research Category

Basic Science

Abstract Title

Uncovering a Novel Targetable Relationship Between Lactate Metabolism and Progenitor Cell Identity in Medulloblastoma

Authors

Name	Role	Profession
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Tanveer Sharif	Principal Investigator	Associate Professor

Background

Medulloblastoma (MB) is the most prevalent childhood brain malignancy, with group 3 (G3) MB being its most aggressive subgroup. G3 MB originates from transient progenitors of the human cerebellar rhombic lip (RL) during early gestation. However, the mechanisms that sustain and perpetuate this progenitor cell identity during G3 MB tumorigenesis remain poorly understood.

Objective

Given the growing appreciation for the role of metabolism in cancer proliferation and aggressiveness, we hypothesized that metabolic alterations crucial to G3 MB oncogenesis could be leveraged as therapeutic targets.

Methods

We performed immunofluorescence staining and analyzed available sequencing datasets from human embryonic hindbrain tissues. Mechanistic investigation was performed in patient-derived G3 MB cells using chromatin and protein immunoprecipitation, mass spectrometry, cycloheximide protein stability assay, point mutations, inducible CRISPR-Cas9 knockout system, and pharmacological inhibition. The therapeutic approach was tested in vitro using cell counts, stemness and migration assays, and in the patient-derived orthotopic xenograft (PDOX) G3 MB animal model.

Results

In this project, we uncovered a novel reciprocal relationship between lactate metabolism and a major progenitor cell identity driver and crucial G3 MB oncogene, OTX2. We observed that OTX2 directly regulates lactate dehydrogenase A (LDHA) expression, the enzyme producing lactate. Meanwhile, high lactate levels induced OTX2 lactylation at lysine 278, increasing OTX2 stability and protein abundance by about 2-fold ($p=0.0008$). This self-sustaining metabolic–transcriptional circuit was also recapitulated in RL progenitors, implicating it as a developmental mechanism priming G3 MB oncogenesis. Targeting this reciprocal relationship with blood-brain-barrier-permeable LDHA inhibitor Stiripentol greatly reduced G3 MB proliferation (0.57-fold, $p<0.0001$), stemness, and migration, impairing the aggressiveness of this deadly malignancy. These findings also translated into reduced tumor burden and significantly prolonged animal survival in a PDOX animal model (HR:0.3847, $p=0.0156$).

Conclusion

Altogether, our study identifies OTX2 lactylation as a key mechanism driving G3 MB stemness and

progression, highlighting lactate metabolism as a promising therapeutic target.

Table/Figure File

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