Investigating the Role of Galectin-3 in Up-regulation of CXCR2 and Subsequent Tumor Progression and Drug Resistance in Pediatric Medulloblastoma

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Introduction:

- Brain tumors are the leading cause of childhood cancer mortality, with medulloblastoma (MB) representing the most frequent malignant brain tumor. The identification of cancer stem cell (CSC) populations, termed brain tumor-initiating cells (BTICs) in MB, has played a vital role in drug resistance, and cancer relapse.

- Galectin-3 (Gal-3), a lectin with preference for β-galactoside-containing carbohydrates, is a structurally unique member of the galectin family. It is ubiquitously expressed in various mammalian tissues with a wide distribution from the intracellular environment to the extracellular space.

- Notably, as Gal-3 overexpression is associated with tumor progression and cancer drug resistance, it has been identified as a valuable therapeutic target in the fight against cancers.

- However, the exact role of Gal-3 in medulloblastoma tumor pathophysiology is yet unknown.

Objective:

Investigate whether Galectin-3 promotes stem-like property of medulloblastoma in ex vivo model.
Methods:

Tissue slice preparation and analysis: This research was approved by the Institutional Review Board for Human Research in the Office of Research Integrity at the Medical University of South Carolina (MUSC). Subjects gave their written, informed consent to participate, and the research was conducted in accordance with the principles of the Declaration of Helsinki.

Standard Stoppini Slice Culture Technique was used. 250 µm GB slice cultures were prepared under sterile conditions using a McIlwain tissue chopper (Ted Pella Inc., Redding, CA) as described below. The slices were treated with or without Gal-3 RNAi or inhibitor (500 nM) for 72 hr. These slices were analyzed using standard Immunohistochemistry and western-blots (Figure 1).

![Figure 1. Methods and workflow](image-url)
Results:

Figure 2. Observed higher levels of stem/progenitor cell markers (Oct4, Sox2, CD133 and Nanog) and Gal-3 expression in MB slices as compared to normal tissues.

Figure 3. Treatments with either Gal-3 RNAi or Gal-3 inhibitor:TD-139 suppresses cancer stem cell properties in ex vivo slice culture.

Figure 4. Treatments with either Gal-3 RNAi or Gal-3 inhibitor:TD-139, drug resistance (MDR1, MPR1, and Bcl-2) protein expression in ex vivo slice culture.

Figure 5: Treatments with either Gal-3 RNAi or Gal-3 inhibitor:TD-139 reduces cell viability in ex vivo slice culture.
Figure 6. CXCL6, CXCL7 and CXCR2 were down-regulated in Gal-3-knockdown or Gal-3 inhibitor treated MB tumor slices.

Figure 7. CXCR2 overexpression in Gal-3-knockdown or TD-139 treated MB slices restored their viability.
**Discussion:**

- Our study shows an elevated expression of Gal-3 in medulloblastoma
- Treatment with Gal-3 inhibitor (TD139) shows significant cancer stem cell suppression ex-vivo
- Treatment with Gal-3 inhibitor (TD139) shows significant reduction in drug resistance protein expression as well as increase in CXCR2 expression.
- Gal-3 reduces tumor invasiveness and progression, likely through regulation of the CXCR2 receptor.
- These results indicate that highly expressed Gal-3 may up-regulate CXCR2 to augment MB invasiveness and progression.
Summary points:

- Galectin-3 overexpression is associated with tumor progression and cancer drug resistance
- Galectin-3 role in medulloblastoma pathophysiology has been unknown
- Gal-3 reduces tumor invasiveness and progression, likely through regulation of the CXCR2 receptor.
- Gal-3 may be a prognostic and innovative target for the treatment of MB.