CHRD 2022: Abstract & Poster Submission Form

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Research Category
◉ Basic Science
○ Clinical
○ Community Health / Policy

Role in the project
☑ Design
☑ Perform Experiments
☑ Analyze Data
☑ Write Abstract
☐

Title
OTX2 is a novel regulator of alternative splicing in Group 3 medulloblastoma

Background

Brain tumors are the most lethal form of childhood cancer. Group 3 medulloblastoma (MB) exhibits the worst prognosis of the MB subgroups. Overexpression/amplification of OTX2 is a hallmark of Group 3 MB and is primarily known to regulate tumor growth through regulation of the cell cycle.

Objective

We sought to explore non-conical functions for OTX2 in Group 3 MB tumor progression and identified a novel role for OTX2 in regulating alternative splicing events.

Methods

RNA-sequencing was performed to identify non-canonical roles for OTX2. Pseudotime mapping was used to identify the developmental trajectories of differentially spliced genes (DSG) on the developing rhombic lip (RL). Splice-blocking morpholinos were used to functionally validate alternatively spliced exons of the DSG identified by RNA-sequencing and pseudotime mapping in vitro and in vivo.

Results

Significant splicing alterations with alternatively spliced exons being the most common event were identified in two OTX2-silenced Group 3 MB tumorsphere models. Further interrogation of all types of splicing alterations revealed 48 DSG common to both cell lines. In Group 3 patient tumors, we identified a significant correlation between percent spliced-in exons and OTX2 expression with enrichment for neurodevelopmental genes. In addition, 11 of the 48 DSG identified in vitro were also correlated with OTX2 expression in patient tumors. Pseudotime mapping of DSG onto the developing RL from which Group 3 MB originates, showed overlap with RL lineages, including the majority of the 11 shared DSG. Functional validation of two DSG, PPHLN1 and MADD revealed that exon-skipping altered tumorigenic properties of Group 3 MB cells in vitro. Treatment of Group 3 MB cells with PPHLN1 splice-blocking morpholino prior to cerebellar injection into xenografts was sufficient to significantly impair tumor initiation and growth in vivo.

Conclusion

Collectively, our work identifies an entirely novel OTX2-driven regulatory layer that plays a critical role in Group 3 MB tumor progression.

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