

Mutations in Medullablastoma Cause Unique Cerebellum Development Issues

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JR Schoenborn

Medullablastoma is a type of brain cancer that develops in the cerebellum, a portion of the brain that plays a vital role in coordinating muscular activities such as walking, balance and coordination. Although medullablastoma is relatively rare in the overall population, it is the most common malignant brain tumor in children, comprising up to 20% of newly diagnosed childhood brain cancer cases per year in the United States. During development, the cerebellum goes through several waves of robust proliferation; genomic aberrations that arise during this period can lead to medulloblastoma. Dr. Jim Olson and colleagues in the Clinical Research Division have examined how two mutations commonly observed in human cancers affect brain development, motor function, and medullablastoma occurrence in mouse models. While both mutations cause medulloblastoma at similar ages, one mutation leads to severely impaired cerebellar development early in life. These defects in cell shape and organization may promote medullablastoma in this model.

Histology and transcriptional profiling has revealed four categories of medulloblastoma, each with distinct molecular features and clinical outcomes. Of these, the Shh category results from mutations that constitutively activate the Sonic hedgehog (Shh) signaling pathway. The Shh pathway is a key signaling pathway that regulates the formation of organs during embryonic development. Inappropriate activation of the Shh pathway results in aberrant cellular proliferation. Clinically, the Shh cancers display a significant heterogeneity in tumor histopathology and patients' clinical outcomes. Because of this heterogeneity, the Shh category, which makes up 25-30% of medulloblastoma cases, has an intermediate risk for disease-free survival. The underlying mechanisms behind this heterogeneity remain unclear and may yield more detailed information on risk or treatment responses for Shh subcategories.

Signaling via the Shh pathway is necessary for proper development of the brain and central nervous system. A key signal transducing protein in the Shh pathway is Smo (*Smoothed*). Two activating mutations in Smo's transmembrane domain are observed in human cancers: S537N and W539L. To address how these mutations affect cerebellar development and progression to medulloblastoma, the authors modeled these mutations in mice. As in humans, the mutations led to medulloblastoma. However, while mice carrying the W539L mutation had relatively normal brain development, mice with a S537N mutation had severe defects in their cerebellums, especially early in life - prior to

medulloblastoma. Their cerebellums were characterized by hyperproliferation of cells, poor regional organization of the cerebellum, and atypical cellular shapes. Furthermore, the two mutations created different transcriptional profiles early in mouse brain development, likely resulting from differences in the cell types that were present. Despite this, mice had relatively normal cognitive function and phenotypes.

Because these mutations are separated by one amino acid and both result in constitutive activation of Shh, it will be of interest to model how each affects Shh protein structure and stability. In particular, understanding how each mutation directly affects downstream factors in the Shh signaling pathway will be critical to understanding their role in brain development and cancer formation. Furthermore, a more refined analysis of the tumors derived from mouse models carrying each mutation may yield more details about differences in cancer that are currently unappreciated.

[Dey J, Ditzler S, Knoblauch SE, Hatton BA, Schelter JM, Clearly MA, Mecham B, Rorke-Adams LB, Olson JM.](#) 2012. A distinct Smoothened mutation causes severe cerebellar developmental defects and medulloblastoma in a novel transgenic mouse model. *Molecular and Cellular Biology*. DOI:10.1128/MCB.00862-12.

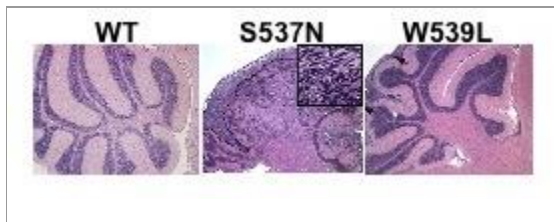


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Smoothened mutations cause distinct morphological differences during development. Shown: H&E staining of brain sections from postnatal day 28.