Sonic hedgehog medulloblastoma

- Taking the "lazy" way identifies KCNB2 as a regulator of SHH-MB maintenance
- Sonic hedgehog medulloblastomas are dependent on Netrin-1 for survival
- Tumor-associated macrophage-derived exosomes modulate the immunotherapeutic sensitivity of SHH-medulloblastoma by targeting m6A-modified FOXD1
- Chromatin modification abnormalities by CHD7 and KMT2C loss promote medulloblastoma progression
- Genetic modeling of ELP1-associated Sonic hedgehog medulloblastoma identifies MDM2 as a selective therapeutic target
- The Molecular Basis of Pediatric Brain Tumors: A Review with Clinical Implications
- Adult Medulloblastoma: Clinicomolecular Spectrum, An Institutional Experience
- Tumor-associated macrophages correlate with better outcome in SHH medulloblastoma

---

Key Features of SHH Medulloblastoma

Origin: Tumor arises from granule neuron precursors in the cerebellum.

Age Distribution:

Bimodal: mostly seen in infants (<3 years) and adults (>16 years).

Less common in older children (3–16 years).

Location: Often located laterally in the cerebellar hemispheres.

Histology: Can be classic, desmoplastic/nodular (more common in SHH), or large cell/anaplastic.

Genetics: Involves mutations in components of the SHH signaling pathway, such as:

PTCH1

SMO

SUFU

TP53 (especially in adults or those with poor prognosis)

Prognosis

Intermediate overall, but varies:

Infants with desmoplastic histology do relatively well.

TP53-mutated SHH medulloblastomas have poor prognosis.

Diagnosis

MRI of the brain: Shows a cerebellar mass, often lateralized.

Lumbar puncture: To assess for CSF dissemination.

Molecular profiling: Essential to classify the tumor into subgroups.

Histopathology: Confirms tumor type and histological variant.

Treatment

Surgery: Maximal safe resection.

Radiotherapy: Age-dependent. Often delayed or avoided in infants.

Chemotherapy: Used in all age groups; may be intensified in high-risk cases.

Targeted therapy (in trials/selected cases):

SMO inhibitors (e.g., vismodegib) are being explored for SHH-driven tumors, especially those with upstream SHH pathway mutations (e.g., PTCH1).

Limited efficacy if mutations are downstream (e.g., SUFU or TP53).

Follow-Up

Regular MRI and clinical monitoring.

Endocrine and neurocognitive assessment due to treatment-related effects.

Medulloblastoma, SHH-activated, and TP53-mutant

Medulloblastoma, SHH-activated, and TP53-mutant.

Medulloblastoma, SHH-activated, and TP53-wildtype

Medulloblastoma, SHH-activated, and TP53-wildtype

Medulloblastoma (MB) is one of the most frequent malignant brain tumors of children, and a large set of these tumors is characterized by aberrant activation of the Sonic hedgehog pathway.

Recurrent somatic single nucleotide variants (SNVs) in cancer are largely confined to protein-coding genes, and are rare in most pediatric cancers.

Suzuki et al. reported highly recurrent hotspot mutations of U1 spliceosomal small nuclear RNAs (snRNAs) in ~50% of Sonic hedgehog medulloblastomas (Shh-MB), which were not present across other medulloblastoma subgroups. This U1-snRNA hotspot mutation (r.3a>g), was identified in <0.1% of 2,442 cancers across 36 other tumour types. Largely absent from infant Shh-MB, the mutation occurs in 97% of adults (Shhδ), and 25% of adolescents (Shhα). The U1-snRNA mutation occurs in the 5' splice site binding region, and snRNA mutant tumours have significantly disrupted RNA splicing with an excess of 5' cryptic splicing events. Mutant U1-snRNA-mediated alternative splicing inactivates tumour suppressor genes (PTCH1), and activates oncogenes (GLI2, CCND2), represents a novel target for therapy, and constitutes a highly recurrent and tissue-specific mutation of a non-protein coding gene in cancer [1].

While some tumors initially respond to inhibition of the SHH pathway component Smoothened (SMO), tumors ultimately recur due to downstream resistance mechanisms, indicating a need for novel therapeutic options.

Recurrent mutations in chromatin modifiers are specifically prevalent in adolescent or adult patients with Sonic hedgehog-associated medulloblastoma (SHH MB).

Merk et al. report that mutations in the acetyltransferase CREBBP have opposing effects during the development of the cerebellum, the primary site of origin of SHH MB.

Data reveal that loss of CREBBP in cerebellar granule neuron progenitors (GNPs) during embryonic development of mice compromises GNP development, in part by downregulation of brain derived neurotrophic factor (Bdnf). Interestingly, concomitant cerebellar hypoplasia was also observed in patients with Rubinstein Taybi syndrome, a congenital disorder caused by germline mutations of CREBBP. By contrast, loss of Crebbp in GNPs during postnatal development synergizes with oncogenic activation of SHH signaling to drive MB growth, thereby explaining the enrichment of somatic CREBBP mutations in SHH MB of adult patients. Together, this data provide insights into time-sensitive consequences of CREBBP mutations and corresponding associations with human diseases [2].

Shammassian et al., report the unique case of a 12-year-old boy with a cerebellar medulloblastoma positive for sonic hedgehog (Shh) that contained intraaxial mature ectopic salivary gland rests. The patient underwent clinical and radiological monitoring postoperatively, until he died of disseminated disease. An autopsy showed no evidence of salivary glands within disseminated lesions. The intraaxial presence of salivary gland rests and concomitant Shh positivity of the described tumor point to a disorder in differentiation as opposed to ectopic developmental foci, which are uniformly dural based in the described literature. The authors demonstrate the characteristic “papilionaceous” appearance of the salivary glands with mucicarmine stain and highlight the role of Shh signaling in explaining the intraaxial presence of seromucous gland analogs. This article reports the first intraaxial posterior fossa tumor with heterotopic salivary gland rests, and it provides molecular and embryopathological insights into the development of these lesions [3].

Treatment

SHH medulloblastoma treatment

International retrospective cohort studies

An international multi-institutional study explores post-relapse survival (PRS) and prognostic factors in 147 young children diagnosed with relapsed SHH medulloblastoma of the Desmoplastic nodular medulloblastoma subtype. All patients were initially treated without craniospinal irradiation (CSI), and were under 6 years of age at initial diagnosis. The study spans over two decades (1995–2017), providing a unique longitudinal lens into evolving salvage strategies [4].

Key Findings

- **3-year PRS**: 61.6% (95% CI, 52.2–69.6).
- **Median age at relapse**: 3.4 years.
- **Local relapse** (40.8%) was significantly associated with:
  - Higher rates of salvage surgery ($p < 0.001$)
  - Use of low-dose CSI (≤ 24 Gy, $p < 0.001$)
  - Use of focal radiotherapy ($p = 0.008$)
- **Patients not receiving CSI** (40.5%) were more likely to receive:
  - High-dose chemotherapy with autologous stem cell rescue ($p < 0.001$)
- In multivariable analysis:
  - **CSI** improved survival significantly (HR 0.33, $p = 0.04$)
  - **HDC+AuHCR** had a strong trend toward benefit, but fell short of statistical significance (HR 0.24, $p = 0.065$)

Critical Review

This study fills an important gap in the literature by focusing specifically on relapsed SHH medulloblastoma in very young children, a group traditionally excluded from CSI at diagnosis due to neurotoxicity concerns.

One of the strengths of the study is its **sample size and international scope**, making it one of the most comprehensive assessments of salvage therapy in this rare subset. Additionally, the use of **propensity score analyses** enhances the validity of the survival comparisons, helping mitigate confounding factors inherent to retrospective studies.

However, limitations are present:

- The **retrospective design** inherently limits causal inference.
- Data heterogeneity over 22 years raises concerns about **evolving standards of care** and radiotherapy techniques.
- Some treatment decisions may reflect **institutional bias** rather than patient-specific risk stratification.
- The **non-significant p-value** for HDC+AuHCR, despite its strong HR, suggests underpowering

for certain subgroups, warranting cautious interpretation.

Perhaps most importantly, the study underscores the **lack of standard salvage strategies** and the ongoing dilemma between efficacy and toxicity, particularly with CSI in very young patients.

Clinical Implications

- Initial therapy must aim to achieve a cure and avoid relapse, as salvage options carry significant toxicities.
- In cases of **local relapse with resectable disease**, **low-dose CSI** or **focal RT** may offer survival benefit with reduced long-term toxicity.
- When CSI is contraindicated or declined, **marrow-ablative chemotherapy** remains an important, albeit imperfect, salvage option.
- There is an urgent need for **collaborative prospective trials** to define optimal salvage protocols and reduce reliance on toxic therapies.

Final Thoughts

This study is a significant contribution to pediatric neurooncology, highlighting both progress and persisting challenges in treating early childhood SHH medulloblastoma relapses. It lays a foundation for refining therapeutic strategies that balance survival with neurocognitive preservation, especially in the youngest and most vulnerable patients.

1)
Suzuki H, Kumar SA, Shuai S, Diaz-Navarro A, Gutierrez-Fernandez A, De Antonellis P, Cavalli FMG, Juraschka K, Farooq H, Shibahara I, Vladoiu MC, Zhang J, Abeysundara N, Przelicki D, Skowron P, Gauer N, Luu B, Daniels C, Wu X, Forget A, Momin A, Wang J, Dong W, Kim SK, Grajkowska WA, Jouvet A, Fèvre-Montange M, Garrè ML, Rao AAN, Giannini C, Kros JM, French PJ, Jabado N, Ng HK, Poon WS, Eberhart CG, Pollack IF, Olson JM, Weiss WA, Kumabe T, López-Aguilar E, Lach B, Massimino M, Van Meir EG, Rubin JB, Vibhakar R, Chambless LB, Kijima N, Klekner A, Bognár L, Chan JA, Faria CC, Ragoussis J, Pfister SM, Goldenberg A, Wechsler-Reya RJ, Bailey SD, Garzia L, Morrissy AS, Marra MA, Huang X, Malkin D, Ayrault O, Ramaswamy V, Puente XS, Calarco JA, Stein L, Taylor MD. Recurrent non-coding U1-snRNA mutations drive cryptic splicing in Shh medulloblastoma. Nature. 2019 Oct 9. doi: 10.1038/s41586-019-1650-0. [Epub ahead of print] PubMed PMID: 31597162.
2)
Merk DJ, Ohli J, Merk ND, Thatikonda V, Morrissy S, Schoof M, Schmid SN, Harrison L, Filser S, Ahlfeld J, Erkek S, Raithatha K, Andreska T, Weißhaar M, Launspach M, Neumann JE, Shakarami M, Plenker D, Marra MA, Li Y, Mungall AJ, Moore RA, Ma Y, Jones SJM, Lutz B, Ertl-Wagner B, Rossi A, Wagener R, Siebert R, Jung A, Eberhart CG, Lach B, Sendtner M, Pfister SM, Taylor MD, Chavez L, Kool M, Schüller U. Opposing Effects of CREBBP Mutations Govern the Phenotype of Rubinstein-Taybi Syndrome and Adult SHH Medulloblastoma. Dev Cell. 2018 Mar 9. pii: S1534-5807(18)30107-2. doi: 10.1016/j.devcel.2018.02.012. [Epub ahead of print] PubMed PMID: 29551561.
3)
Shammassian B, Manjila S, Cox E, Onwuzulike K, Wang D, Rodgers M, Stearns D, Selman WR. Mature salivary gland rests within sonic hedgehog-positive medulloblastoma: case report and insights into the molecular genetics and embryopathology of ectopic intracranial salivary gland analogs. J Neurosurg Pediatr. 2016 Dec;25(6):708-712. PubMed PMID: 27635979.
4)
Erker C, Mynarek M, Simbozel M, Craig BT, Harrod VL, Cappellano AM, Cohen KJ, Lopez VS, Morales-La Madrid A, Cacciotti C, Baroni L, Salloum R, Margol AS, Michaiel G, Aguilera D, Mazewski CM, Kline CN,

Finlay JL, Abdelbaki MS, Murray JC, Dorris K, Crooks B, Ginn KF, Amayiri N, Tippelt S, Fleischhack G, Tonn S, Gerber NU, Lassaletta A, Hansford JR, Khan S, Gilheeney SW, Hoffman LM, Zapotocky M, Larouche V, Shah S, Ramaswamy V, Gajjar A, Perreault S, Mueller S, Hukin J, Cheng S, Wang ZJ, Matheson K, Bailey S, Bouffet E, Clifford SC, Robinson G, Dufour C, Rutkowski S, Lafay-Cousin L. Salvage therapies for first relapse of SHH medulloblastoma in early childhood. Neuro Oncol. 2025 Apr 4:noaf092. doi: 10.1093/neuonc/noaf092. Epub ahead of print. PMID: 40186336.