Pediatric Medulloblastoma Pathogenesis

Medulloblastoma is the most common malignant brain tumor in children. It arises in the cerebellum and originates from primitive neural progenitor cells. Its pathogenesis involves disruptions in developmental signaling pathways and distinct genetic alterations.

Molecular Subgroups (WHO 2021)

Medulloblastoma Subgroups

Developmental Disruption

Medulloblastoma subgroups reflect disruption of specific cerebellar developmental programs:

- **WNT tumors** arise from the lower rhombic lip.
- **SHH tumors** derive from granule neuron precursors in the external granular layer (EGL).
- **Groups 3 and 4** may originate from more primitive stem-like neuroepithelial cells.

Genetic and Epigenetic Drivers

- **Oncogene activation**: MYC, MYCN, CTNNB1
- **Tumor suppressor loss**: TP53, PTCH1, SUFU
- **Chromosomal abnormalities**: i(17q), chromosome 8, 11
- **Epigenetic changes**: subgroup-specific DNA methylation profiles

Tumor Microenvironment

- Infiltrative behavior into brainstem or leptomeninges is common.
- Angiogenesis, immune modulation, and stromal interactions support tumor growth.

⚖ Risk Stratification

- Based on molecular subgroup, metastatic status, age, and extent of resection.
- High-risk features: MYC amplification (Group 3), SHH + TP53 mutation, residual tumor.

Future Directions

- Single-cell RNA sequencing reveals intratumoral heterogeneity.
- Patient-derived organoids and murine models provide insight into tumor origin.
- Integration of molecular classification into trials is shaping precision therapy.