Medulloblastoma molecular biology

Advances in molecular profiling have uncovered significant heterogeneity among medulloblastomas and led to the identification of four distinct subgroups (wingless [Medulloblastoma, WNT-activated], sonic hedgehog medulloblastoma [SHH], group 3 medulloblastoma, and group 4 medulloblastoma) that represent distinct disease entities in both underlying biology and clinical characteristics. The rapidly expanding repertoire of tools to study developmental and cancer biology is providing a wealth of knowledge about these embryonal tumors and is continuously refining the understanding of this complex cancer. In a review of Juraschka and Taylor, the history of discovery in medulloblastoma is discussed, setting a foundation to outline the current state of understanding of the molecular underpinnings of this disease, with a focus on genomic events that define the aforementioned subgroups and evolving areas of focus, such as the cell of origin of medulloblastoma and medulloblastoma subtypes. With these recent discoveries in mind, the current state of medulloblastoma treatment and clinical trials are reviewed, including a novel risk stratification system that accounts for the molecular biomarkers of patients with a high risk for refractory disease. Lastly, critical areas of focus for future basic science and clinical research on this disease are discussed, such as the complexities of medulloblastoma metastases and recurrence as well as the priorities and strategies to implement in future clinical trials [1)].

Pomeroy et al., demonstrated that medulloblastomas are molecularly distinct from other brain tumours including primitive neuroectodermal tumors (PNETs), atypical teratoid/rhabdoid tumours (AT/RTs) and malignant gliomas. Previously unrecognized evidence supporting the derivation of medulloblastomas from cerebellar granule cells through activation of the Sonic Hedgehog (SHH) pathway was also revealed.

They showed further that the clinical outcome of children with medulloblastomas is highly predictable on the basis of the gene expression profiles of their tumours at diagnosis [2)].

The molecular genetic alterations in medulloblastoma can be divided into 3 groups:

1.- Non-random chromosomal abnormalities (e.g. consistent deletion of 17p markers) has been shown in 35-40 %.

2.- Information from gene profiling:

ZIC and NSCL1 were the genes most closely correlated with medulloblastoma.

Certain genes were associated with more favorable outcome (using 8 genes a pattern associated with 80% 5-year survival compared to 17% when the pattern was lacking) [3)].

3.- abnormalities in signal transduction pathways: e.g. neurotrophin signaling pathway (important in cerebellar development) or Sonic hedgehog (Shh) [4)].

Sterol synthesis is required for Sonic hedgehog signaling pathway.

Errors in Shh signal transduction play important roles in the formation of human tumors, including

medulloblastoma (MB). It is not clear which products of sterol synthesis are necessary for Shh signal transduction or how they act. Here we show that cholesterol or specific oxysterols are the critical products of sterol synthesis required for Shh pathway signal transduction in MB cells. In MB cells, sterol synthesis inhibitors reduce Shh target gene transcription and block Shh pathway-dependent proliferation. These effects of sterol synthesis inhibitors can be reversed by exogenous cholesterol or specific oxysterols. We also show that certain oxysterols can maximally activate Shh target gene transcription through the Smoothened (Smo) protein as effectively as the known Smo full agonist, SAG. Thus, sterols are required and sufficient for Shh pathway activation. These results suggest that oxysterols may be critical regulators of Smo, and thereby Shh signal transduction. Inhibition of Shh signaling by sterol synthesis inhibitors may offer a novel approach to the treatment of MB and other Shh pathway-dependent human tumors [5)].

1)
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