Group 4 medulloblastoma

Group 4 medulloblastoma is one of the most common pediatric brain tumors. They are the most common from medulloblastoma classification (followed by Group 3 medulloblastoma, Medulloblastoma, SHH-activated, and Medulloblastoma, WNT-activated), and typically arise from the Cerebellar vermis.

Epidemiology

Group 4 medulloblastoma is the most prevalent biological subtype, comprising approximately 40% of all medulloblastoma patients, predominantly between ages 3 and 16 years, and yet, its pathogenesis is the least understood [1], and have a predilection for males, with a 2:1 male to female ratio [2] [3].

They are most frequently encountered in children (4-16 years of age), not infrequently in adults (second only to SHH in frequency) and are uncommon in infants [4].

Pathogenesis

BMI1 has been implicated in medulloblastoma pathogenesis and poor outcome

Pathology

The majority of grade 4 tumors are of classic histology, with the rest being of large cell / anaplastic histology [5].

The molecular dissection of the CHD7-BMI1-MAPK regulatory axis in BMI1 High; CHD7 Low medulloblastoma identifies this signature as a proxy to predict MAPK functional activation, which can be effectively drugged in preclinical models, and paves the way for further exploration of combined BMI1 and MAPK targeting in Group 4 medulloblastoma patients [6].

Specifically, proteomic and phosphoproteomic analyses identify aberrant ERBB4-SRC signaling in group 4. Hence, enforced expression of an activated SRC combined with p53 inactivation induces murine tumors that resemble group 4 medulloblastoma. Therefore, our integrative proteogenomics approach unveils an oncogenic pathway and potential therapeutic vulnerability in the most common medulloblastoma subgroup [7].

To characterize medulloblastoma at the phosphoprotein-signaling level, Zomerman et al. performed high-throughput peptide phosphorylation profiling on a large cohort of SHH (Sonic Hedgehog), group 3, and group 4 medulloblastomas. They identified two major protein-signaling profiles. One profile was associated with rapid death post-recurrence and resembled MYC-like signaling for which MYC lesions

are sufficient but not necessary. The second profile showed enrichment for DNA damage, as well as apoptotic and neuronal signaling. The integrative analysis demonstrated that heterogeneous transcriptional input converges on these protein-signaling profiles: all SHH and a subset of group 3 patients exhibited the MYC-like protein-signaling profile; the majority of the other group 3 subset and group 4 patients displayed the DNA damage/apoptotic/neuronal signaling profile. Functional analysis of enriched pathways highlighted cell-cycle progression and protein synthesis as therapeutic targets for MYC-like medulloblastoma [8].

Radiographic features

The radiographic features of group 4 tumors are those that we typically associate with medulloblastomas; midline masses arising from the vermis. They are fairly well defined with limited contrast enhancement [9]

see Medulloblastoma Diagnosis.

Treatment

Surgery is the first line of therapy (as is the case in all groups) with the aim being histological proof, molecular subtyping, and maximal tumor resection, with adjuvant therapy, depending on an overall risk profile

see Medulloblastoma Treatment.

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Outcome

The incidence of CNS metastatic disease in Group 4 tumors at diagnosis is common, found in 31% of all cases, and is even more frequent in infants (36%) [11]

Overall, group 4 tumors have a poor prognosis, somewhat better than group 3 tumors, but significantly worse than SHH and WNT subtypes [12] [13]

In adults, the prognosis is very poor, whereas in children it is intermediate [14]

Prognosis is also influenced by histological subtype, with large cell/anaplastic histology having a worse prognosis 2. [15]

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