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MINI-SYMPOSIUM

Mini-symposium in medulloblastoma genomics in the modern molecular era

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In this mini-symposium, four review articles describe recent advances in our understanding of the pathobiology of medulloblastoma. Medulloblastoma is the commonest malignant brain tumor of childhood and has been the subject of intense scientific investigation over several decades. Insights gained from this research, particularly a better understanding of the tumor's heterogeneity and origins, have guided improvements in classification and treatment (11). However, even though overall survival with current therapeutic regimens stands at approximately 75% (85% for standard-risk disease), a cure is associated with significant long-term morbidities. Furthermore, outcome after relapse is poor, and very few effective therapies are available for clinicians to deploy in this eventuality. The four articles guide readers through the latest research of particular relevance to the pressing needs of managing this disease. The reader will find state-of-the-art information on the status of medulloblastoma classification and pathologic diagnosis (1), the detailed hierarchy of medulloblastoma molecular variants (7), the importance of metastatic disease (13), and medulloblastoma mouse models (17).

Since publication of the consensus paper on medulloblastoma molecular groups, as defined by DNA methylation or gene expression profiling, and their incorporation into the updated fourth edition of the World Health Organization (WHO) classification in 2016 (9,19), clinical research studies have sought to determine how best to combine morphologic features and molecular alterations, including mutations and copy number variants, for the optimum care of medulloblastoma patients. Such combinations provide diagnostic and prognostic information, such as the poor outcome of SHH-activated anaplastic tumors with *TP53* mutation (18), that transcends what was previously possible with histology alone. However, incorporating the new molecular landscape into clinical practice has created challenges. For example, how should adjuvant therapy for children with a good-prognosis WNT group medulloblastoma be reduced to a level that will minimize toxicity while assuring a cure? Additionally, the molecular landscape has recently become more complex (11). Many novel genetic alterations, both germline and somatic, have been discovered, and the analysis of large numbers of medulloblastomas by methylome profiling has provided increased granularity, subgroups with distinct clinical and genetic characteristics emerging at a level below the four consensus groups.

Two of the mini-symposium articles present complementary information on the molecular alterations associated with clinical and pathological features of the disease. State-of-the-art diagnosis is the focus of the article by Dr. Brent Orr (1). Following a brief review of the "classic" medulloblastoma and its histologic subtypes: large cell/ anaplastic (LC/A), desmoplastic/nodular (D/N), and medulloblastoma with extensive nodularity (MBEN), information is provided on important histologic patterns not listed among medulloblastoma variants in the WHO classification, such as the "myoblastic" (medullomyoblastoma) and "classic/biphasic" phenotypes. These are rare but important to recognize, because they can cause confusion during morphologic interpretation and have distinct clinical and molecular associations; for example, "classic biphasic" tumors, which mimic SHH group D/N tumors, fall into the non-WNT/non-SHH category. A description of the morphologic and genetic features of tumors

in each of the four molecular groups precedes a review of diagnostic methods used to determine group assignment or to detect genetic abnormalities with clinical utility, such as *TP53* mutation. Among the diagnostic methods, methylome profiling, with its ability to test DNA from fixed tissue, represents the "gold standard" for defining medulloblastoma groups. While this method is not yet widely available, particularly in the USA, it does not suffer from some of the shortcomings associated with alternative methods that use the nanoString™ platform or immunohistochemistry (3,12).

The article by Drs. Kumar, Liu, and Northcott provides a detailed account of how subgroups of medulloblastoma emerge from the methylome profiling of large cohorts of tumors (7). The authors describe the distinct clinicopathologic and genetic associations of these subgroups, in a tier below the four principal groups. It is clear that these will have clinical utility. Among SHH group tumors, the SHH-β and SSH-γ subgroups consist mainly of medulloblastomas from infants and have a distinct prognosis. SHH-β tumors have a higher frequency of metastatic disease at presentation and a relatively poor prognosis when compared with SSH-γ tumors (15). Multiple studies have demonstrated group 3 and group 4 medulloblastomas to have distinct clinical and genetic associations; for example, patients with group 3 tumors have a poorer outcome, and group 3 is enriched for tumors with *MYC* overexpression/amplification. However, group 3 and group 4 tumors show some overlap on methylome profiling and, with sufficient tumors in the analysis, now break out into subgroups (2,10,18). Data provided in the referenced studies show that group 3/4 subgroups have distinct genetic clinicopathologic and genetic associations, and Drs. Kumar, Liu, and Northcott merge these data to propose a consensus scheme with eight subgroups. Both review articles address the clinical and pathological importance of genetic predisposition to medulloblastoma. This too varies across molecular groups. Such predisposition is rare in patients with tumors from groups 3 and 4 but occurs in approximately 20% of patients with SHH tumors, mutations in *PTCH1*, *SUFU*, *TP53*, or *BRCA2* being most common.

Metastatic disease is the major cause of mortality among children with medulloblastoma, and its biology is the focus of the article by Drs. Van Ommeren, Garzia, Holgado, Ramaswamy, and Taylor (13). In particularly aggressive forms of the disease—SHH tumors with an anaplastic morphology and *TP53* or *MYCN* amplification and anaplastic group 3 tumors with *MYC* amplification—metastatic disease at initial diagnosis is not uncommon (11). Research on this subject has been slow, because paired primary and metastatic tumor samples are not readily available, although some experimental models are beginning to show promising results. Molecular drivers suggested by these and a comparative analysis of tumors with and without dissemination include PDGFRA and ERBB2, and downstream activation of the MAPK pathway is more prominent in metastatic tumors when compared with their counterparts at diagnosis (20). An intriguing development in the pathobiology of metastatic medulloblastoma is that leptomeningeal tumor deposits can be derived from circulating tumor cells; instead of spreading through the neuraxis via CSF pathways, metastatic tumor cells in the leptomeninges have travelled through the bloodstream (5). The CCL2/CCR2 signaling pathway could be implicated in this process; *CCL2* is differentially expressed between primary and metastatic group 3 medulloblastomas, and upregulation of CCL2 can increase the rate of metastasis in an allograft mouse model of group 3 tumors. An additional related finding is that the CCL2/CCR2 signaling pathway is involved in regulating the exit of leukocytes from the hematogenous compartment (8).

Mouse models have played an important role in our understanding of medulloblastoma biology and are crucial for preclinical testing. The various approaches to modeling medulloblastoma are reviewed in an article by Drs. Roussel and Stripay and comprise the use of established cell lines, orthotopic transplant of genetically modified precursors, patient-derived orthotopic xenograft models, and genetically engineered mouse models, including those based around polyethylenimine-mediated transfection or *in utero*-electroporation of plasmids that carry genes of interest. Mouse models are now available for medulloblastomas from each of the four molecular groups. In addition, now that the genetic associations of medulloblastoma subgroups are being defined, there is potential for even more focused modeling. In this context, it would be important to create a pathogenic genetic alteration in the correct cell type, the relevant cerebellar progenitor, for successful modeling. Preclinical testing increasingly relies on mouse models, as patient-derived orthotopic xenografts are now considered the gold standard for such experiments. Most medulloblastoma preclinical studies report the use of SHH and Group 3 tumors because of their availability. As well as establishing the efficacy of a drug, preclinical testing is invaluable for alerting clinicians to potential adverse effects, such as those on bone growth exhibited by Smoothened inhibitors used to target some SHH medulloblastomas (4,6,14,16).

The four articles in the following mini-symposium provide detailed accounts of topics central to current medulloblastoma research and clinical practice. Medulloblastoma remains a challenging disease. The improved outcomes of the last three decades are gratifying; however, aggressive types of medulloblastoma associated with metastatic disease and morbidities associated with the adverse effects of current therapies focus attention on the progress still to be made. Hopefully, insights gained through the research and clinical innovations described in these articles will contribute to further therapeutic advances in the future.

REFERENCES

1. Brent O (2020) Pathology, diagnostics, and classification of medulloblastoma. *Brain Pathol* **30**:664–678.
2. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B *et al* (2017) Intertumoral heterogeneity within medulloblastoma subgroups. *Cancer Cell* **31**:737–754.e6.
3. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G *et al* (2011) Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol* **121**:381–396.

4. Gajjar A, Stewart CF, Ellison DW, Kaste S, Kun LE, Packer RJ *et al* (2013) Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. *Clin Cancer Res* **19**:6305–6312.
5. Garzia L, Kijima N, Morrissy AS, De Antonellis P, Guerreiro-Stucklin A, Holgado BL *et al* (2018) A hematogenous route for medulloblastoma leptomeningeal metastases. *Cell* **173**:1549.
6. Kimura H, Ng JM, Curran T (2008) Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell* **13**:249–260.
7. Kumar R, Liu APY, Northcott PA (2020) Medulloblastoma genomics in the modern molecular era. *Brain Pathol* **30**:679–690.
8. Lim SY, Yuzhalin AE, Gordon-Weeks AN, Muschel RJ (2016) Targeting the CCL2-CCR2 signaling axis in cancer metastasis. *Oncotarget* **7**:28697–28710.
9. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK *et al* (2016) The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. *Acta Neuropathol* **131**:803–820.
10. Northcott PA, Buchhalter I, Morrissy AS, Hovestadt V, Weischenfeldt J, Ehrenberger T *et al* (2017) The whole-genome landscape of medulloblastoma subtypes. *Nature* **547**:311–317.
11. Northcott PA, Robinson GW, Kratz CP, Mabbott DJ, Pomeroy SL, Clifford SC *et al* (2019) Medulloblastoma. *Nat Rev Dis Primers* **5**:11.
12. Northcott PA, Shih DJ, Remke M, Cho YJ, Kool M, Hawkins C *et al* (2012) Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. *Acta Neuropathol* **123**:615–626.
13. Van Ommeren R, Garzia L, Holgado BL, Ramaswamy V, Taylor MD, (2020) The molecular biology of medulloblastoma metastasis. *Brain Pathol* **30**:691–702.
14. Robinson GW, Kaste SC, Chemaitilly W, Bowers DC, Laughton S, Smith A *et al* (2017) Irreversible growth plate fusions in children with medulloblastoma treated with a targeted hedgehog pathway inhibitor. *Oncotarget* **8**:69295–69302.
15. Robinson GW, Rudneva VA, Buchhalter I, Billups CA, Waszak SM, Smith KS *et al* (2018) Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. *Lancet Oncol* **19**:768–784.
16. Romer JT, Kimura H, Magdaleno S, Sasai K, Fuller C, Baines H *et al* (2004) Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in Ptc1(+/-)p53(-/-) mice. *Cancer Cell* **6**:229–240.
17. Roussel MF, Stripay JL (2020) Modeling pediatric medulloblastoma. *Brain Pathol* **30**:703–712.
18. Schwalbe EC, Lindsey JC, Nakjang S, Crosier S, Smith AJ, Hicks D *et al* (2017) Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. *Lancet Oncol* **18**:958–971.
19. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC *et al* (2012) Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* **123**:465–472.
20. Zhao X, Ponomaryov T, Ornell KJ, Zhou P, Dabral SK, Pak E *et al* (2015) RAS/MAPK Activation drives resistance to Smo inhibition, metastasis, and tumor evolution in Shh pathway-dependent tumors. *Cancer Res* **75**:3623–3635.