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PIK3CA mutations in meningioma

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See the article by Abedalthagafi et al, on pages 649–655.

The most common tumors seen in daily neuro-oncology practice are meningiomas, which account for more than one-third of all primary CNS tumors.[1] The majority of meningiomas are WHO grade I (~80%), which are generally noninvasive, localized, and slowly growing tumors, followed by atypical meningiomas (WHO grade II; 15%–20%), and malignant meningiomas (WHO grade III; 1%–4%).[2] Meningiomas show heterogeneous histology in addition to a variable clinical course, even in benign WHO grade I meningiomas.[2] Grade I meningiomas occasionally exhibit signs of recurrence, which cannot be explained by histologic features alone, and this phenomenon is well-recognized in clinical practice.

The treatment of a symptomatic and growing meningioma is primarily surgical resection, and the likelihood of recurrence is directly related to the extent of surgical resection. Radiotherapy is a therapeutic option for recurrent, grade II and III meningiomas,[3–6] while chemotherapy presently has a minimal role in the management of meningiomas.[7,8] The genomic and molecular landscape of meningiomas has received some attention, with interest in understanding the biology of these tumors raising hope to inform therapeutic targets. A variety of chromosomal alterations have been described, with deletions of chromosomes 1 and 14 having independent prognostic value for prediction of relapse-free survival.[9] The tumor suppressor gene, neurofibromin 2 (NF2) located on chromosome 22, is mutated or lost in a substantial proportion of cases. Corroborating this biology is the propensity of neurofibromatosis type 2 patients to be diagnosed with meningiomas. The availability of next-generation sequencing has allowed more complete investigations of the genomic makeup of meningiomas in a number of recent studies.[10,11] Using exome-sequencing, mutations in TRAF7, KLF4, SMO, and AKT1 were identified in addition to NF2. Some clinicopathologic correlations were observed, with SMO and AKT1 mutations enriched in skull base meningiomas, which were more likely to be grade I.

Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. PIK3CA represents the catalytic subunit, utilizing ATP to phosphorylate phosphatidylinositols. Mutations in PIK3CA have been identified in a variety of cancers, including gliomas.[12–14] Mutations in PIK3CA activate PI3 kinase, and hotspot mutations in PIK3CA that are common and lead to constitutive activation include H1047R, E542K, and E545K. The role of PIK3CA mutations in meningioma have been implicated in tumor progression but are not clearly established. A prior study reported point mutations in the kinase domain (exon20) in 2 cases of atypical and malignant meningiomas.[15] A third case of point mutation in PIK3CA was reported in a patient with malignant meningioma.[16]

In the study published in this issue of *Neuro-Oncology* by Abedalthagafi et al, 150 meningiomas, including 104 WHO grade I, 41 grade II, and 5 grade III meningiomas were studied using high-resolution array-comparative genomic hybridization (aCGH), and well as screening for mutations in AKT1, KLF4, NF2, PIK3CA, SMO, and TRAF7. Of the 150 samples, 55 were NF2- mutated, and a total of 85 samples showed loss of chromosome 22. As described previously by other groups, mutually exclusive events between NF2 mutations and mutations in AKT1, KLF4, SMO, and TRAF7. Among the 95 NF2–wild type samples, 23 had mutations in TRAF7, 10 cases had KLF4 (K409Q) mutations, 9 had AKT1(E17K) mutations, and 6 showed mutations in SMO. New to this study was the characterization of PIK3CA mutations in the context of these previously established alterations. Overall PIK3CA mutations were found in 7 cases; 4.7% of all and 7.4% of non-NF2 meningioma cases. The PIK3CA mutations included 3 H1047R and 1 E545K as well as additional mutations. Notably, PIK3CA mutations were mutually exclusive of mutations in AKT1 and SMO but coexisted with TRAF7 mutations. PIK3CA-mutated tumors tended to be grade I and occurred in the skull base. The authors also examined common copy number alterations (CNAs) in meningioma, and evaluated these by using a "cytogenetic abnormality score" (CAS), based on a sum of the number of CNAs in the individual tumor. All or most of the cases with mutations in AKT1, SMO, and PIK3CA had a CAS of 0, indicating a "quiet" genome. Interestingly, one of the PIK3CA-mutant tumors was an outlier, in that it did not arise from the skull base, showed some aggressive histologic features, and also exhibited numerous CNAs commonly found in WHO grade II meningiomas including losses of 1p 10, 14, 18, and 2 with a CAS equal to 5, which suggested a distinct pathobiology compared with the majority of

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PIK3CA-mutated tumors. Combining the PIK3CA- and AKT1-mutant tumors together, activating alterations of the PI3K signaling pathway were seen in 16 of the 95 tumors in which an NF2 mutation was not present.

This study is the first to focus on how a key relevant and potentially targetable growth signaling pathway correlates with the mutational landscape and grade of meningiomas. Current investigations are underway to target SMO and NF2 mutations in meningioma, and this paper provides additional evidence that perhaps PI3kinase, a known oncogene, can be used as a target for meningioma. The authors correctly point to the future by suggesting the possibility of blood-based detection of PIK3CA mutations in meningioma, which could potentially lead to the possibility for neoadjuvant therapy, specifically in difficult-to -approach skull base regions that could potentially reduce morbidity from surgery and/or radiotherapy for these lesions. As with most contributory studies, this work raises new questions that will build upon these findings. What are the mutations and genomic alterations that contribute to WHO malignancy grade, tumor recurrence, and resistance to radiotherapy? Can targeting PIK3CA in radiation-refractory cases prevent or delay tumor recurrence? What is the relation of PIK3CA mutation and other mutations with previously described DNA CNAs and additional molecular changes exhibited by these tumors? With the increased interest in meningiomas spurred by this and other groups, elucidation of new possibilities for therapeutic approaches are likely to be unveiled in the coming years.

References

1. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. *Neuro Oncol*. 2013;15(suppl 2): ii1–i56.
2. van Alkemade H, de Leau M, Dieleman EM, et al. Impaired survival and long-term neurological problems in benign meningioma. *Neuro Oncol*. 2012;14(5):658–666.
3. Durand A, Labrousse F, Jouvet A, et al. WHO grade II and III meningiomas: a study of prognostic factors. *J Neurooncol*. 2009; 95(3):367–375.
4. Marosi C, Hassler M, Roessler K, et al. Meningioma. *Crit Rev Oncol Hematol*. 2008;67(2):153–171.
5. Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. *Curr Neurol Neurosci Rep*. 2009;9(3):231–240.
6. Gondi V, Tome WA, Mehta MP. Fractionated radiotherapy for intracranial meningiomas. *J Neurooncol*. 2010;99(3):349–356.
7. Wen PY, Quant E, Drappatz J, Beroukhim R, Norden AD. Medical therapies for meningiomas. *J Neurooncol*. 2010;99(3):365–378.
8. Miller R Jr., DeCandio ML, Dixon-Mah Y, et al. Molecular Targets and Treatment of Meningioma. *J Neurol Neurosurg*. 2014;1(1).
9. Domingues P, Gonzalez-Tablas M, Otero A, et al. Genetic/molecular alterations of meningiomas and the signaling pathways targeted. *Oncotarget*. 2015;6(13):10671–10688.
10. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45(3):285–289.
11. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077–1080.
12. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science*. 2004;304(5670): 554.
13. Broderick DK, Di C, Parrett TJ, et al. Mutations of PIK3CA in anaplastic oligodendrogliomas, high- grade astrocytomas, and medulloblastomas. *Cancer Res*. 2004;64(15):5048–5050.
14. Gallia GL, Rand V, Siu IM, et al. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. *Mol Cancer Res*. 2006;4(10): 709–714.
15. Bujko M, Kober P, Tysarowski A, et al. and mutations in meningiomas. *Oncol Lett*. 2014;7(6):2019–2022.
16. Pang JC, Chung NY, Chan NH, Poon WS, Thomas T, Ng HK. Rare mutation of PIK3CA in meningiomas. *Acta Neuropathol*. 2006; 111(3):284–285.