NEURO-ONCOLOGY

New therapeutic targets identified in meningiomas

Meningiomas are the most common neoplasm of the CNS and account for almost one-third of primary tumours. In a recent study, Rameen Beroukhi and colleagues at Harvard Medical School used whole-genome and whole-exome sequencing of the DNA in meningiomas to identify mutations in the tumour-suppressor gene *NF2*, and oncogenic mutations in *AKT1* and *SMO* that could provide new targets for therapy.

These aggressive tumours are treated by surgical resection, which is associated with high morbidity. However, the meningioma recurrence rate is high and few chemotherapeutic options exist for these patients. “It has been particularly disheartening that we have no clearly effective medical treatments for these tumours,” states Beroukhi. “Our hope is that

genomic characterization of meningiomas might identify both mechanisms by which they arise and effective therapeutic agents.”

The researchers sequenced DNA from grade I–III meningiomas to look for somatic gene alterations, rearrangements, mutations, insertions and/or deletions. In a subset of tumours, including one with chromothripsis—the simultaneous rearrangement of one or more chromosomes—the investigators identified genes that were most frequently mutated, and compared the rate of mutations within these individual genes against background rates of mutation in the tumour sample. Fortunately, they discovered that meningioma genomes are far simpler than those of lung cancer and melanoma, suggesting that meningioma tumorigenesis involves only a few driver events. Treatments that target these events could, therefore, be potentially curative.

Beroukhi and co-workers identified mutations in three genes already known to be involved in different types of cancer: *NF2*, *SMO* and *AKT1*. *SMO* is a member of the Hedgehog signalling pathway, and tumours with mutations in *SMO* or *AKT1*–*MTOR* showed distinct meningothelial histopathology, in contrast to meningiomas with *NF2* mutations,

which had mainly fibroblastic and/or transitional histopathology. Beroukhi’s team also showed that tumours with mutations in *SMO*, *AKT1* or *MTOR* had strong immunoreactivity for markers characteristic of Hedgehog and PI3K–Akt–mTOR pathway activation, suggesting that these pathways might interact in meningioma oncogenesis.

“A particularly hopeful aspect of these findings is that inhibitors of *SMO*, *AKT1* and *MTOR* exist in the clinic, either as FDA-approved agents or in clinical trials,” explains Beroukhi. “Patients whose meningiomas exhibit these mutations may be especially likely to benefit from treatment using these drugs.” These findings also suggest that genomic analysis might identify new oncogenic mechanisms in meningiomas. The researchers plan to investigate other genetic drivers of tumorigenesis, as well as exploring whether the known mutations induce tumour formation, and whether patients respond to treatment with the appropriate inhibitors.

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Original article Brastianos, K. P. et al. Genomic sequencing of meningiomas identifies oncogenic *SMO* and *AKT1* mutations. *Nat. Genet.* doi:10.1038/ng.2526