Genomic and Epigenomic Landscape in Meningioma

Wenya Linda Bi, MD, PhD[a,b], Yu Mei, MD, PhD[a], Pankaj K. Agarwalla, MD[b], Rameen Beroukhim, MD, PhD[b], Ian F. Dunn, MD[a,*]

KEYWORDS

• Meningioma • Genomics • Epigenetics • Molecular taxonomy • Precision medicine

KEY POINTS

- The natural history of meningiomas is incompletely predicted by their histopathologic grade and treatment history.
- Recurrent somatic mutations in *NF2*, *TRAF7*, *KLF4*, *AKT1*, and *SMO* are collectively present in approximately 80% of sporadic meningiomas, as identified by next-generation sequencing.
- Epigenetic alterations, particularly methylation changes, influence the transcriptional accessibility and consequent expression of a gene, without change in the DNA sequence.
- Epigenetic alterations serve as a complementary strategy for biologic modulation of targeted therapies in meningioma.

INTRODUCTION

Meningiomas are the most common primary intracranial neoplasms in adults, accounting for 35.8% of all primary central nervous system (CNS) tumors and more than 53% of all benign CNS tumors diagnosed in the United States.[1] The majority of meningiomas are considered benign,[2] although a small proportion display malignant behavior characterized by invasive growth patterns and/or markedly higher recurrence rates. These are classified by the World Health Organization as grades I, II, and III, with higher grades associated with significantly greater rates of morbidity and mortality despite aggressive multimodality treatment.[3]

Patients with grade I, or benign, meningiomas have a 10-year overall survival rate of 80% and a progression-free survival rate of approximately 74% to 96%, which is dependent on treatment modality, extent of resection, location of tumor, and likely age.[4–6] Grade II meningiomas are associated with up to 8-fold greater recurrence rates than grade I meningiomas, with a 10-year overall survival of 53% to 79% and progression-free survival of 23% to 78%, depending on the extent of resection and adjuvant therapies.[7–10] Grade III meningiomas are associated with a 10-year overall survival rate of 14% to 34% and progression-free survival rate of 0%.[8,11]

Although histologic grade serves as a powerful tool in prognostication of the natural history, it inconsistently predicts biologic behavior; meningiomas with benign histologic features can recur at significant rates despite aggressive resection, whereas meningiomas with high-grade features respond variably to adjuvant treatment, such as radiation. Attempts to further stratify meningiomas into histologic subtypes within each grade also fail to enhance predictive value for patient outcomes consistently. In recent decades, a paradigm shift toward molecular taxonomy has transformed the management of several tumor types. Within the

Disclosure Statement: All authors contributed to this article and attest to no conflicts of interest. All authors have no financial disclosures.

[a] Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 15 Francis Street, PBB-3, Boston, MA, USA; [b] Department of Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

* Corresponding author. Department of Neurosurgery, Brigham and Women's Hospital, 15 Francis Street, Boston, MA 02115.

E-mail address: idunn@partners.org

Neurosurg Clin N Am 27 (2016) 167–179
http://dx.doi.org/10.1016/j.nec.2015.11.009
1042-3680/16/$ – see front matter

CNS, medulloblastomas, glioblastomas, and ependymomas provide benchmarks for integrating molecular diagnoses with clinical decision making for adjuvant treatment and predicting clinical course.[12–14] Recent advances in meningioma genomics and epigenomics have yielded greater understanding of their biology and provide an initial framework for their molecular stratification. This review highlights contemporary concepts in the genomics and epigenomics of intracranial meningiomas and their applications in diagnosis, prognosis, and management.

GENOMICS AND EPIGENOMICS IN MENINGIOMA

Genomic alterations encompass mutations, insertions, deletions, and rearrangements across the genome. Elucidation of critical oncogenic drivers in a number of cancers (eg, *BRAF* in melanoma[15] or *cKIT* in gastrointestinal stromal tumors and chronic myelogenous leukemia[16]) has enabled targeted therapies in the so-called mutation-to-drug paradigm. Such approaches have not been possible in meningioma until recently, when unbiased genome- and exome-wide sequencing approaches have implicated a central core of genetic mutations that are associated with a substantial percentage of meningiomas.[17,18] These alterations have highlighted an association between genotype and phenotype in meningiomas, and have suggested potential targets for pharmacotherapeutics.

However, approximately 20% of meningiomas do not have an identifiable oncogenic driver mutation to date.[19] In these, as well as other meningiomas, epigenomic alterations may play a significant role in tumor development and progression.[20] Epigenomic modifications include DNA nucleotide methylation, microRNA interactions, histone packaging, and chromatin restructuring, all of which alter the transcriptional accessibility of the primary genetic script without change in the actual gene sequence.[21] Of these, methylation has been the most extensively studied, with approximately 77% of meningiomas harboring at least 1 methylated gene and 25% with 3 or more such alterations.[22] Notably, the ability of cells to introduce and reverse epigenetic modifications affords additional opportunity for fine modulation and targeted inhibition of tumor growth.[23]

Just as an improved understanding of genomic and epigenomic alterations has changed the classification and treatment of cancers such as chronic myelogenous leukemia, lymphomas, melanoma, and lung cancer, similar interrogation of the meningioma genome and epigenome hold significant promise for novel clinical trials for patients harboring these tumors.[24,25]

Genetic Alterations

Initial insight into the genetic alterations that lead to meningiomas was derived from associated familial syndromes. The first and most thoroughly described of these syndromes is neurofibromatosis 2 (NF2), in which 50% to 75% of patients develop 1 or more meningiomas. The underlying gene, *NF2*, is a well-defined tumor suppressor that encodes the protein Merlin. Mutation, allelic inactivation, or loss of the tumor suppressor *NF2* gene and its parent chromosome 22 have been implicated in approximately 40% to 60% of sporadic meningiomas in addition to those afflicted with neurofibromatosis.[17,18,26,27] *NF2* likely plays an early driver role in meningioma formation, given its alteration in both low-grade and high-grade tumors,[28] as well as the development of meningiomas in *NF2* knockout mice.[29,30]

In addition, the recent application of next-generation DNA sequencing approaches has identified recurrent somatic mutations in 4 genes that collectively are present in approximately 40% of sporadic meningiomas, usually without associated *NF2* mutation or chromosome 22 loss (**Fig. 1**).[17,18] These genes are the proapoptotic E3 ubiquitin ligase *TNF receptor-associated factor 7* (*TRAF7*), the pluripotency transcription factor *Kruppel-like factor 4* (*KLF4*), the protooncogene *v-Akt murine thymoma viral oncogene homolog 1* (*AKT1*), and the Hedgehog pathway signaling member *smoothened* (*SMO*).

Mutations in *TRAF7*, located on chromosome 16p13, are observed in 12% to 25% of meningiomas.[18] A majority of meningiomas with *TRAF7* mutations also harbor mutations in *KLF4* or *AKT1* mutations, but not both.[18,31] In contrast, *TRAF7* mutations rarely co-occur with *SMO* mutations, *NF2* mutations, or chromosome 22 loss.[18] The mechanism and downstream effectors of this mutation remain to be elucidated.

Approximately 15% of grade I meningiomas possess a recurrent mutation in the transcription factor gene *KLF4*, located on chromosome 9q31, with a resultant lysine to glutamine substitution at codon 409 (K409Q). *KLF4* mutations co-occur with *TRAF7* mutations and are exclusive of *NF2* and *AKT1* mutations.[18] During development, *KLF4* promotes reprogramming of differentiated somatic cells back to a pluripotent state.[32] Alteration of this pluripotent transcription factor may represent a recapitulation of embryologic mechanisms to drive tumor formation.

Another 6.8% of meningiomas harbor a recurrent mutation in *AKT1*, located on chromosome 14q32,