High-grade meningiomas: biology and implications

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The epochal developments in the treatment of meningioma—microsurgery, skull base techniques, and radiation therapy—will be appended to include the rational application of targeted and immune therapeutics, previously ill-fitting concepts for a tumor that has traditionally been regarded as a surgical disease. The genomic and immunological architecture of these tumors continues to be defined in ever-greater detail. Grade I meningiomas are driven by NF2 alterations or mutations in AKT1, SMO, TRAF7, PIK3CA, KLF4, POLR2A, SUFU, and SMARCB1. Higher-grade tumors, however, are driven nearly exclusively by NF2/chr22 loss and are marked by infrequent targetable mutations, although they may harbor a greater mutation burden overall. TERT mutations may be more common in tumors that progress in histological grade; SMARCE1 alteration has become a signature of the clear cell subtype; and BAP1 in rhabdoid variants may confer sensitivity to pharmacological inhibition. Compared with grade I meningiomas, the most prominent alteration in grade II and III meningiomas is a significant increase in chromosomal gains and losses, or copy number alterations, which may have behavioral implications. Furthermore, integrated genomic analyses suggest phenotypic subgrouping by methylation profile and a specific role for PRC2 complex activation. Lastly, there exists a complex phylogenetic relationship among recurrent high-grade tumors, which continues to underscore a role for the most traditional therapy in our arsenal: surgery.

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MENINGIOMAS, the most common primary tumors of the central nervous system in adults, have inspired significant advances in the evolution of neurosurgery (the story of meningioma is the story of microneurosurgery) and, more recently, in the application of lessons learned from biology to the management of skull base pathologies. Furthermore, the lessons learned from current study of human tumors—i.e., the elucidation of biology, the role of molecular criteria for diagnosis and prognostication, and the application of precision medicine treatment strategies— are being applied in earnest to meningiomas. Despite such advances, subsets of meningiomas remain refractory to multimodality therapies, including aggressive surgery, radiation therapy, and pharmacological trials.

Meningiomas are classified into 3 grades by the WHO: grade II and III meningiomas are associated with high rates of recurrence and premature mortality.23 Grade I meningiomas possess fewer than 4 mitoses per 10 microscopic hpf and encompass 9 histological subtypes (meningothelial, fibrous or fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic). Grade II meningiomas include atypical, clear cell, and chordoid morphological variants and are defined by 4–19 mitoses per 10 hpf, brain invasion, or the presence of 3 of 5 histopathological features associated with atypia.23 These atypical features include sheet-like growth, spontaneous necrosis, high nuclear-to-cytoplasmatic ratio, prominent nucleoli, and increased cellularity. The presence of 1 or 2 atypical features in a grade I meningioma, even if these features are not able to promote the tumor to a grade II tumor formally, is associated with an increased risk of progression and recurrence.24

Grade III meningiomas have a mitotic index of 20 or greater per 10 hpf and incorporate anaplastic, papillary, and rhabdoid subtypes. Grade III meningiomas inevitably recur within 10 years (usually less) and, as such, are considered malignant.17,25

Efforts to mitigate the recurrence of high-grade meningioma have been blunted by a dearth of treatment options and biological targets. Since the initial discovery of neurofibromin (NF2), the causative gene for neurofibromato-
sis type 2 at 22q12.2, numerous mutations, deletions, and rearrangements resulting in inactivation of NF2 have been described in meningioma as an oncogenic driver.\textsuperscript{3,10,13,18,27} Additional recurrent somatic mutations in the ubiquitin ligase tumor necrosis factor receptor–associated factor 7 (TRAF7), the pluripotency transcription factor Kruppel-like factor 4 (KLF4), the proto-oncogene v-Akt murine thymoma viral oncogene homolog 1 (AKT1), the Hedgehog pathway signaling member smoothened (SMO), the oncogene phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), the gene for the catalytic subunit of RNA polymerase II (POLR2A), the Switch/Sucrose nonfermentable (SWI-SNF) chromatin-remodeling complex gene SMARCB1, and others of lower incidence have been identified using next-generation sequencing approaches in sporadic meningiomas, usually in the absence of concurrent NF2 or chromosome 22 alterations (Table 1).\textsuperscript{1,8,10,13,14,21} Furthermore, these recurrent mutations, outside of NF2, are largely observed in grade I meningiomas but rarely in grade II or III meningiomas.\textsuperscript{8}

We aim to review the distinct genomic alterations observed in grade II and III meningiomas, discuss their diagnostic and therapeutic implications, and hypothesize on the implications of such molecular alterations for the ontogeny of high-grade meningiomas.

### Emerging Themes From Genomic Analyses

#### Higher Rates of Clinically Relevant Genomic Disruption Are Present in Grade II and III Meningiomas

The most prominent alteration in grade II and III meningiomas, compared with grade I meningiomas, is a significant increase in chromosomal gains and losses, or copy number alterations. Aside from the angiomatous subtype of grade I meningiomas, which harbor multiple polysomies across the genome, grade I sporadic meningiomas, or those not associated with an inherited familial syndrome, typically possess no chromosome alterations outside focal or broad loss on chromosome 22 in 40%–70% of cases. In comparison, high-grade meningiomas are associated with both a significantly higher incidence of chromosome 22 and/or NF2 loss and express incremental loss of chromosomes 1p, 6q, 10, 14q, and 18q with increasing grade (Fig. 1).\textsuperscript{8,11,23}

Loss of 1p is the most frequent copy number alteration, following chromosome 22 loss. Its presence in the chromosomal profile of a meningioma portends more aggressive biological behavior and may call for closer surveillance. Interestingly, chromosome 1 loss is observed significantly less frequently among grade III rhabdoid meningiomas, a particularly aggressive subtype, compared with other high-grade subtypes.\textsuperscript{8} Amplification of chromosomes 1q, 5, 7, 12, 15q, 17q, 20, and 21q is also observed in high-grade meningiomas with variable incidence but occur less frequently overall than deletion events (Fig. 1).\textsuperscript{1} On a focal level, loss of 9p21, harboring the cyclin-dependent inhibitors CDKN2A and CDKN2B, is suggested of increased aggressive behavior among meningiomas and correlates with decreased survival in anaplastic meningiomas.\textsuperscript{26}

Genome disruption, as the aggregate sum of copy number losses and gains, is of clinical interest as it might, in part, predict the risk of tumor recurrence, independent of meningioma grade and treatment status.\textsuperscript{4} Grade I meningiomas that subsequently recur exhibit a higher burden of genomic disruption than those without subsequent recurrence.\textsuperscript{8} This observation suggests a role for integrating molecular features into the pathologic diagnosis for meningioma to further refine its prognostic value.

Genome disruption also exhibits a strong association with the location of meningiomas, independent of tumor grade (W.L. Bi et al., unpublished data). Midline skull base meningiomas harbor zero or rare copy number alterations, while midline convexity (falcine, parasagittal) meningiomas possess abundant chromosomal alterations, with lateral skull base and lateral convexity meningiomas spanning an intermediate range between these 2 extremes. These patterns echo previous observations that distinct putative driver mutations in meningioma cluster in different anatomical locations, and suggest divergent ontogenies for meningioma.

The mechanism for genome disruption remains to be elucidated, although several observations offer speculation on a distinct role for the widespread recurrent chromosomal alterations observed in high-grade meningioma. First, copy number alterations may precede the acquisition of most mutations, outside of NF2, in high-grade meningiomas. Analysis of serial resections of human meningioma from the same patient reveals that copy number alterations are largely shared across recurrences, whereas mutations are generally unique to a single tumor among multiple recurrences.\textsuperscript{8} Second, meningiomas harbor a high incidence of complex rearrangements that link together geographically distinct regions of the genome.\textsuperscript{8} Since structural alterations result in copy number variation, such complex rearrangements might contribute to a proportion of

| WHO Grade & | Mutant Gene | Comment |
|-------------|-------------|---------|
| I           | NF2         | Associated w/ chromosome 22 loss |
|             | TRAF7       |         |
|             | AKT1        |         |
|             | SMO         |         |
|             | PIK3CA      |         |
|             | KLF4        |         |
|             | POLR2A      |         |
|             | SMARCB1     |         |
| II          | NF2         |         |
|             | SMARCB1     | Germline & somatic |
|             | SMARCE1     | Germline & somatic; associated w/ clear cell subtype |
|             | TERT        | Associated w/ histological progression in grade |
| III         | NF2         | Associated w/ rhabdoid subtype |
|             | BAP1        |         |
|             | TERT        | Associated w/ histological progression in grade |

*Table 1: Recurrent mutations observed in meningiomas*
copy number events in select high-grade tumors. Third, distinct pathways may lead to the generation of an atypical meningioma, one involving genome disruption on the background of NF2 loss and another implicating concurrent SMARCB1 mutation with NF2 alteration but without genome disruption. Meningiomas with concurrent NF2 and SMARCB1 alterations demonstrate a predisposition for the falx in some reports, which is also the location associated with the highest burden of genomic disruption across all anatomical regions giving rise to meningioma (W.L. Bi et al., unpublished data). Taken together, the relationship between genomic signature and meningioma origin merits deeper interrogation in future studies.

High-Grade Meningiomas Differ From Grade I Meningiomas in Mutation Profile

As with genome disruption, high-grade meningiomas are characterized by mutational profiles that differ from those of grade I tumors. High-grade meningiomas express more mutations than grade I meningiomas, on average, although the number of somatic protein-altering mutations may not significantly differ between grade I and grade II atypical meningiomas. Increased somatic mutation burden, along with methylation signatures, was associated with decreased overall survival in an integrated molecular analysis of grade I–III meningiomas.

Notably, half of all meningioma mutations are predicted to be neoantigens. High-grade meningiomas, concordantly, have a higher quantity of predicted neoantigens than grade I tumors. Meningiomas offer an advantage, as they are situated outside of the blood-brain barrier and have been demonstrated to attract a robust immune infiltrate and express prominent levels of immune checkpoint markers, especially among high-grade tumors. These qualities suggest a potential role for immunotherapy strategies for select meningioma patients, especially those with high-grade meningiomas with robust mutation burden, which is under clinical trial investigation.

High-grade meningiomas are associated with few specific recurrent somatic mutations outside of NF2, which is in stark contrast to grade I meningioma. SMARCE1 mutations in clear cell meningioma and BAP1 mutation in a subset of rhabdoid meningiomas have been reported, but the majority of high-grade meningiomas have yet to be associated with other putative driver mutations. SMARCB1 and other low-incidence mutations are observed in rare grade I and grade II meningiomas, with converging lines of evidence suggestive of a collective role for chromatin regulators in meningioma.

In meningiomas with demonstrated progression from lower grade to higher grade, mutations of the TERT promoter are observed in one-quarter of cases. In contrast, TERT mutations are not regularly observed among de novo atypical and anaplastic meningiomas or radiation-induced meningiomas. However, emergence of TERT promoter mutations was detected in regions of a grade III meningioma that were more histologically aggressive than histologically benign areas, a finding that supports differential TERT expression across geographic regions of high-grade tumors, which is a potential confounding influence in the assessment of isolated cores from meningiomas for genomic analysis.

Methylation Signatures and Transcriptional Networks Define Subgroups of Meningioma With Prognostic Significance

Integrated molecular analysis from DNA to RNA to expression and epigenetic markers has revealed additional...
Meningiomas Exhibit Spatial and Temporal Heterogeneity

There is an increasing appreciation that genomic profiles may differ within an individual tumor and may change in recurrent specimens; that is, that there is spatial and temporal heterogeneity. Recent data have shown that grade II and III meningiomas are characterized by these features.

Multifocal sampling of regions that appear more histologically benign and areas that possess more histologically aggressive features from a single anaplastic meningioma revealed stepwise acquisition of novel mutations, including ARID1A (an SWI/SNF complex member) and TERT, where copy number alterations across regions were largely shared.

Such heterogeneity could lead to acquired resistance in patients treated with targeted therapy. Indeed, we have assessed the relationship of different areas of particular tumors and found that only 9% of mutations were shared between any 2 regions.

Analysis of high-grade meningioma samples reveals that the majority of mutations are not shared across serial recurrences. This may suggest a proclivity for passenger mutations that are not associated with an oncogenic driver or trigger to arise over time. In comparison, a recurrent high-grade meningioma with multiple chromosomal alterations typically possesses a majority of those alterations on first encounter at the primary resection.

One therapeutic implication of intra- and intertumoral heterogeneity and the absence of a dominant clone in recurrent tumors is that aggressive resection will continue to be a critical weapon in our arsenal of treatment options.

Radiation Exerts Unique Influences on the Genomic Profile of Meningioma

Meningiomas that arise due to distant radiation exposure, or radiation-induced meningiomas, have similar or higher copy number alterations compared with those with no prior radiation exposure. Loss of 1p resulting from deletion or rearrangement, in particular, has been reported at a high incidence among radiation-induced meningiomas, in addition to loss of 22q, even among histologically grade I tumors. Radiation-induced meningiomas also possess NF2 fusion events at a striking frequency that is not observed in sporadic meningiomas.

Interestingly, meningiomas exposed to recent adjuvant radiation therapy contained significantly more chromosomal alterations than either radiation-induced meningiomas or radiation-naive meningiomas. Given the association of genome disruption with long-term recurrence risk, this observation frames deeper exploration for the timing of adjuvant radiation therapy in meningioma.

Conclusions

The biology of high-grade meningiomas frequently triumphs over existing medical strategies in evading cure. Recurrent mutations observed in grade I meningiomas are largely absent from grade II–III tumors, aside from NF2. In comparison, distinct methylation, gene expression, and copy number profiles mark high-grade meningiomas, affording phenotypic subgroups with prognostic associations and novel therapeutic opportunities. Evolving decryption of the genomic and immunological landscape of these tumors, across space and time, will continue to widen our entourage of pharmacological options in complement to the traditional arsenal of surgery.

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