Molecular Advances in Central Nervous System Mesenchymal Tumors

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KEYWORDS

• Meningioma • Solitary fibrous tumor • Hemangioblastoma • Genomics

Key points

- Integrated molecular, genomic, and immunologic models of meningioma complement classic histopathologic grading schemas in predicting prognosis.
- Benign meningiomas are characterized by recurrent putative oncogenic mutations while aggressive meningiomas feature recurrent chromosomal gains and losses as well as distinct epigenetic signatures, suggestive of distinct pathways for tumorigenesis.
- The NAB2-STAT6 gene fusion is pathognomonic of solitary fibrous tumors, although the molecular drivers of aggressive variants of these tumors remain to be elucidated.

ABSTRACT

Mesenchymal tumors of the central nervous system (CNS) comprise an array of neoplasms that may arise from or secondarily affect the CNS and its immediate surroundings. This review focuses on meningiomas and solitary fibrous tumors, the most common primary CNS mesenchymal tumors, and discusses recent advances in unveiling the molecular landscapes of these neoplasms. An effort is made to underscore those molecular findings most relevant to tumor diagnostics and prognostication from a practical perspective. As molecular techniques become more readily used at the clinical level, such alterations may strengthen formal grading schemes and lend themselves to treatment with targeted therapies.

Mesenchymal tumors are composed of diverse neoplasms that may arise anywhere throughout the body. Some originate from or secondarily affect the central nervous system (CNS) and its immediate surroundings, including dura, bone, and soft tissue. The most commonly encountered primary mesenchymal tumors of CNS origin are meningioma, the most common primary brain tumor in adults within the United States,[1] followed by solitary fibrous tumors (SFTs), which account for fewer than 1% of intracranial neoplasms.[2] Recent discoveries have shed greater insight into the molecular landscapes underlying these 2 tumors. As an exhaustive review of all mesenchymal tumors that may involve the CNS would not be possible in a limited review article, this review focuses on advances in these 2 entities, with an emphasis on underscoring those findings most relevant to tumor diagnostics and prognostication from a practical perspective.

MENINGIOMAS

Meningiomas are the most common primary CNS tumor in adults, occurring at an incidence of approximately 2.3 to 5.5 cases per 100,000 people

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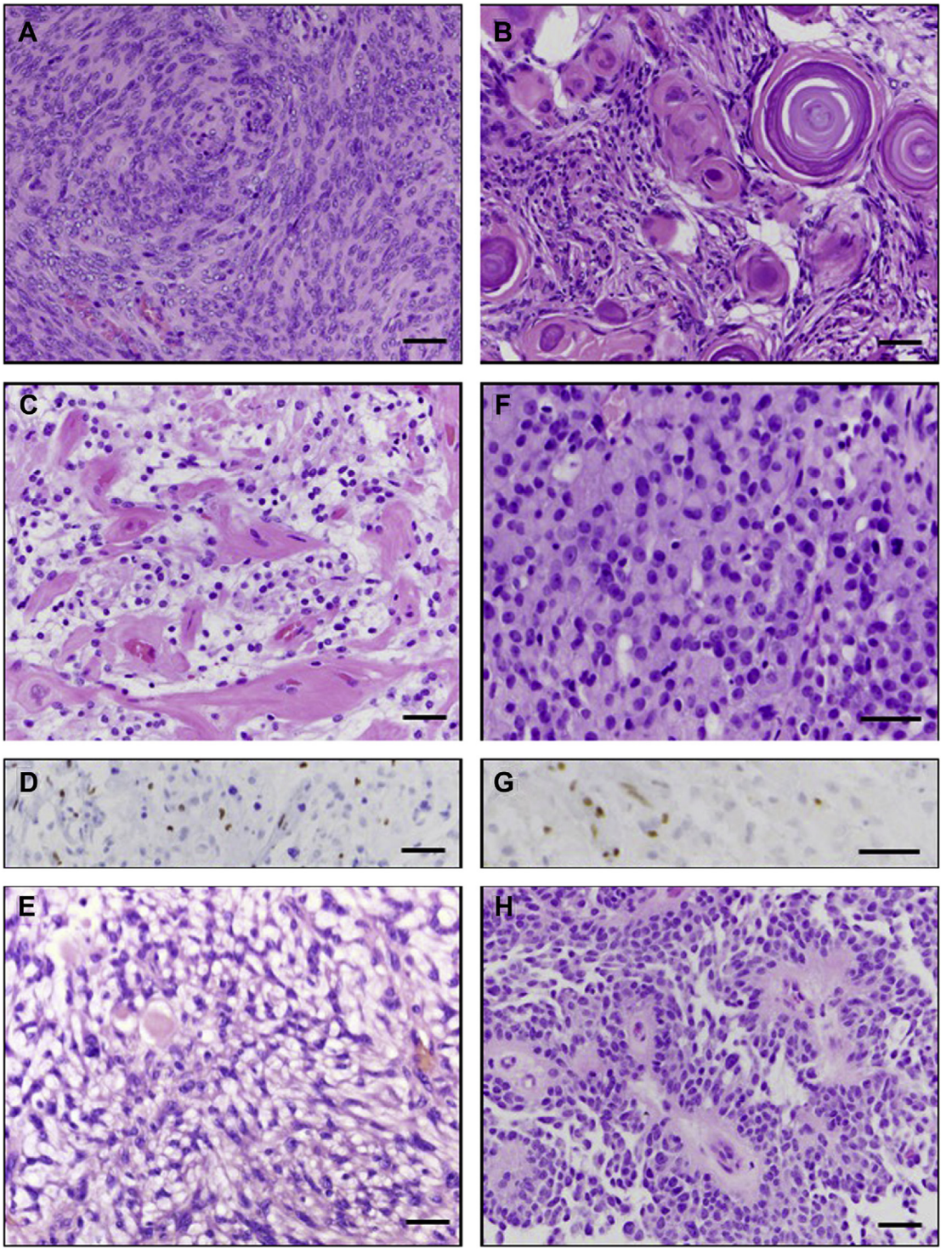

Fig. 1. (*A*, *B*) Typical histology of meningioma demonstrating whorled and lobulated architecture with a syncytial appearance (meningothelial variant, *A*), sometimes with psammoma bodies (psammomatous variant, *B*). (*C*–*E*) Grade II histologic variants of meningioma including clear cell meningioma (*C*), in which immunohistochemistry for SMARCE1 frequently demonstrates protein loss in tumor cells (*D*, note preservation of staining in admixed non-neoplastic cells), and chordoid meningioma (*E*). Clear cell meningioma is characterized by clear, glycogen-rich cytoplasm and prominent collagen bundles, whereas chordoid meningioma resembles chordoma and is characterized by trabeculae of vacuolated cells with a mucoid matrix. (*F*–*H*) Grade III histologic variants of meningioma including rhabdoid meningioma (*F*), in which immunohistochemistry for BAP1 may demonstrate protein loss in tumor cells (*G*, note preservation of staining in admixed non-neoplastic cells), and papillary meningioma (*H*). Rhabdoid meningiomas are characterized by an epithelioid or rhabdoid cytology with prominent nucleoli, whereas papillary meningiomas have a perivascular, pseudopapillary architecture. Other atypical or anaplastic features in these tumors are common. Scale bars = 20 μm.

during their life span.[3,4] Histologically, they are quintessentially characterized by a lobular, whorled architecture with a syncytial appearance, sometimes with psammoma bodies (**Fig. 1**A, B), although numerous variations exist. Although approximately 85% of tumors are World Health Organization (WHO) grade I, and often curable with surgical resection, a portion of these tumors present management challenges.[5] More aggressive meningiomas, classified as WHO grade II-III, exhibit invasive behavior and are prone to recurrence. For those aggressive tumors that recur despite multiple surgeries and radiation therapy, a need for effective adjuvant therapy remains.

Over the past decade, understanding of the molecular drivers of meningioma growth and behavior has grown. Numerous driver mutations have been identified, and modern genetic analysis has demonstrated the presence of a high degree of copy number variations (CNVs), especially in high-grade meningioma. Early studies have suggested that high-grade tumors may exist in an immune-suppressed tumor microenvironment, thereby heralding interest in the application of immunotherapies to meningioma.

EMBRYOLOGY

Meningiomas arise from a cell population within the cerebral meninges, the 3-layered protective covering that lines the CNS. The meninges that cover the cerebral hemispheres are derived from neural crest cells, which are a pluripotent population of cells that delaminate from the neural plate-ectoderm junction to migrate and differentiate into a number of cell types. In contrast, the meninges that line the midbrain and hindbrain are derived from cephalic mesoderm.[6] Classically, meningiomas are believed to originate from the cap cells of the arachnoid layer of the meninges. These cells line the arachnoid villi and protrude into venous sinuses, with the physiologic function of draining cerebrospinal fluid into venous space.

Experimental investigation has identified a common prostaglandin D2 synthase positive (PGDS+) primordial meningeal cell that gives rise to the inner layer of the dura mater (dural border cells) and the outer layer of the arachnoid. These cells are of neural crest origin in the telencephalon and of mesodermal origin in the midbrain. Of note, inactivation of NF2 alone in these PGDS+ precursor cells is sufficient for development of meningothelial and fibroblastic meningiomas in a murine model, supporting their role as a progenitor of meningiomas, and the concept that loss of NF2 is an early driver event in tumorigenesis.[7]

CURRENT HISTOLOGIC GRADING CRITERIA AND LIMITATIONS

Traditionally, the most critical pathologic determination that must be made by the neuropathologist when assessing meningiomas is assignment of grade, an objective means of predicting overall aggressiveness, including likelihood of tumor recurrence. Meningiomas are classically assigned to 1 of 3 grades (WHO grade I–III) based on histologic features, which roughly predict prognostic outcomes: benign meningiomas (grade I) have a 10-year overall survival of approximately 80% to 90%,[8–10] atypical meningiomas (grade II) 53% to 79%,[11–13] and anaplastic meningiomas (grade III) 14% to 34%[11,14]; corresponding progression-

Box 1
Meningioma grading criteria

Grade 1 (Benign):

Mitoses less than 4/10 high-powered fields (HPF)

AND no other criteria (below) for higher grade fulfilled

Grade II (Atypical):

Mitoses more than 4/10 HPF but fewer than 20/10 HPF

OR 3 or more of the following histologic criteria:

- Increased cellularity
- Sheetlike growth
- Prominent nucleoli
- Small cell change
- Spontaneous necrosis

OR one of the following histologic variants:

- Clear cell meningioma
- Chordoid meningioma

OR brain invasion

Grade III (Anaplastic):

Mitoses more than 20/10 HPF

OR one of the following histologic variants:

- Rhabdoid meningioma
- Papillary meningioma

Adapted from Louis, D.N., et al., *WHO classification of tumours of the central nervous system*. Revised 4th edition. ed. World Health Organization classification of tumours. 2016, Lyon: International Agency For Research On Cancer; with permission.

free survival is 79% to 90% for benign,[8–10] 23% to 78% for atypical,[11–13] and 0% for anaplastic meningiomas.[11,14] Not surprisingly, these outcomes are further influenced by nonhistologic parameters, such as extent of resection, tumor location, age, and use of adjuvant therapies.

The histologic parameters determining meningioma grade have remained almost constant for more than 15 years, with minor nuances (**Box 1**).[2,15,16] In the most recent, 2016, edition of the *WHO Classification of Tumors of the Central Nervous System*, brain invasion is now deemed sufficient criterion for grade II designation, even in the absence of other atypical features.[2] Previously, such invasion has been associated with adverse prognostic outcome but was not included in formal grading criteria.[15–17]

In practice, the most objective and therefore reliable grading feature is mitotic activity, which is the only parameter that can establish a grade III (anaplastic) diagnosis. Atypical features such as small cell change and sheetlike growth can formally be used to establish a grade II diagnosis when 3 or more are present; however, these are somewhat subjective and caution should be exercised when using them as sole criteria for assigning higher grade; preferably, such features should support a higher grade already determined by mitotic index or presence of brain invasion. In addition, mitotic activity is ideally commensurate with the MIB-1 proliferative index, although their relationship may be inconsistent.

Numerous histologic variants of meningioma are also recognized, with the majority thought to be prognostically inconsequential (see **Fig. 1**). Those of prognostic importance for the pathologist to report include clear cell and chordoid meningioma, which are grade II tumors by default, as well as rhabdoid and papillary meningioma, which are grade III.[2] Such histologic variants can be diagnosed even in the absence of other atypical or anaplastic features; if the histology is not well-developed or sparsely distributed, the prognostic implications of assigning a higher grade must be weighed. This is exemplified in a study of meningiomas with rhabdoid histology lacking other features of anaplasia, demonstrating that only a subset may be more aggressive than their nonrhabdoid counterparts.[18]

The ambiguity of assigning tumor grade based solely on atypical or aggressive histologic features, and the observation of grade I meningioma recurrence despite benign histopathology and aggressive treatment,[19] highlights the imperfections of the existing morphology-based grading scheme. To counter these limitations, integrated molecular models including genetic mutations, CNV, and methylation profiles have been presented to better predict tumor recurrence.[20–23] We therefore review molecular alterations that inform meningioma grade, aggressiveness, and prognosis (**Table 1**).

MOLECULAR ALTERATIONS INFORMING MENINGIOMA AGGRESSIVENESS

Cytogenetics

Meningiomas harbor stereotypical chromosomal losses and gains, or CNVs, which inform clinical aggressiveness. Generally, the number of CNVs correlates with histologic grade and risk of tumor recurrence. Grade I tumors have 0 or 1 CNVs, typically monosomy of chromosome 22, whereas grade II and III tumors express an increasing burden of chromosomal alterations.[24–28] Mechanistically, CNVs are presumed to cause dysregulation of oncogene or tumor suppressor gene activity.[29]

Table 1
Molecular alterations associated with meningioma and grade correlations

	Grade 1 (Benign)	Grade II (Atypical)	Grade III (Anaplastic)
Cytogenetics	Monosomy 22	Polysomy Iq, 9q, 12q, 15q, 17q, and 20q Loss of *Ip*, 6q, 10, 14q, and 18q	1–2 copy loss of 9p, including 9p21, encompassing CDKN2A/CDKN2B Amplification of 17q23, encompassing PS6K
Mutations	*NF2* *AKT1, SMO, TRAF7, KLF4, POLR2A*	*SMARCE1* (clear cell meningioma) TERT promoter	*BAP1* (rhabdoid meningioma)

Adapted from Louis, D.N., et al., WHO classification of tumours of the central nervous system. Revised 4th edition. ed. World Health Organization classification of tumours. 2016, Lyon: International Agency For Research On Cancer.

Monosomy 22 is the most commonly observed copy number variation, found in 40% to 70% of meningiomas, and frequently the only cytogenetic abnormality present in grade I tumors.[30,31] The angiomatous histologic subtype offers an exception given their molecular signature of multiple polysomies, despite benign or grade I designation.[32] Atypical and anaplastic meningiomas harbor additional losses in 1p, 6q, 9p, 10, 14q, and 18q with gains in 1q, 9q, 12q, 15q, 17q, and 20q.[2,30] Chromosome 1p and 14q loss are the second and third most common genetic alterations after monosomy 22, respectively. Loss of chromosome 1p has been shown to be associated with higher likelihood of recurrence in grade I tumors, and therefore is thought to be a poor prognostic marker independent of histologic grade.[25,33] Loss of both 22q and 1p is a strong predictor of decreased recurrence-free survival.[21] Genetic mutations driving neoplasia on chromosome 1p in sporadic meningiomas have yet to be identified.

Anaplastic meningiomas are particularly associated with loss of chromosome 9p, including the tumor suppressor proteins CDKN2A, CDK4, and ARF located at 9p21. Even among histologically anaplastic meningiomas, CDKN2A deletion and inactivating mutations were associated with poorer outcome.[34,35] Amplification of 17q23 encompassing the *PS6K* oncogene has also been documented in a small subset of anaplastic meningiomas.[36] Although cytogenetic abnormalities predicting more aggressive behavior are not used for formal grading at this time, their presence in histologically benign tumors is important for the pathologist to note, as these tumors should be regarded as potentially behaving more aggressively.

Molecular Signatures of Aggressive Histologic Variants

The identification of histologic subtypes of meningioma that behave more aggressively and are assigned a higher grade, independent of other aggressive histologic features, suggests that there may be underlying molecular correlates to such variants; these signatures may aid in a more definitive diagnosis as well as yield insights into mechanisms of tumorigenesis. These molecular perturbations were frequently identified as germline mutations in cases of familial meningioma, with subsequent appreciation for their presence in sporadic meningiomas.

Patients with mutations in *SMARCE1*, a gene involved in chromatin remodeling, have a propensity to develop spinal and cranial clear cell meningiomas.[37–39] This has been observed in familial hereditary settings as well as sporadic clear cell meningiomas. In chordoid meningiomas, an unbalanced translocation between chromosomes 1 and 3 has been reported but is not yet defined as a consistent signature.[40]

Inactivating mutations in the BAP1 protein, a tumor suppressor that is a ubiquitin carboxy-terminal hydrolase, have been identified in families with a propensity to develop rhabdoid meningiomas as well as in sporadic rhabdoid meningiomas.[41–43] *BAP1* germline mutations also predispose to uveal and cutaneous melanoma, mesothelioma, and other tumors. Tumors with such inactivating mutations usually also have loss of heterozygosity of chromosome 3p encompassing the *BAP1* gene, and almost uniformly have loss of BAP1 protein expression detectable by immunohistochemistry (IHC). Notably, patients with meningiomas with BAP1 loss were found to have significantly shorter times to progression than those with similar histologic grade with intact BAP1 expression.[41] Furthermore, given there is also some histologic overlap of these tumors with papillary meningiomas,[44] this raises the question if *BAP1* mutations may also be an underlying molecular driver in this subtype. Immunohistochemistry allows ready detection of BAP1 protein loss and may guide identification of more aggressive rhabdoid meningiomas in clinical practice. Patients with BAP1-inactivated rhabdoid meningiomas should be assessed for germline mutations as part of an inherited syndrome.

Genetic Mutations

Beyond cytogenetic alterations and gene mutations associated with more aggressive histologic subtypes, several genetic aberrations have been identified that may predict more aggressive behavior. One such event is activating mutations in the *TERT* promoter, which have been shown to be associated with higher-grade meningiomas, although occur in only a subset of these malignancies.[45–47] Such mutations have been identified in approximately 6.5% to 11.0% of meningiomas, but may reach closer to 20% in grade III tumors.[46,47] TERT encodes telomerase, key to maintaining telomere length, and is a key oncogenic driver in many tumors. Furthermore, regardless of grade, meningiomas with such mutations have been shown to have significantly shorter progression-free survival, and therefore appear to be predictive of poor prognosis.

Alterations of the Switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, which is a family of proteins involved in chromatin remodeling, are observed at higher rates in

anaplastic meningiomas, and are associated with worse overall prognosis.[23] Mutations in several members of this complex have been identified, including *SMARCE1*, *SMARCB1*, *SMARCA4*, *PBRM1*, and *ARID1A*.[23,48,49] *SMARCE1*, as discussed previously, is pathognomonic of clear cell meningiomas. In addition, high-grade meningiomas have been found to have upregulation of the polycomb repressive complex 2 (PRC2) and its catalytic domain, which functions in balance with the SWI/SNF complex.[49] The upregulation of PRC2 and downregulation of SWI/SNF demonstrates the important role of chromatin regulation in meningiomas.

Although few other mutations with poor prognostic significance have been recognized, several recurrent genetic mutations have been identified that are associated with meningiomas as a whole and may inform mechanisms of tumorigenesis. Along these lines, no discussion of gene mutations in meningiomas would be complete without mention of *NF2*, the gene encoding the protein Merlin, in which germline inactivating mutations are causal of the syndrome neurofibromatosis type 2. Patients with this syndrome have a predisposition to developing multiple meningiomas,[28] among other neoplasms, which generally have loss of Merlin protein expression through a classic 2-hit event such as acquisition of monosomy 22.[31,50] Interestingly, *NF2* inactivating mutations are also the most common genetic mutations in sporadic meningiomas, occurring in approximately 60% of tumors, and also frequently occur in tandem with loss of heterozygosity of this genetic locus.[51,52] *NF2*-mutant meningiomas are associated with fibrous or transitional histology.[53,54] These mutations appear to be early and likely initiating events in tumorigenesis, and are found roughly equally across all meningioma grades.[55] Notably, numerous other genetically inherited syndromes have also been associated with development of meningiomas, suggesting a multifactorial means of tumorigenesis.

In sporadic meningiomas, other somatic mutations have been identified, including mutations in AKT serine/threonine kinase 1 (*AKT1*), smoothened (*SMO*), tumor necrosis factor (TNF)-receptor associated factor 7 (TRAF7), and Kruppel-like factor 4 (*KLF4*).[26,56–58] These tumors comprise approximately 40% of meningiomas, preferentially occur at the skull base, are generally grade I in nature, and are mutually exclusive of *NF2* mutations. Those meningiomas with *AKT1* or *SMO* mutations are enriched along the midline anterior skull base and are frequently meningothelial in histologic subtype. Those with *TRAF7* mutations may have concomitant mutations in *AKT1* or *KLF4*, and those with the latter are generally of the secretory histologic subtype.[59] Finally, in non-NF2 mutant tumors lacking any of these drivers, recurrent mutations have also been found in *POLR2A*, encoding the catalytic subunit of RNA polymerase II, preferentially associated with sellar tumors and of the meningothelial histologic subtype.[60] Notably, as all of these mutations are found in association with lower grade tumors, their presence may suggest a more benign clinical course.

Last, mutations in *PIK3CA*, a known oncogene mutated in 15% of human cancers[61] has been demonstrated in 4% to 7% of meningiomas,[62,63] leading to constitutive activation of downstream AKT1 and mammalian target of rapamycin (mTOR) signaling and, thus, cellular proliferation and progression through the cell cycle. *PIK3CA* activating mutations appear mutually exclusive of *NF2*, *SMO*, and *AKT1*.[62,63] The *SUFU* gene, which is involved in the hedgehog signaling pathway, has also been found to be mutated in approximately 1% of sporadic meningiomas, with germline mutations present in familial cases.[60]

DNA Methylation

Epigenetic regulation of the genome plays a significant role in gene regulation and cancer biology. Hypermethylation of certain segments of the genome leads to repression of gene expression in those regions, and this has important consequences for tumorigenesis. Global DNA hypomethylation and focal DNA hypermethylation are associated with tumor development, and this has been found in meningioma.[64] Differential methylation status between low-grade and high-grade meningiomas has been identified in important genes including *TMP3*, *CDKN2A*, and *TP73*.[65] Several studies have conducted large-scale methylation profiling and identified separate subclasses of meningiomas following unsupervised clustering analysis. Methylation-based subgroups successfully categorized patients in similar risk groups, and effectively predicted risk for tumor recurrence.[20,66] These findings show that epigenetic characteristics can be an important source of prognostic information. There is great interest in development of a clinically validated methylome-based predictor to aid in clinical decision making; however, such techniques are available at only a handful of institutions at present, and largely remain a research tool.

MOLECULAR MARKERS IN MENINGIOMA DIAGNOSTICS

Although the histologic diagnosis of meningioma is generally straightforward, there can be histologic

mimics, the most common of which is solitary fibrous tumor (see later in this article), which occasionally may be confused with the fibrous histologic subtype of meningioma. Therefore, immunohistochemical markers that are sensitive and specific for meningiomas can be of diagnostic value. Meningiomas traditionally stain for epithelial membrane antigen (EMA) and somatostatin receptor 2a (SSTR2a), although degree of staining can be quite variable between individual tumors and higher-grade neoplasms may lose expression; these 2 markers are relatively sensitive and specific in the context of a dural-based mass, although there can be confounders.[67,68] Notably, SFTs should be consistently negative for both EMA and SSTR2a. Another molecular marker for meningiomas readily detectable by IHC is progesterone receptor, expressed in most tumors.[69]

Recently, one study has made inroads toward finding lineage-specific transcription factors expressed in meningiomas, which could also be detected by IHC and aid in the diagnosis of such neoplasms.[70] Such lineage-specific transcription factors are used routinely to identify other neoplasms, such as TTF-1 for lung and thyroid tumors, OLIG-2 for gliomas, and GATA-3 for breast and urothelial cancer. Identified markers include SIX1, FOXC1, MEOX2, which are readily assayable by IHC and therefore could be used in clinical practice. This study demonstrated relative sensitivity and specificity of these markers for meningioma; however, further validation over multiple trials will be necessary.

A COMBINED IMMUNOLOGIC AND GENOMIC APPROACH TO INVESTIGATING MENINGIOMAS

As molecular biology techniques advance in parallel with the rapid progression of genomic analysis, increasing interest has emerged in combining the two approaches to investigate the role of the immune system in mesenchymal tumors. The characterization of the immune *gestalt* of meningiomas date back to the 1980s,[71] but pose several limitations. First, only a handful of studies to date have examined the tumor microenvironment of meningiomas, with limited sample sizes, which hinder the ability to extrapolate these data to all meningiomas. Furthermore, the techniques used in previous investigations, most commonly IHC and flow cytometry, select for limited immunologic markers without ability to explore all possible cell types. Newer protocols that aim to improve this coverage include bulk and single-cell RNA-sequencing, multiplexed immunofluorescence for in situ visualization of immune infiltrates, and mass cytometry by time of flight for multiple epitope analysis compared with traditional cytometry.

Existing data suggest that the immunophenotype of meningiomas comprise a predominant macrophagic infiltrate.[71–77] Although some investigations indicate a correlation between macrophage density and WHO grade,[71,76,78] others found no such association.[72,75] The antitumoral versus anti-inflammatory, and perhaps protumoral, functionality of the existent macrophage populations in meningioma also merits closer inspection. Similarly, the observed degree of lymphocytic infiltrate and its subpopulations (B cell vs T cell, CD4+ vs CD8+ T-cell predominance) varies significantly between the different studies.[75,79,80]

One possibility for immune variations in meningiomas may derive from the individual genomic makeup of these tumors (**Fig. 2**). For example, PIK3C/AKT pathway signaling contributes to T lymphocyte fate determination: constitutive AKT signaling suppresses the regulatory T-cell lineage in vitro, whereas pharmaceutical inhibition of mTOR promotes effector memory CD8+ T-cell generation as observed in vivo. Given that *AKT1* mutations are largely confined to grade I meningiomas, the possibility arises that the same mutation is at once the tumorigenic driver and an enabler of antitumoral immune responses that inhibit a transition to malignancy. Contradictory to this hypothesis is the finding that the immune checkpoint proteins PD-L2 and B7-H3, which enable tumoral evasion of the immune system, are upregulated in meningiomas with PIK3C/AKT pathway mutations.[81] Further investigation is therefore warranted to understand the immunogenomic dynamics surrounding this signaling cascade.

Similarly, TRAF7 lies downstream of the TNF-alpha cascade and therefore mediates a proinflammatory response (see **Fig. 2**). Constitutive activation of TRAF7 could potentially facilitate a paradoxic oncogenesis and immune attack phenotype as in *AKT1*-mutant tumors. Identification of GREM2 downregulation in higher-grade meningiomas supports the converse of this hypothesis: loss of immune signaling facilitates tumor progression.[82] GREM2 inhibits bone morphogenetic protein (BMP) signaling, which lies upstream of transforming growth factor beta-1 (TGF-β1) expression; this pathway in turn regulates lymphocyte survival and proliferation. Previous studies have established the protective effects of BMP and TGF-β1 activity against meningioma progression; loss of this activity via downregulation of GREM2 could therefore attenuate immunologic efficacy against these tumors, explaining the resulting malignant phenotypes.[82]

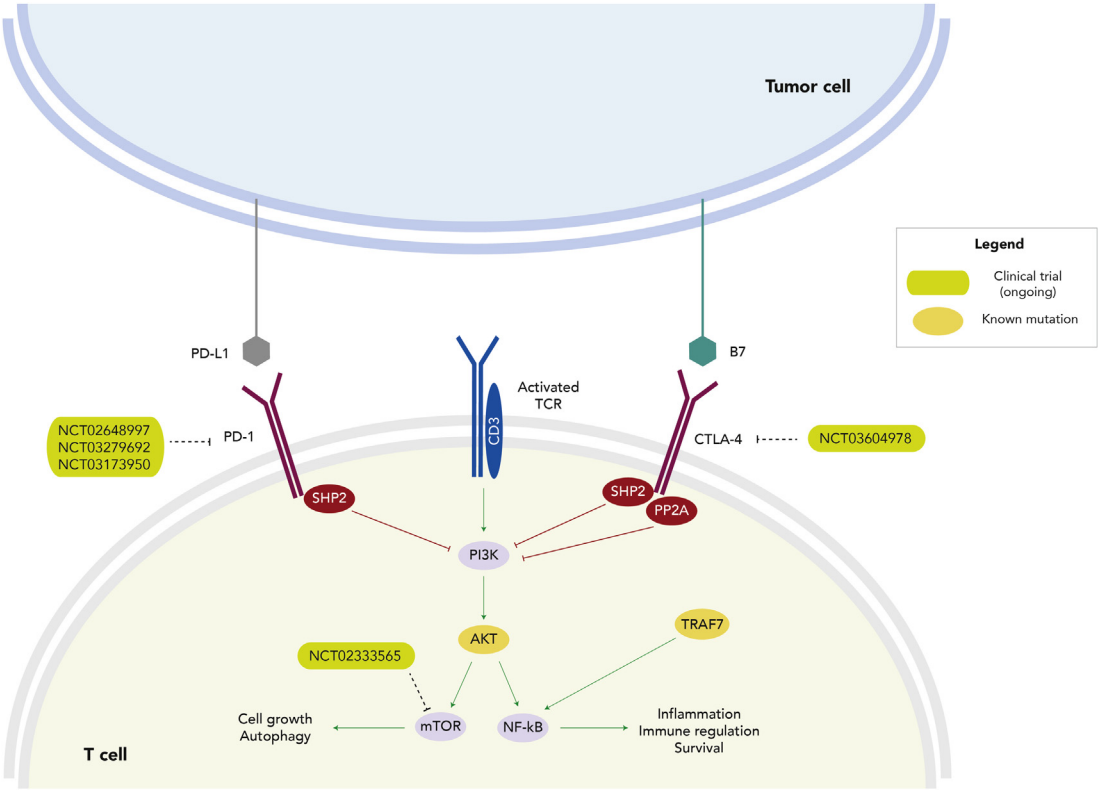

Fig. 2. Immune pathways implicated in meningiomas and current clinical trials targeting those pathways.

The few existing immunogenomic studies of meningiomas support a genomic influence on the immune microenvironment of meningiomas. For instance, a transcriptomic analysis of de novo meningiomas demonstrates enriched expression of genes regulating inflammatory, interferon-gamma, and allograft rejection responses in grade I tumors. Corresponding immunohistochemical staining for CD45, a pan-leukocyte marker, of this cohort supports a differential immune response; grade I tumors had significantly higher infiltration than grade II or III meningiomas.[82] Another group investigating radiation-induced meningiomas carrying NF2-fusion events report significant differences in immunophenotype between their cohorts and meningiomas harboring other known driver mutations. RNA-sequencing analysis indicated increased expression of both inflammatory genes (STAT-4, IGF-1) and immunosuppressive factors (PD-1) in *NF2*-fusion meningiomas,[83] whereas IHC revealed exhaustion of inflammatory cells in the form of increased PD-L1 staining and decreased CD3+ lymphocyte presence compared with non-*NF2*-fusion tumors.[84,85]

Last, tumor transcriptomic analysis and subsequent linear regression revealed immunologic gene expression to be vitally correlated with meningioma location after controlling for WHO grade; specifically, skull base meningiomas displayed significantly higher immune upregulation than did convexity meningiomas.[86] Cytokine-based interrogation of the immune populations at these 2 sites may also reconcile the seemingly contradictory observations of proinflammatory and immunosuppressive myeloid subpopulations from previous data. Antitumoral M1 macrophages were highly correlated to skull base location by network analysis, whereas oncogenic mast cells predominated convexity meningiomas.[86] Together, these data suggest significant variation in immune microenvironment across intracranial sites that may explain historical (albeit controversial) correlations between malignancy and meningioma location.

SOLITARY FIBROUS TUMOR/ HEMANGIOPERICYTOMA

SFTs are rare fibroblastic neoplasms most commonly arising within pleura; however, may occur at almost any anatomic site, including the CNS.[87] Those of CNS origin make up less than

1% of primary CNS tumors, and invariably arise from a dural location.[2,88,89] They largely effect middle-aged adults in the fourth and fifth decades of life, with a slight male predominance. Histologically these tumors are monomorphic, spindled cells that take on a jumbled, yet characteristic architecture commonly referred to as a "patternless pattern," separated by thick bands of collagen and thin-walled, staghorn vessels.

The term "hemangiopericytoma" is an obsolete term for these neoplasms when used outside of the CNS, as it historically encompassed a variety of neoplastic entities with similar architectural patterns, including SFTs, all now designated with more specific names[90]; it has been done away with in the realm of soft tissue and pulmonary pathology. Despite this, the term persists in the practice of neuropathology, and up until the 2016 *WHO Classification of Tumors of the Central Nervous System*, higher-grade SFTs, which were more cellular with less intervening stroma were separately classified as hemangiopericytomas.[16] The finding that almost all of these tumors harbor an NAB2-STAT6 gene fusion, now regarded as a specific and pathognomonic genetic alteration defining SFTs, effectively eliminated hemangiopericytoma as a separate entity. However, only within the CNS, SFTs presently are formally classified as solitary fibrous tumor/hemangiopericytoma in the 2016 WHO classification[2]; this classification will likely be done away with in future editions.

GRADING

Grading of SFTs within the CNS, like formal nomenclature, is also different from those at other anatomic sites. CNS SFTs are graded from WHO grade I-III, with a distinction between those of traditional SFT histology (grade I, benign) or hemangiopericytoma histology (grade II or III, malignant),[2] although admittedly such morphologic phenotypes are not always discrete and there is a phenotypic spectrum. The importance of this distinction rests on studies demonstrating that those of SFT phenotype display benign behavior with little likelihood of recurrence given full surgical resection, whereas those of hemangiopericytoma phenotype have a significant risk of recurrence and metastasis (>70% recurrence with 10-year follow-up with ~20% of patients developing extracranial metastases). Further distinction between grade II and III tumors rests on mitotic count, with more than 5 mitoses/10 high-powered fields (HPF) achieving a grade III designation.

Outside the CNS, a distinction between SFT and hemangiopericytoma histology is not made, with mitotic count (>4/10 HPFs) being the most important prognostic determinant of malignancy.[87,91] The prognostic relevance of mitotic count has also been demonstrated in SFTs of the CNS, independent of other parameters, including histologic phenotype.[92] An argument for aligning grading criteria for CNS SFTs with those used at other anatomic sites could thus be made. Along these lines, whether a recently proposed and widely adopted risk stratification model for nonmeningeal SFTs is relevant to CNS tumors also remains an open question worthy of further study.[93]

MOLECULAR MARKERS OF SOLITARY FIBROUS TUMORS

Until 2013, a molecular signature for SFTs remained elusive, although immunohistochemically they were known typically to express CD34 and CD99 with a subset positive for Bcl-2, none of these markers sensitive or specific for this entity.[90] A major breakthrough in the understanding of the molecular signature of these tumors arose with the identification of a chromosomal inversion at the 12q13 locus in the vast majority of these neoplasms, resulting in fusion of the NAB2 and STAT6 genes.[94–96] Numerous variations of this translocation have been identified, all of which result in the nuclear localization domain of NAB2 being fused to STAT6, a cytoplasmic transcription factor. The result is nuclear localization of the resulting fusion protein and transcriptional activation; this fusion product has been demonstrated to induce proliferation in cell culture and is likely the initiating driver in SFT tumorigenesis.[94] Notably, NAB2 and STAT6 are positioned in close proximity on chromosome 12, and thus molecular tests, such as fluorescence in situ hybridization, may give false negative results. To this end, IHC demonstrating nuclear localization of STAT6 seems to be an even more sensitive and specific surrogate marker for the presence of this fusion transcript, and absence of this marker in a suspected SFT should call such a diagnosis into question.[97,98]

MOLECULAR MARKERS INFORMING SOLITARY FIBROUS TUMOR AGGRESSIVENESS

Given an evolving understanding of histologic determinants of SFT aggressiveness within the CNS, molecular determinants informing malignant potential would be invaluable for grading and prognostication. Compared with meningiomas, aggressive molecular signatures of SFTs are more sparsely understood, in part because

of the relative rarity of these tumors. In a study of nonmeningeal SFTs,[99] the most common NAB2-STAT6 fusion, NAB2ex4-STAT6ex2/3, was observed in tumors with classic SFT histology, a less aggressive clinical course, and an older patient population. The NAB2ex6-STAT6ex16/17 fusion, in contrast, was associated with hemangiopericytoma histology, more aggressive behavior, and found in younger patients. Subsequent study of meningeal SFTs found similar correlations, although no prognostic significance was detected, likely due to small sample size.[100] Importantly, such fusion variants target different functional domains of both the NAB2 and STAT6 genes, thereby providing a functional molecular correlate by which variable oncogenicity could be conferred. As in meningiomas, *TERT* promoter mutations have recently been documented in SFTs and appear to confer increased aggressiveness.[101,102] Such alterations might be incorporated into future grading schemes, as molecular methods become more accessible to general pathology practice.

SUMMARY

The past several years have seen numerous developments in the discovery of molecular alterations both defining meningiomas and SFTs, as well as those that may predict tumor aggressiveness. As techniques of molecular biology become more readily used at the clinical level, such alterations undoubtedly will become formally incorporated into tumor grading and prognostication, including even now cutting-edge technologies such as DNA methylation profiling. In addition, as molecular profiling of these tumors becomes more commonplace and more tumors are routinely profiled, further insights into such molecular alterations, how they drive tumorigenesis, and how they may predict aggressiveness as well as susceptibility to targeted therapies will be further gained.

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