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REVIEW ARTICLE

Germline and somatic mutations in meningiomas

Miriam J. Smith*
Manchester Centre for Genomic Medicine, St Mary's Hospital, University of Manchester, Manchester, UK

Meningiomas arise from the arachnoid layer of the meninges that surround the brain and spine. They account for over one third of all primary central nervous system tumors in adults and confer a significant risk of location-dependent morbidity due to compression or displacement. A significant increase in risk of meningiomas is associated with neurofibromatosis type 2 (NF2) disease through mutation of the *NF2* gene. In addition, approximately 5% of individuals with schwannomatosis disease develop meningiomas, through mutation of the SWI/SNF chromatin remodeling complex subunit, *SMARCB1*. Recently, a second SWI/SNF complex subunit, *SMARCE1*, was identified as a cause of clear cell meningiomas, indicating a wider role for this complex in meningioma disease. The sonic hedgehog (SHH)-GLI1 signaling pathway gene, *SUFU*, has also been identified as the cause of hereditary multiple meningiomas in a large Finnish family. The recent identification of somatic mutations in components of the SHH-GLI1 and AKT1-MTOR signaling pathways indicates the potential for cross talk of these pathways in the development of meningiomas. This review describes the known meningioma predisposition genes and their links to the recently identified somatic mutations.

Keywords *SMARCB1*, *SMARCE1*, *SUFU*, *AKT1*, meningioma

Meningiomas are the most common primary central nervous system tumors in adults (1). Over 90% of meningiomas are single and sporadic. Fewer than 2% of meningiomas are classed as malignant; however, 20–35% of meningiomas, initially classed as benign, have been reclassified as atypical since the World Health Organization (WHO) grading system changed in 2007 (2). These tumors tend to occur at an earlier age and have a seven-to eightfold increased rate of recurrence. Atypical meningiomas also confer a reduced survival rate with an approximately twofold increased risk of death by 3–5 years after diagnosis (3).

Benign meningiomas carry a significant risk of location-dependent morbidity due to compression or displacement. Spinal meningiomas can cause back pain and numbness and weakness of the arms or legs, suprasellar and intraorbital meningiomas can cause vision problems and swelling or bulging of the eye, and olfactory groove meningiomas can cause loss of sense of smell. Intraventricular meningiomas may cause headaches and changes in mental function due to increased pressure resulting from reduced flow of cerebrospinal fluid, whereas meningiomas within the convexity can cause various focal neurological deficits that are restricted to a specific region, such as weakness or paresthesia in one side of the face, or one arm or leg.

Many meningiomas are well-delineated tumors that respond well to surgical excision, although meningiomas that occur in the skull base can be difficult to access and remove. Meningioma growth can be unpredictable. Some meningiomas show a linear growth pattern that may be fast or slow and may be dependent on the level of calcification (4), whereas others show a saltatory growth pattern with variable periods of quiescence (5). There are many histologic subtypes of meningioma. Meningothelial, fibroblastic, and transitional meningiomas, as well as the psammomatous, secretory, microcystic, angiomatous, lymphoplasmacyte-rich, and metaplastic variants are all classed as grade I. Clear cell, chordoid and atypical subtypes are classed as grade II, whereas the anaplastic, rhabdoid, and papillary variants are all classed as grade III. Most meningiomas have a mixed histology and are categorized by the dominant component.

Of the known causes for sporadic meningiomas, ionizing radiation is probably the most common. A hormonal aspect to meningioma development has also been suggested, as there is a 2.3:1 overall female/male ratio for meningiomas (6), and even higher ratios, of between 4:1 and 9:1, have been reported for spinal meningiomas (7–10). It has also been observed that the gender bias is reversed in

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* Corresponding author.
E-mail address: miriam.smith@manchester.ac.uk.

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meningiomas that develop before 20 years of age (11,12) and that the appearance of meningiomas in women can correlate with, or worsen during, pregnancy (13,14). There is no definitive evidence for this hormonal influence and although the accelerated growth of meningiomas during pregnancy has been attributed to raised progesterone levels (15), the proportion of meningiomas expressing progesterone receptors is not significantly different between males and females (16) and a recent study has shown that the effects of pregnancy on meningioma growth may be more likely to be due to temporary hemodynamic changes (14).

The most common genetic cause of meningiomas is mutation of the *NF2* gene. Germline mutations of *NF2* cause the tumor suppressor syndrome neurofibromatosis type 2 (NF2), which predisposes individuals to schwannomas and ependymomas as well as meningiomas. Other individuals without a family history of NF2 disease harbor multiple meningiomas that are likely to be caused by an underlying genetic cause. Cases with more than one meningioma, but no other clinical features of NF2 or schwannomatosis, may arise because of independent sporadic tumors (17), mosaic NF2 with no mutation identified in the blood (18), or clonal spread of a single sporadic tumor (19,20). The identification of different *NF2* mutations in each tumor indicates that the tumors arose independently. Identical, biallelic *NF2* mutations in each tumor indicates mosaic NF2 or clonal spread. Identical somatic mutations in other genes or X-inactivation of the same X chromosome (19) indicates clonal spread of a single tumor. Rare families also exist with a history of meningiomas, inherited in an autosomal dominant fashion, outside of the context of NF2 disease (13,21).

Two of the SWI/SNF chromatin remodeling complex subunits, SMARCB1 (22) and SMARCE1 (13), have been implicated in meningioma disease. Germline mutations of *SMARCB1* confer a risk of meningiomas as part of the schwannomatosis phenotype. More recently, loss-of-function mutations in *SMARCE1* were found to specifically predispose carriers to clear cell meningiomas (13,23).

The human SWI/SNF chromatin remodeling complex is made up of between 9 and 12 subunits (24), which work together to activate or repress genes throughout the genome. Each complex includes one of the two ATPase subunits, *SMARCA2* or *SMARCA4*; the evolutionarily conserved core subunits, *SMARCB1*, *SMARCC1*, and *SMARCC2*; and additional complex-specific variant subunits (24) (Figure 1A and B). *SMARCE1* is not conserved in lower eukaryotes, but it has been found to exist in all mammalian forms of the complex (25). Several reports have found associations between the SWI/SNF complex and various forms of cancer (26). For example, somatic *SMARCA4* mutations have been found in medulloblastomas of the wingless-related integration site (WNT) and sonic hedgehog (SHH) subtypes (27). In addition to *SMARCE1*, other SWI/SNF subunits have recently been associated with clear cell tumors. Somatic *ARID1A* mutations are associated with ovarian clear cell carcinomas (28), and somatic *PBRM1* mutations are associated with clear cell renal cell carcinomas (29).

Mutations of *SMARCB1* have been associated with several forms of cancer (30). Germline *SMARCB1* mutations are known to cause the highly aggressive pediatric cancer atypical teratoid/rhabdoid tumors (AT/RT) (31), as well as the benign tumor predisposition syndrome schwannomatosis (32). The type of *SMARCB1* mutation and its location within the gene are significantly different between these two syndromes (33), indicating different mechanisms of tumor development in different syndromes caused by the same gene.

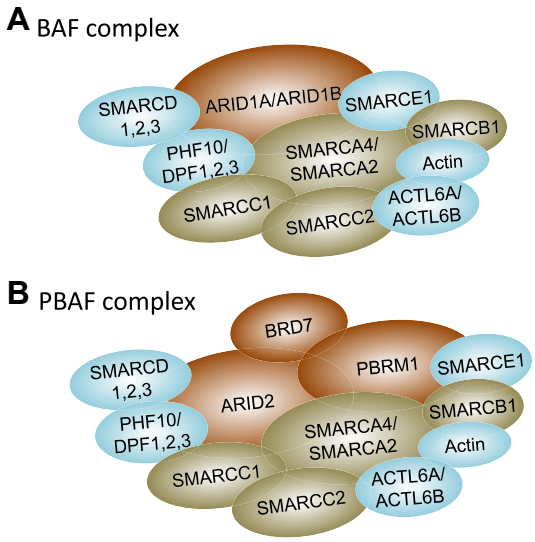

Figure 1 Schematic diagram of the human SWI/SNF chromatin remodeling complex: (A) a BAF complex containing either an ARID1A or an ARID1B subunit and (B) a PBAF complex containing a PBRM1 subunit.

A nontruncating mutation in the Shh-Gli1 pathway gene, *SUFU*, was identified as the cause of multiple meningiomas in a single large Finnish family (21). SUFU, SMARCB1, and SMARCE1 have all been associated with a predisposition to meningiomas and are all known to bind the Shh pathway transcription factor, Gli1 (34). Somatic mutations identified in the Shh-Gli and Akt1-mTor signaling pathways in non-NF2-associated meningiomas (35,36) indicate the potential for cross talk of these pathways in the development of meningioma tumors.

Genetic risk factors

NF2-associated meningiomas

NF2

Germline mutation of the *NF2* gene is the most commonly identified genetic risk factor for multiple meningioma disease. Multiple meningiomas often occur as part of the NF2 tumor suppressor syndrome. Germline *NF2* mutations are detectable in over 90% of all cases of nonmosaic NF2 disease and confer a significant risk of meningiomas, with approximately 50% of people with NF2 developing at least one intracranial meningioma during their lifetime. The presence of intracranial meningiomas in NF2 is associated with the likelihood of disease mortality.

The risk of meningiomas in NF2 disease has been demonstrated to correlate with the type and location of mutations within the gene, with a greater risk of developing a meningioma associated with truncating mutations than

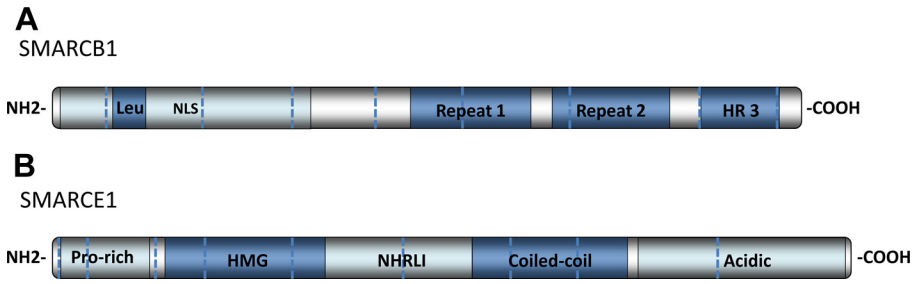

Figure 2 Schematic diagrams of (A) the SMARCB1 protein and (B) the SMARCE1 protein with protein domains. Dotted lines indicate exon boundaries. *Abbreviations*: Leu, Leucine zipper region; NLS, nuclear localization signal; HR, homology region; Pro-rich, proline-rich.

nontruncating mutations and with mutations occurring toward the 5′ end of the gene than the 3′ end of the gene (11). It was also noted that males are more likely than females to develop meningiomas before 20 years of age, whereas females are more likely than males to develop meningiomas over the age of 20 years (11).

Somatic biallelic inactivation of the *NF2* gene can also be found in almost two thirds of sporadic meningiomas. Most meningiomas that occur in NF2 disease have a fibroblastic or transitional histology. Differences in the frequency of *NF2* mutations identified in different subtypes of meningiomas have been described, with mutations found in 70% and 83% of fibroblastic and transitional meningiomas, respectively, in comparison with only 25% of meningothelial meningiomas (37).

Meningiomas occurring in NF2 disease are generally considered to be more aggressive than sporadic meningiomas, because of an increased proliferation potential (38,39); however, this difference could be due to a selection bias toward the individuals who present for surgery (40).

Non-NF2-associated meningiomas

SMARCB1

Somatic *SMARCB1* mutations have been identified in rare cases of sporadic meningiomas (41), and more recently, it has been suggested that schwannomatosis disease may confer a slight increase in risk of meningiomas, with approximately 5% of individuals with schwannomatosis developing one or more meningiomas (42). Rare schwannomatosis families have also been described, with different affected family members developing only schwannomas or only meningiomas (22,43). *SMARCB1*-associated meningiomas appear to have a predilection for the falx cerebri (43). In both schwannomatosis and NF2 disease, meningiomas may be the presenting or sole manifestation of the disease. *NF2* and *SMARCB1* are located 6 MB apart on chromosome 22, and somatic loss of most, or all, of the chromosome 22q arm during tumor development means that they are frequently lost in combination.

Germline *SMARCB1* mutations are known to cause both schwannomatosis (32) and AT/RT (31,44), two conditions with very different prognoses. The spectrum of mutations differs between these conditions, with truncating mutations in the central exons and large intragenic and whole gene deletions being common in AT/RT, whereas nontruncating mutations at the beginning and end of *SMARCB1* and a recurrent 3′ untranslated region mutation, c.*82C>T, are common in schwannomatosis (33,42). A schematic diagram of SMARCB1 is shown in Figure 2A. Recently, germline nontruncating mutations in exons 8 and 9 of *SMARCB1* have also been associated with Coffin–Siris syndrome (45), a developmental disorder with no known increased risk of tumor development. A single case of Coffin–Siris has been reported with both Coffin–Siris and multiple schwannomas (46). Interestingly, one of the *SMARCB1* mutations associated with Coffin–Siris, pArg377His, has also been reported as a recurrent somatic mutation in four of 126 meningiomas (41). A single frameshift mutation in the adjacent codon, which removes the native stop codon and leads to an extended transcript, was identified in a single meningioma in a screen of an additional 80 meningiomas, although only exons 1, 4, 5, and 9 were screened in this study (47). The screening of germline DNA from a series of 45 individuals with non-NF2-associated multiple meningiomas did not identify any *SMARCB1* mutations (48). Together, these studies show that *SMARCB1* mutations are an occasional cause of meningioma predisposition, and that they can occur somatically in sporadic meningiomas, and suggest that the timing and order in which the mutations occur can alter the resulting phenotype.

SMARCE1

The occurrence of familial multiple meningiomas outside of the context of NF2 disease is extremely rare. Recently, germline loss-of-function mutations in the *SMARCE1* chromatin remodeling factor were identified in three families with multiple spinal clear cell meningiomas (13). Germline *SMARCE1* mutations have subsequently been identified in cranial meningiomas, but they appear to be specific for the clear cell histological subtype (23). Interestingly, somatic loss of *SMARCE1* was identified in a cranial clear cell meningioma from a patient with a clinical diagnosis of NF2 disease who had developed multiple schwannomas and meningiomas but who did not have an identified germline *NF2* mutation. No germline *SMARCE1* mutation was identified in this patient. Meningiomas occurring in NF2 disease are normally transitional or fibroblastic, and clear cell tumors are very rare. It is unclear whether the progression of these tumors follows the same path as those due to germline *SMARCE1* mutations. Clear cell meningiomas are classified as WHO grade II because of an apparent high recurrence rate; however, the risk of recurrence seen in the small number of *SMARCE1*-related clear cell meningiomas reported to date appears to be low.

Almost all identified *SMARCE1* mutations have been truncating mutations, predicted to result in complete loss of the protein product. However, they have also all occurred between exons 5 and 9, which encompass the high molecular weight group (HMG) domain and a conserved NHRLI domain, indicating that these regions may be of particular importance to the expression and/or structural integrity of the protein (Figure 2B). Indeed, the only pathogenic mutations with the potential to produce an expressed protein (c.237+2C>T and c.374_395inv22) both disrupt the HMG domain. No case of meningiomas associated with a germline *SMARCE1* mutation has so far been identified with any clinical feature of Coffin–Siris syndrome, although a single *SMARCE1* mutation found in a Coffin–Siris patient (36) was a nontruncating mutation, a mutation predicted to result in expression of a hypomorphic protein rather than complete loss of protein.

Both SMARCB1 and SMARCE1 have DNA-binding properties, but neither is essential for the DNA-binding properties of the SWI/SNF complex as a whole. The extent of their roles in gene regulation and the mechanism by which they are involved in meningioma development require further investigation.

SUFU

A *SUFU* missense mutation, c.367C>T (p.Arg123Cys), has been associated with inherited multiple meningioma disease in a single large family with five affected siblings (21). Wider screening for germline mutations in 121 individuals did not identify any further mutations, indicating that *SUFU* mutation is an infrequent cause of meningioma.

Occasionally, meningiomas are seen in Gorlin syndrome (also known as nevoid basal cell carcinoma syndrome (NBCCS)), which is caused by mutations in *PTCH1*, which is also part of the Shh signaling pathway. Recently, three families with classic Gorlin syndrome associated with childhood medulloblastoma were shown to harbor germline *SUFU* mutations (49). Two of the 10 affected family members within those three families also developed meningiomas, although both of these patients had undergone radiation therapy for childhood medulloblastoma. It is uncertain how much of their risk of meningioma was due to a genetic predisposition and how much was due to the secondary effects of radiation treatment. Although meningiomas are a known risk of radiotherapy, there is evidence that pre-existing genetic mutations in Shh pathway genes increase this risk further (50–52). In the large Finnish *SUFU* family with multiple meningiomas, one family member developed a childhood medulloblastoma and another developed a basal cell carcinoma; however, it appears that these family members did not carry the *SUFU* mutation. The level of risk of meningiomas caused by *SUFU* mutations remains unclear. Table 1 lists the genes described in this article as meningioma predisposition genes and the genes known to be mutated somatically in tumors.

Somatic mutations

Chromosomal regions

Microsatellite analysis, array comparative genomic hybridization, and fluorescence in situ hybridization studies have identified several chromosomal regions somatically associated with meningioma development. In grade II meningiomas, chromosomal losses have been identified on 1p, 22q, 14q, 18q, 10, and 6q, with gains identified on 20q, 12q, 15q, 1q, 9q, and 17q, whereas in grade III meningiomas, additional losses have been identified on 6q, 10, and 14q (53,54).

Table 1 Genes described as meningioma predisposition genes and genes mutated only somatically

Predisposition genes	Somatically altered genes
SHH-GLI pathway	
	SMO
Regulation of SHH-GLI pathway	
SUFU	*AKT1*
SMARCB1	*KLF4*
SMARCE1	
Not known to be associated with SHH-GLI pathway	
NF2	*TRAF7*
	EPB41L3
Meningioma progression genes	
	PTEN
	P14ARF
	CDKN2A
	CDKN2B

Specific genes associated with meningioma progression are still being discovered; however, the mutation of phosphatase and tensin homologue (*PTEN*) on chromosome 10 (55,56) and *CDKN2A* (*p14ARF*) and *CDKN2B* on chromosome 9 (57) have been found to correlate with malignant progression.

EPB41L3

Downregulation of *EPB41L3* (also known as *DAL-1*) expression and corresponding loss of the EPB41L3 protein have been detected in meningiomas; EPB41L3 is often lost in conjunction with the NF2 protein product, merlin (58). This relationship appears to be specific to meningiomas, as the same is not seen in schwannomas (58). Germline *EPB41L3* mutations have not been identified in tumors showing protein loss, although small somatic deletions in the *EPB41L3* region have been detected by SNP analysis (59). In addition, an *EPB41L3* knockout mouse model showed no differences in cell proliferation or growth characteristics and showed no increased risk of cancer (60). These studies indicate that *EPB41L3* loss is not an initiating event in meningioma growth but that it occurs as a secondary effect during tumor development in NF2-associated meningiomas.

SHH-GLI pathway mutations

Two large studies investigating somatic mutations in meningiomas identified several mutations in non-NF2 meningiomas in the G-protein-coupled receptor, Smoothened (*SMO*), and a recurrent mutation in the MTOR pathway–associated serine-threonine protein kinase V-AKT murine thymoma viral oncogene homologue 1 (*AKT1*) (35,36). Additionally, mutations in two further genes, the E3 ubiquitin protein ligase, TNF receptor–associated factor 7 (*TRAF7*) and the Krüppel-like factor 4 (*KLF4*) were identified in one study (35). Somatic mutations in *KLF4* and *SMO* were

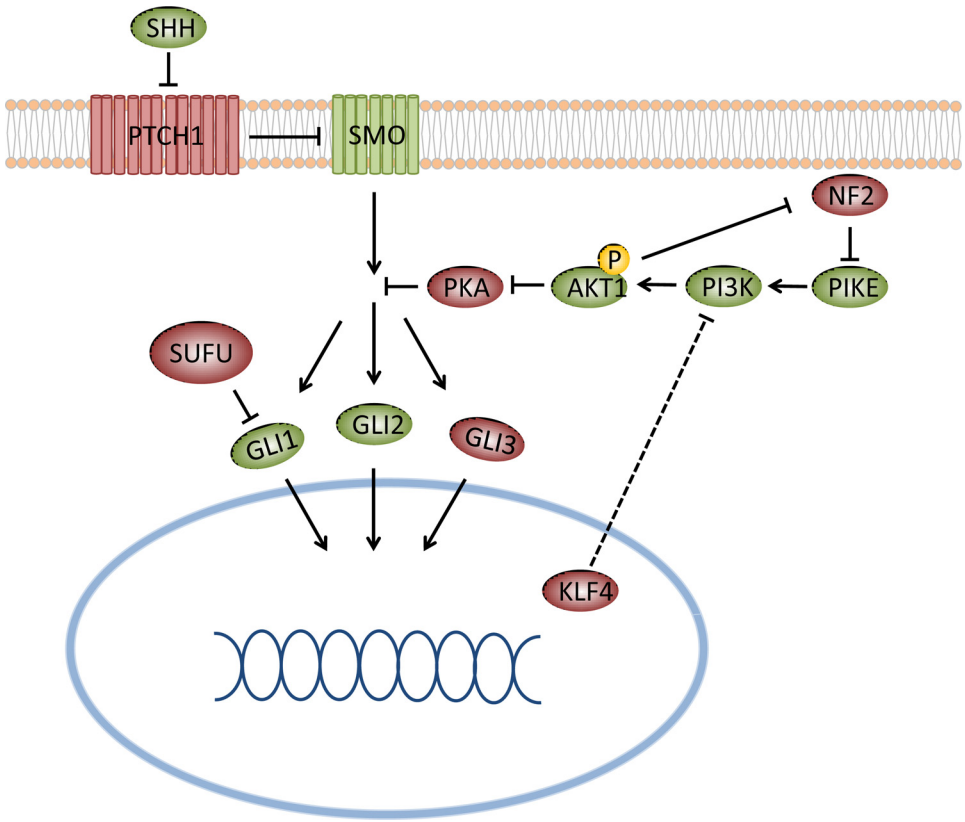

Figure 3 Diagram of the SHH-GLI signaling pathway indicating points of pathway interaction. Elements leading to activation of the pathway are indicated in green and elements that inhibit the pathway are indicated in red. *Abbreviation*: P, phosphate group. (Color versions of these illustrations are available on the journal's website at www.cancergeneticsjournal.org.)

found to occur mutually exclusively of meningiomas with *NF2* involvement. *TRAF7* was frequently co-mutated with *AKT1* or *KLF4*, whereas *AKT1* and *KLF4* mutations were mutually exclusive of each other.

Mutations in all of these genes appear to segregate with differences in histological subtype and tumor location. Meningiomas that occur due to germline *NF2* mutations tend to be transitional, fibroblastic, or meningothelial and to be located within the lateral and posterior skull base, whereas non-NF2 meningiomas are more medially located. Meningiomas occurring in association with schwannomatosis disease, which is caused by germline *SMARCB1* mutations, are predominantly found in the falx cerebri (43). Germline *SMARCE1* mutations cause clear cell meningiomas that may be located in the brain or spine. Somatic mutations in *SMO* were found in meningiomas of the medial anterior skull base. Meningiomas harboring somatic mutations in either *SMO* or *AKT1* are more likely to have meningothelial histology, whereas meningiomas harboring *TRAF7* or *KLF4* mutations are more likely to have a secretory component. The reasons for the specific involvement of different genes in each histological subtype are unclear, but they may become clearer as further genetic determinants and their connecting pathways are investigated.

Shh-Gli1 pathway

The Shh signaling pathway is known to be involved in cell fate determination, proliferation, and patterning in many cell types and in most organs during embryo development. The SHH ligand activates this signaling cascade by binding to the transmembrane receptor, PTCH1, causing PTCH1 to release its inhibition of the G-protein-coupled receptor SMO. SMO is then free to dissociate from the cell membrane and promote activation and nuclear translocation of the glioma-associated oncogene transcription factors GLI1, GLI2, and GLI3. A diagram of the SHH pathway is shown in Figure 3. GLI1 and GLI2 are transcriptional activators of downstream genetic targets, whereas GLI3 represses transcription. SUFU acts to regulate GLI1-mediated transcriptional activation (61). SUFU, SMARCB1, and SMARCE1 have all been implicated in a predisposition to meningioma disease (13,21,62) and have all been found to interact with GLI1 (34).

Regions of the GLI1 N-terminus are involved in recruitment of histone deacetylase complexes, via SUFU, which are involved in DNA folding within chromosomes. The roles of SMARCB1 and SMARCE1 in this pathway are unclear, although the SWI/SNF complex is known to activate or repress many genes throughout the genome. Differing protein binding properties of these components suggest a role in targeting the complex for activation or repression of specific genes. Both SMARCB1 and SMARCE1 have DNA binding capabilities (25,63); however, neither is essential for the DNA binding properties of the SWI/SNF complex as a whole.

Shh pathway interactions

Somatic mutations identified in *SMO* and *AKT1* in meningiomas have been shown to result in upregulation of the SHH pathway (36). SMO directly upregulates the expression of

downstream targets through increased activation and translocation of the GLI transcription factors. Indeed, one of the *SMO* mutations identified in meningiomas has been seen previously as a somatic mutation in basal cell carcinomas (64). AKT1 activates the SHH pathway through phosphatidylinositol-3 kinase-dependent phosphorylation, as phosphorylated AKT1 antagonizes protein kinase A (PKA)–dependent inactivation of GLI (65). The recurrent *AKT1* mutation p.Glu17Lys has been detected previously in breast cancer, colorectal cancer, and ovarian cancer (66). This mutation activates PI3-kinase-dependent signaling through aberrant localization of AKT1 to the cell membrane (66). Cross talk between the AKT1-MTOR and SHH-GLI1 pathways has also been described in other cancers, including gastric cancers (67,68). SHH signaling was shown to activate the phosphoinositide 3-kinase (PI3K)–AKT1 pathway that promotes epithelial-mesenchyme transition and metastasis of gastric cancer (67).

The SHH-GLI pathway may also be affected in meningiomas resulting from an *NF2* mutation, since wild-type merlin interacts with the brain specific variants of the PI3K enhancer (PIKE), resulting in inhibition of PI3K (69). AKT-dependent phosphorylation of merlin results in loss of merlin binding to PIKE and causes degradation of merlin through ubiquitination (70).

KLF4 is a transcription factor (71,72) that plays a role in proliferation, differentiation, and the induction of a pluripotent stem cell state. KLF4 inhibits cell proliferation via the platelet-derived growth factor receptor (PDGFR)–mediated PI3K pathway (73). In addition to the mutations identified in meningiomas, KLF4 has been shown to act as a tumor suppressor in medulloblastoma (74) and glioblastoma (75) tumors; however, depending on cellular conditions, KLF4 has been found to act as both a tumor suppressor and an oncogene (76). An oncogenic role has been identified in squamous cell carcinoma (77) and in leukemias and lymphomas (78).

Somatic mutations in tumor necrosis factor receptor–associated factor 7 (TRAF7) were found in 72 of 300 meningiomas screened in one large study, and over 90% of these mutations were located in the C-terminal WD40 domains (35). TRAF7 is an E3 ubiquitin ligase involved in the TNF and NF-κB signaling pathways (79,80). It also induces caspase-dependent apoptosis via its RING finger domain (79). It has no known role in the SHH-GLI signaling pathway, but it is known to bind to MEKK3 through its WD40 domains, leading to activation of the JNK and p38 MAP kinases (79). These functions would be disrupted by the mutations identified in meningiomas.

Conclusion

Meningiomas are a diverse group of tumors with varied histology and growth patterns. The heterogeneity in germline and somatic mutations indicates a complex network of pathway interactions involving the SHH-GLI1 and AKT1-MTOR signaling pathways, which require further investigation. Further studies are also needed to understand the role of chromatin remodeling factors in these pathways and how the meningioma-associated mutations lead to tumor formation. Categorization by of meningiomas by histology, location, and genetic mutation, and a better understanding of the mechanisms of meningioma development, will help in the refinement of stratified therapies and treatment plans.

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