



Potential Molecular Mechanisms of Recurrent and Progressive Meningiomas: A Review of the Latest Literature

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Specialty section:

This article was submitted to
Neuro-Oncology and
Neurosurgical Oncology,
a section of the journal
Frontiers in Oncology

Received: 07 January 2022

Accepted: 28 April 2022

Published: 30 May 2022

Citation:

Peng W, Wu P, Yuan M, Yuan B,
Zhu L, Zhou J and Li Q (2022) Potential
Molecular Mechanisms of Recurrent
and Progressive Meningiomas:
A Review of the Latest Literature.
Front. Oncol. 12:850463.
doi: 10.3389/fonc.2022.850463

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Meningiomas, the most frequent primary intracranial tumors of the central nervous system in adults, originate from the meninges and meningeal spaces. Surgical resection and adjuvant radiation are considered the preferred treatment options. Although most meningiomas are benign and slow-growing, some patients suffer from tumor recurrence and disease progression, eventually resulting in poorer clinical outcomes, including malignant transformation and death. It is thus crucial to identify these “high-risk” tumors early; this requires an in-depth understanding of the molecular and genetic alterations, thereby providing a theoretical foundation for establishing personalized and precise treatment in the future. Here, we review the most up-to-date knowledge of the cellular biological alterations involved in the progression of meningiomas, including cell proliferation, neo-angiogenesis, inhibition of apoptosis, and immunogenicity. Focused genetic alterations, including chromosomal abnormalities and DNA methylation patterns, are summarized and discussed in detail. We also present latest therapeutic targets and clinical trials for meningiomas' treatment. A further understanding of cellular biological and genetic alterations will provide new prospects for the accurate screening and treatment of recurrent and progressive meningiomas.

Keywords: meningioma, mechanisms, cell proliferation, neo-angiogenesis, apoptosis, immunogenicity, genetic alterations

INTRODUCTION

Meningiomas generally originate from the meninges and meningeal spaces. They are the most frequently occurring primary intracranial tumors of the central nervous system in adults, with an incidence of 7.86 cases per 100,000 people every year (1). According to the 2021 World Health Organization (WHO) tumor classification, meningiomas are classified as benign (>80%), atypical (15%–20%), and anaplastic (1.0%–3.0%), depending on the mitotic rate, brain invasion, or specific histological features (2–4). Although the majority (~80%) of meningiomas are benign and could be cured or become stable through surgical resection, some present with high-risk behaviors and poor prognosis, including early or high-rate recurrence and rapidly progressive course even after radiotherapy (5). More interestingly, among meningiomas with benign pathological features, 7–25% histologically tend to relapse or become malignant after surgical resection (6). Atypical and anaplastic meningiomas are naturally substantially more aggressive, and their recurrence rates in 5 years reach up to 30–50% and 90%, respectively (7, 8). Radiotherapy is recommended for partially resected Grade II and all Grade III meningiomas. Nevertheless, a subset of patients with Grade II meningiomas may live through a benign clinical course with no need for radiotherapy (9). The histological grade does not fully reflect the biological behavior of meningiomas to currently guide treatment. Hence, there is a need to explore useful predictors of the clinical behavior or overall prognosis of meningiomas.

Previous studies have shown that the risk factors of meningiomas are complex, including age, sex, radiation, trauma, diabetes mellitus, and arterial hypertension (1, 7), and the progression of recurrent meningiomas involves numerous factors, including Simpson grade IV/V resection, a larger tumor size, tumor location, high vascular endothelial growth factor receptor (VEGFR) expression, WHO Grade II/III, high Ki-67 expression, and lack of progesterone receptor expression (10). Recurrent meningiomas may be accompanied with malignant transformation and multiple treatments or limited optional drugs, making management much more challenging (7, 11). Therefore, a further understanding of the molecular mechanisms underlying the recurrence or progression will help predict the clinical behavior, which is beneficial for early recognition of high-risk meningiomas and timely adjustment of treatment protocols.

Abbreviations: WHO, World Health Organization; FOXM1, Forkhead box protein M1; VEGFR, Vascular endothelial growth factor receptor; MDM2, Murine double minute 2 protein; FAK, Focal adhesion kinase; CDKN2A/B, Cyclin-dependent kinase inhibitor 2A/B; DMD, Dystrophin-encoding and muscular dystrophy-associated; AKT1, v-Akt murine thymoma viral oncogene; HIF-1 α , Hypoxia-inducible factor 1 α ; PI3K, Phosphatidylinositol 3-kinase; mTOR, mammalian Target of rapamycin; CDK, Cyclin-dependent kinase; BAP1, Breast cancer 1-associated protein-1; TERTp, promoter of Telomerase reverse transcriptase; p-CREB, phosphorylated Cyclic-AMP responsive element-binding protein; RAS, Rat sarcoma; PFS, Progression-free survival; KLF4, Krüppel-like factor 4; VEGF, Vascular endothelial growth factor; MC, Methylation classification; PD-1, Programmed death 1; PD-L1, Programmed death-ligand 1.

In addition to the traditional WHO grading, the latest studies on meningiomas have provided insights into the genomic alterations, including DNA somatic copy number, DNA point mutation, DNA methylation, and transcriptomic and proteomic data (12). Advances in molecular classification through DNA methylation have gradually been approved by researchers (1, 6, 9, 12, 13). Similar to other central nervous system neoplasms, such as glioma, Nassiri reported that meningiomas could be classified into different molecular groups with distinct and prototypical biological features after a comprehensive analysis combining copy number, DNA methylation, and mRNA sequencing data (12), complementing existing WHO grades. Here, based on the most up-to-date biomedical research knowledge, we review the potential cellular biological mechanisms and molecules involved in the recurrence or progression of meningiomas from several perspectives, including the excessive proliferation of tumor cells, neo-angiogenesis, inhibition of apoptosis, immunogenicity, and genetic alterations involving chromosomes and genes related to meningiomas (3, 13). Further, we summarize existing therapeutic targets and clinical trials for meningiomas' treatment. We expect this information to allow for an exploration of more accurate prognostic markers and potential targeted therapies for meningiomas.

CELL PROLIFERATION

Recurrent or progressive meningiomas usually begin with excessive cell growth and proliferation. Evidence suggests that tumor cell growth and proliferation are tightly linked to cell-cycle dysregulation (4). Disordered cell-cycle proteins, the uncontrolled regulation of transcription factors, and mutations in cell-cycle-related genes can promote cell proliferation and differentiation in meningioma (14–17). The cell-cycle-related proteins topoisomerase II α and mitotin, which play important roles in regulating mitotic chromosome condensation and separation (18), are positively associated with a high risk of meningioma recurrence (15). Forkhead box protein M1 (FOXM1), a master transcription factor for cell growth and proliferation, is closely associated with hepatocellular carcinoma (19), prostate cancer (20), glioma (21), and basal cell carcinoma (22). FOXM1 is thought to accelerate G1/S and G2/M transition to promote mitotic progression (14). A recent comprehensive molecular profiling study indicated that the expression of FOXM1 is relevant to increased proliferation and poor clinical prognosis (23). Similarly, the results obtained in a newly established model of meningioma showed that FOXM1 overexpression increases proliferation in benign meningioma, whereas its depletion decreases proliferation in malignant meningioma (24). As such, thiothrepton, a FOXM1 inhibitor, combined with radiation therapy, was found to noticeably prevent the proliferation of malignant meningioma cells (**Figure 1**) (24).

Gene mutations in v-Akt murine thymoma viral oncogene (AKT1), homolog 1 smoothed, frizzled class receptor (SMO), focal adhesion kinase (FAK), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), and dystrophin-encoding and muscular

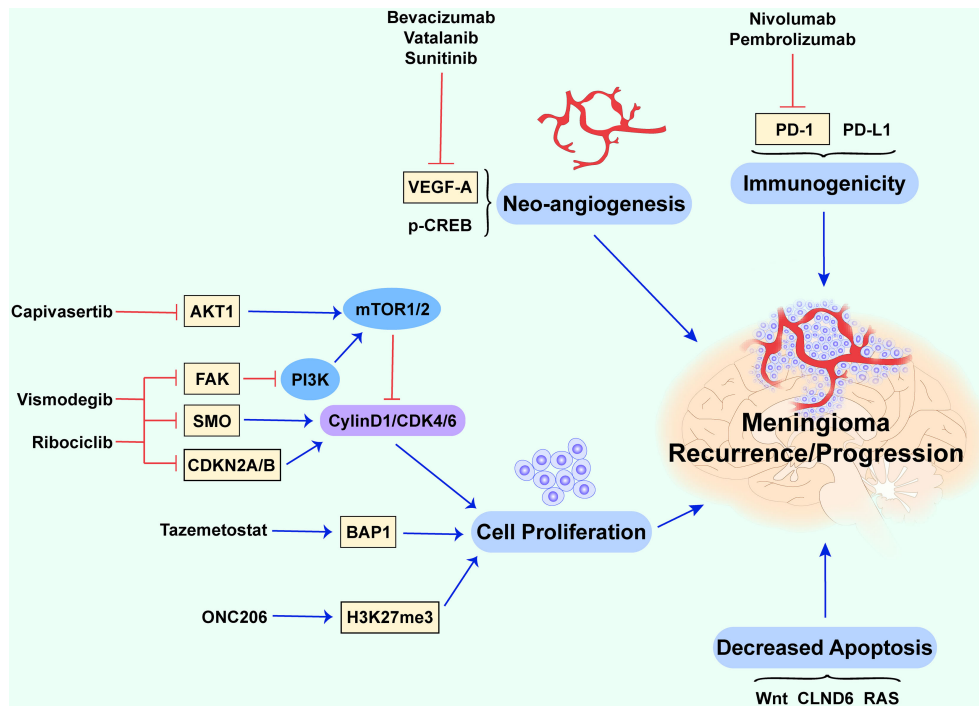


FIGURE 1 | Potential biological mechanisms of recurrent and progressive meningiomas. This figure briefly summarizes several cellular biological mechanisms and molecules contributing to recurrent and progressive meningiomas. The abnormal proliferation of tumor cells, downregulation of apoptotic processes, neo-angiogenesis, and immunogenicity together promote recurrence and progression (the red lines show an inhibitory effect and the blue arrows show a promoting effect).

dystrophy-associated (*DMD*) are also considered to be associated with cell proliferation in meningioma (17). *AKT1* encodes the AKT1 kinase (a serine/threonine-protein kinase), and the overactivation of AKT1 can lead to uncontrolled cell growth and proliferation *via* the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway (**Figure 1**) (25, 26). mTOR, mainly regulated by the PI3K/AKT pathway, is highly expressed in various tumors and is closely associated with cell growth and proliferation (17). Studies have indicated that the overactivation of mTOR results in a high mitotic index (27) and contributes to the recurrence of meningioma (28) and poorer outcomes (27).

SMO mutations lead to cell-specific proliferation and mediate the development of meningioma through uncontrolled activation of the sonic hedgehog signaling pathway (25, 29, 30). *FAK*, which encodes a cytoplasmic protein tyrosine kinase that mediates cell growth, proliferation, and survival, is overexpressed in some meningiomas (31). Ribociclib, a cyclin-dependent kinase (CDK) inhibitor, was evaluated for its effect on other highly mutated genes (other than the common *NF2*), such as *AKT1* and *SMO* (NCT02933736) (**Table 1**) (38). Moreover, a national Alliance-sponsored cooperative group phase II clinical trial evaluated the efficacy of *SMO*, *AKT1*, and *NF2*, respectively (NCT02523014/A071401) (5). Vismodegib, included in an ongoing Alliance clinical trial, is a hedgehog pathway-targeting

agent tested for *SMO*/*PTCH1*-mutated progressive/recurrent meningiomas (NCT02523014) (32).

CDKN2A encodes p16INK4A and p14ARF, and *CDKN2B* encodes p15INK4B, p15INK4B and p16INK4A prevent S-phase entry by inhibiting the CDK4/cyclin D complex and are generally mutated in Grade II and III meningiomas. p14ARF prevents cell proliferation in the G1 phase and decelerates p53 degradation through downregulation of the proto-oncogene murine double minute 2 protein (*MDM2*) (41). The mutation or deletion of *CDKN2A* and *CDKN2B* has been linked to a poorer prognosis in meningioma (42). A CDK inhibitor combined with ribociclib could be a potential treatment approach for meningiomas with mutations in the tumor-suppressor genes *CDKN2A* and *CDKN2B* (NCT02933736) (32). Moreover, mutations in the tumor-suppressor gene *p53* also affect the occurrence and development of meningioma (43). When mutations occur, p53 changes from a tumor suppressor to a tumor promoter owing to structural changes that suppress its roles in inhibiting cell growth and apoptosis, leading to cancer (44). The p53 mutation rate is higher in atypical and malignant meningiomas, and most importantly, it is higher in recurrent than in non-recurrent diseases (45). Some researchers also found that the combination of p53 and Ki67 could be a promising predictor of recurrence in meningiomas (45). *DMD* encodes dystrophin, which regulates cytoskeleton remodeling and cell proliferation in response to extracellular signal stimulation (46, 47). The deletion of *DMD* contributes to progressive meningioma and a

TABLE 1 | Summarization of key molecules and potential targeted therapy in recurrent and progressive meningiomas.

	Targets	Inhibitors	Ongoing Clinical Trial	Reference
Cell proliferation	AKT1	Capivasertib	NCT02523014	(5, 32)
		Ribociclib	NCT02933736	
	SMO	Vismodegib	NCT02523014	(5, 32)
		Ribociclib	NCT02933736	
	FAK	Vismodegib	NCT02523014	(5)
	CDKN2A/B	Ribociclib	NCT02933736	(32)
	BAP1	Tazemetostat	NCT02860286	(33)
H3K27me3	ONC206	NCT04541082	(34)	
Neo-angiogenesis	VEGF-A	Bevacizumab Vatalanib Sunitinib Apatinib mesylate	NCT01125046	(35, 36)
		Erlotinib hydrochloride	NCT00348790 NCT00589784 NCT04501705	
			NCT00045110	
Immunogenicity	PD-1	Nivolumab Pembrolizumab	NCT02648997	(37)
			NCT04659811	
			NCT03279692	
			NCT00972335	
Chromosomal abnormalities	NF2 and/or SMARCB1	Everolimus Vistusertib Dasatinib Selumetinib	NCT03095248 NCT00788125 NCT03095248	(5, 35, 38–40)

shorter overall survival (16), partly due to the defective inhibition of cell proliferation leading to disease progression (48). Breast cancer 1-associated protein-1 (BAP1), a deubiquitylating enzyme, is a tumor suppressor. Familial and sporadic BAP1-deficient meningiomas tend to be rare, and aggressive malignant tumors (grade III) are associated with increased aggressiveness and poorer prognosis (49). Tazemetostat, a BAP1 inhibitor, increases the level of the PCR2 complex protein EZH2, activated by BAP1, and might be a potential drug for rhabdoid meningioma caused by BAP1 loss (NCT02860286) (50).

In addition to the genes mentioned previously herein, a 2018 study showed that mutations in the promoter of telomerase reverse transcriptase (*TERTp*) enhance the degree of malignancy of meningiomas and lead to poor prognosis (51). Other studies have corroborated that *TERTp* mutations predict poor survival in progressive/high-grade meningiomas (33, 52, 53). Telomere maintenance is a marker of tumor formation, and most tumors express telomerase to prevent telomere shortening (52). Telomerase activation caused by *TERTp* mutations enforces cell immortalization and promotes the growth of tumors (51), which could be observed in recurrent and malignant tumors (54). Furthermore, a 2021 study revealed that *TERT* alterations are a biomarker of meningioma progression and reduce progression-free survival after adjuvant radiotherapy (55). Hence, we suggest that *TERTp* mutations can significantly predict poor prognosis in meningiomas, but no effective targeted drugs have been found to date.

In recent years, it has been reported that the loss of H3K27 trimethylation (H3K27me3) plays a prominent role in the recurrence of meningioma (56). Further research found that the loss of H3K27me3 predicts early recurrence and death for grade 2, but not for grade 3, meningioma (57). H3K27me3 affects DNA damage repair and contributes to several biological processes, including cell differentiation, proliferation, and stem-cell plasticity (58). The latest study found that ONC206, a DRD2 antagonist and ClpP agonist, is orally bioavailable, penetrates the blood-brain barrier, and exhibits anti-cancer efficacy without toxicity, and it is currently the subject of an ongoing trial (NCT04541082) for H3K27M-mutant, malignant

meningiomas and other central nervous system tumors (34). However, its therapeutic effect on tumorigenesis or cancer recurrence with respect to H3K27me3 requires further clinical trials.

NEO-ANGIOGENESIS

Neo-angiogenesis is one of the most important features of higher-grade meningiomas. On the one hand, it makes the tumor grow rapidly, and on the other hand, it makes surgical resection more difficult based on the rich blood supply. Tumor vessel density is a key feature during oncogenesis and is tightly correlated with the upregulation of vascular endothelial growth factor (VEGF), placental growth factor, and insulin-like growth factor-binding protein-3 (59). A recent follow-up study investigated VEGF and its three receptors in meningiomas and demonstrated a significant increase in VEGF-A levels in WHO grade III meningiomas (60). VEGF-A, an endothelial cell-specific mitogen, contributes to new blood vessel growth (35, 61). Upon overexpression, VEGF-A contributes to the rapid growth of tumors (35) and regulates maturation and stabilization during the late stages of tumors (62). VEGF-A is a powerful mitogenic and angiogenic disulfide-linked homodimer, which is secreted from tumors and increased under conditions of ischemia for the rapid expansion of tumor vessels (63). VEGF-A is tightly associated with refractory or higher-grade meningiomas (35), becoming a potential therapeutic target with the foundation of anti-angiogenic agents blocking the VEGF pathway (64). Antiangiogenic drugs, such as bevacizumab, vatalanib, and sunitinib, were reported to reduce the recurrence rate of meningiomas significantly (1). Two prospective phase II trials involving patients with refractory meningiomas have evaluated the efficacy and safety of bevacizumab (36). One study of 40 patients treated with bevacizumab indicated that the progression-free survival (PFS) at 6 months is 87% for grade I meningiomas, 77% for grade II meningiomas, and 46% for grade III meningiomas (NCT01125046). Another clinical trial in 2016 combining bevacizumab with everolimus found a median PFS of 22 months for those with recurrent and progressive meningiomas

after surgery and/or radiation therapy (95% CI 4.5–26.8). This combination could block disease progression in 88% of patients (NCT00972335) (35, 36). Both vatalanib (NCT00348790) and sunitinib (NCT00589784) are tyrosine kinase inhibitors targeting VEGFR and were shown to act partly on recurrent meningiomas. Furthermore, other trials like those for apatinib mesylate (NCT04501705) and erlotinib hydrochloride (NCT00045110) found on ClinicalTrials.gov have demonstrated that VEGFR is an emerging therapeutic target.

In addition to VEGF-A, phosphorylated cyclic-AMP responsive element-binding protein (p-CREB) is a novel high-risk molecule abundantly expressed in the endothelia of tumor vessels in all meningiomas, and high p-CREB levels are closely associated with the recurrence of meningiomas (65). p-CREB was found in various tumors, including glioma, because of its physical properties, including binding to upstream signaling kinases and downstream genes (66). It is a transcription factor that participates in numerous cellular processes and induces VEGF expression, leading to neo-angiogenesis in meningiomas (65). Barresi et al. reported that p-CREB expression can be identified in tumor vessels but disappears in the vessels of the normal adult and neonatal leptomeninges, implying that p-CREB is related to neo-angiogenesis (65). The relationship between p-CREB and VEGF has not been fully elucidated and requires further study.

The levels of inflammation in perivascular areas of the tumor, induced by ischemia or other proteins, can also affect the neo-angiogenesis of meningiomas. VEGF-A is a downstream target of hypoxia-inducible factor 1 α (HIF-1 α), a molecular marker of hypoxia (67). A large cohort study of 263 patients with meningiomas found that upregulated levels of HIF-1 α and VEGF-A could significantly predict the recurrence of meningiomas (68). Moreover, HIF-1 α and VEGF-A are correlated with peritumoral edema (69), which was demonstrated to be associated with poor prognosis in meningiomas.

RESISTANCE TO APOPTOSIS

Apoptosis, a well-known form of cell death that occurs in response to external stimuli or internal stresses, is generally inhibited in tumor cells, resulting in uncontrolled proliferation (70). Numerous studies have indicated that the Wnt signaling pathway has an important role in resistance to apoptosis in neurological disorders, such as stroke (71, 72), spinal cord injury (73, 74), neuroblastoma (75), and glioma (76). The Wnt signaling pathway was recently reported to be associated with the apoptosis of meningioma cells *via* three pathways, the classical Wnt/ β -catenin signaling, the planar cell polarity pathway, and the Wnt-Ca²⁺ pathway (77–80). Inhibition of the Wnt/ β -catenin pathway by plant medicines leads to apoptosis in human meningioma cells (81). The long non-coding (lnc) RNA SNHG1 was found to inhibit apoptosis in BEN-1-1 and IOMM-Lee cells, and SNHG1 deficiency restrains cell growth and accelerates apoptosis in meningioma cell lines *via* the Wnt pathway (79). Moreover, downregulation of the lncRNA

LINC00702 reportedly inhibits Wnt activity and induces apoptosis in malignant meningioma (78). Thus, the Wnt pathway seems to play a negative regulatory role in the apoptosis of meningioma cells; however, the precise underlying mechanism remains unclear.

Recent studies have reported several potential mechanisms of resistance to apoptosis in meningioma. CD163 is a type I membrane protein, the overexpression of which leads to reduced apoptosis in human meningioma cells (82). CLND6, also called claudin6, is a component of tight junctions that contributes to maintaining cell–cell junctions in epithelial cells (83). The downregulation of CLND6 has been associated with tumor occurrence, and its overexpression accelerates apoptosis in cancer cells (84–87). Additionally, CLND6 has been found to regulate migration and invasion capacities in malignant meningioma cell models (88). Rat sarcoma (RAS) is a member of the small GTPase family that participates in the regulation of embryonic development, differentiation, cell-cycle progression, and cell survival (89). The downregulation of RAS activity leads to significantly reduced ERK and AKT phosphorylation, suppresses proliferation, and induces the apoptosis of human meningioma cells (88). Furthermore, let-7d, a member of the let-7 family, has been regarded as a tumor suppressor in various cancers (90–92). Let-7d promotes apoptosis and suppresses the proliferation of meningioma by targeting AEG-1 (93). Based on a genomics analysis of 300 meningiomas, Clark et al. reported that mutations in TNF receptor-associated factor 7 (TRAF7) are also common, and they identified the accumulation of mutations in Krüppel-like factor 4 (KLF4), AKT1, and SMO (29). TRAF7, a pro-apoptotic protein containing an N-terminal RING finger domain, an adjacent TRAF-type zinc finger domain, a coiled-coil domain, and seven C-terminal WD40 repeats, affects several signaling pathways, including the NF- κ B pathway, and the ubiquitination of proteins, such as c-FLIP (29, 94). TRAF7 is usually mutated together with KLF4, AKT1, or the phosphatidylinositol-4, 5-diphosphate 3-kinase catalytic subunit α protein (PIK3CA) (95, 96). KLF4 is a transcription factor. AKT1 activates the PI3K/mTOR pathway (96). In 2016, mutations in PIK3CA were found to be frequent drivers of certain meningiomas (97). Mutations in TRAF7, KLF4, AKT1, or PIK3CA are commonly associated with grade 1 meningioma, whereas combined mutations might be associated with a high recurrence rate (98). Therefore, therapies targeting the pro-apoptotic roles in recurrence and malignancy *via* different approaches might contribute to improved prognosis.

IMMUNOGENICITY

Subsets of patients still experience a progressive clinical course even after surgery and radiation, because tumors can evade the immune system *via* certain mechanisms, leading to the formation of an immunosuppressive tumor microenvironment, including the upregulation of programmed death-1 (PD-L1), suppressive cells, such as regulatory T cells, or other unknown

proteins (99). Nassiri found that meningiomas are immunogenic, characterized by massive immune infiltration and pertinent pathways including immune regulation and signaling (12). The proteins associated with immune regulation include IL-1, TNF, $\text{ING-}\alpha$, and PD-1. Depending on these data, immunotherapy could be another treatment for these malignant meningiomas (99, 100). *NF2* mutations and the loss of chromosome 22 are frequently observed in these meningiomas (12). Therefore, Yeung et al. explored the immunological landscape of meningiomas in an *NF2*-mutant murine meningioma model and found that these tumors were heavily infiltrated by anti-inflammatory M2 macrophages. Intervention with an anti-CSF1/CSF1R antibody was found to normalize the tumor microenvironment, indicating that targeting the CSF1/CSF1R axis might be a potential treatment for malignant meningiomas (99). PD-1 and PD-L1 are closely associated with higher-grade meningiomas. PD-1 inhibitors, such as nivolumab (NCT02648997) and pembrolizumab (NCT04659811), have a significant effect on preventing the recurrence of meningiomas. A phase II study in 2022 showed that pembrolizumab exerts promising efficacy on a subset of recurrent and progressive grade 2 and 3 meningiomas (NCT03279692). This study reported a lower PFS-6 rate of 0.48 and median PFS of 7.6 months for higher-grade meningiomas compared to those in previous studies (37). Masaki summarized several clinical trials investigating whether PD-1 might affect recurrent meningiomas (100). In addition, the effect of $\text{IFN-}\alpha$ was demonstrated in several highly vascularized tumors, such as gliomas and meningiomas (32). A clinical trial of $\text{IFN-}\alpha$ -2B found that it could improve the prognosis of grade I recurrent meningiomas and induce disease stability (101).

CHROMOSOMAL ABNORMALITIES

Epigenomics studies have revealed that transcriptional and epigenomic regulatory mechanisms occupy an important part in recurrent and progressive meningiomas. Except for gene mutations and some special molecules, chromosomal abnormalities have been the hot topics these years. It was reported that higher rates of copy-number alterations and karyotypic abnormalities are linked to higher-grade meningiomas (9). Chromosome 22 is the most commonly reported abnormal chromosome in meningiomas. It shows alterations in more than half of meningiomas, especially in benign tumors, with a large proportion of deletions of chromosome 22 occurring in the neurofibromatosis type 2 gene (*NF2*) region, which contributes to the development of meningiomas (4, 102). *NF2* promotes contact inhibition and tumor suppression by inhibiting mitotic signaling in the cell cortex (90). However, another study suggested that *NF2* might not be involved in meningioma progression (103). A study including 775 samples revealed that the loss of *NF2* or co-occurrence with recurrent *SMARCB1* mutations frequently occurs in atypical meningiomas. *SMARCB1*, located on chromosome 22, might induce the progression of

meningiomas. In addition, *NF2* alterations combined with abnormalities in *AKT1* and *mTOR* are associated with the overgrowth of various tissues, which could be responsible for the recurrence of meningiomas (104).

Strong expression of *SSTR2A* receptors, inhibition of the osteoglycin/*mTOR* pathway, and activation of *NF2* signaling promote apoptosis in malignant meningioma cells (39, 105). A recent phase II CEVOREM trial showed that the combination of everolimus, an *mTOR* inhibitor, and octreotide, a somatostatin agonist, has an antiproliferative effect on meningiomas (NCT00972335) (39). Atypical *NF2* mutants demonstrate chromosomal instability, which might be related to tumor invasiveness (106). Brigatinib, an inhibitor of multiple tyrosine kinases, was capable of stopping the growth of *NF2*-deficient xenograft meningiomas for the inhibition of multiple tyrosine kinases, including *EphA2*, *Fer*, and focal adhesion kinase 1 (*FAK1*) (107). A *FAK* inhibitor (*GSK2256098*) was identified to significantly improve the survival rates of patients with recurrent or progressive *NF2*-mutated meningiomas (NCT02933736) (108). Further, a phase II trial revealed another *MEK1/2* inhibitor, selumetinib, to have an effect on *NF2*-related meningiomas (NCT03095248) (5, 38). These advances on *NF2*-related meningiomas represent a major step forward in therapeutics.

Except for chromosome 22, loss of chromosome 1p was related to recurrent meningiomas, despite total resection and was involved in the activation of the cell cycle (23, 109). Further, the loss of chromosome 14q and complex karyotypes (multiple chromosome mutations) have also been reported as independent recurrence-specific prognostic indicators of meningiomas or malignancy development (103, 106, 110–112). The genes located on chromosome 1p include *TP73*, *CDKN2C*, *RAD54*, *EPB41*, *GADD45A*, and *ALPL*, while the genes inactivated on chromosome 14q are *NDRG* family member 2 and maternally expressed gene 3 (113). Moreover, the loss of chromosomes 9p, 6q, 10, and 18q or the abnormal gain of 1q, 9q, 12q, 15q, 17q, and 20q has been recently reported (17, 96, 114).

DNA METHYLATION PATTERNS

In addition to those on the aforementioned mutations, studies have been conducted in recent years to understand genetic and epigenetic alterations in meningiomas. Researchers have attempted to compare meningioma grading with DNA methylation classification (MC) (6). Sahm et al. distinguished six methylation classes among 479 patients and found that these classes might predict more current clinical courses than histology (115). DNA MC could finally prove superior to traditional light microscopy in distinguishing recurrent or progressive meningiomas. The DNA MC was divided into two major epigenetic groups, including six subclasses, MC benign 1–3, MC intermediate A and B, and MC malignant, which did not correspond exactly to the WHO grade. Interestingly, most *NF2* mutations were observed in MC benign-1 meningiomas, and other *NF2* mutations were

scattered in the different groups. Mutations in four main genes, *AKT1*, *SMO*, *KLF4*, and *TRAF7*, were identified in MC benign-2 tumors. The frequency of *CDKN2A* and *TERT* mutations was higher in MC intermediate-B and MC malignant groups. MC benign-1 was related to the loss of chromosome 22q, MC benign-3 was related to frequent mutations in chromosome 5, and MC intermediates A/B and MC malignant were related to the loss of chromosome 1p. The loss of chromosome 22q was related to MC intermediate-B and MC malignant (116) (Table 2). All of these mutations were found to be tightly associated with the recurrent or progressive meningiomas described previously herein, proving that DNA methylation patterns are helpful for the risk stratification of meningiomas. The authors also showed that DNA methylation patterns provide a more precise prediction of progression-free survival outcomes at 10 years of follow-up than does WHO grading. The predictive power of single or combined DNA MCs was determined to be stronger than that of WHO grades, especially for meningiomas with a WHO grade I histology and patients at a lower risk of recurrence among WHO grade II meningiomas ($p = 0.0096$) from the Brier prediction test (115). For those genes presenting with mutations associated with any clinical courses, such as *NF2*, DNA methylation guides further risk stratification compared to that with whole-genome sequencing only. Nassiri et al. also found that DNA methylation, combined with clinical factors, leads to a reliable individualized estimation of the 5-year recurrence risk of meningiomas (40). Moreover, DNA methylation patterns could distinguish intracranial meningiomas from metastatic meningiomas. A case report in 2020 showed that DNA methylation clusters distinguished liver metastasis samples from intracranial meningioma samples, indicating that DNA methylation is also a robust method for diagnosing metastatic lesions (117).

A 2022 study classified meningiomas into three methylation groups, similar to the study by Sahm and co-workers (102), and showed that DNA methylation is more accurate than histopathology in identifying high-risk tumors and is closely correlated with gene expression in meningiomas (118). This study further compared the predictive accuracy of DNA methylation with that of RNA-sequencing and cytogenetics and found a strong concordance between these groups. The authors also demonstrated that both DNA promoter methylation and copy-number variability correlated with differential gene

expression (118). Further, a recent study analyzed four types of alterations together, namely DNA somatic copy-number aberrations, DNA somatic point mutations, DNA methylation, and messenger RNA abundance, and found that these could be classified into four groups (M1–4) owing to distinct biology as follows: immunogenic (M1), benign *NF2* wild-type (M2), hypermetabolic (M3), and proliferative (M4) (12) (Table 2). Table 2 describes the different classifications of meningiomas. From the authors' perspective, the M2 group might be associated with angiogenesis and vasculature development. Hypermetabolic (MG3) meningiomas are enriched in protein pathways involved in nucleotide and lipid metabolism and could be related to degradation of the extracellular matrix and endothelial proliferation. Moreover, proliferative (MG4) meningiomas are enriched in proteins and genes regulating the cell cycle and proliferation. Distorted DNA methylation processes can be associated with the most aggressive molecular groups (M3–4). Those patients with MG3 and MG4 meningiomas have significantly shorter times to recurrence (log-rank test, $P = 5 \times 10^{-15}$) (12). No other studies have discussed the direct association between DNA methylation and biological mechanisms. These data show that DNA methylation has a powerful predictive value. The combination of DNA methylation and other features might be a new direction for identifying high-risk recurrent or progressive meningiomas. In the future, classifications based on more molecular features might be more accurate to predict the prognosis and guide the treatment of meningiomas.

CONCLUSIONS AND PERSPECTIVES

Here, we reviewed the potential mechanisms underlying recurrent and progressive meningiomas from focused perspectives, specifically the excessive proliferation of tumor cells, neo-angiogenesis, the inhibition of apoptosis, and genetic alterations. We also describe some potential therapeutic targets and prognostic biomarkers for meningiomas from these perspectives. Although we discussed these pathological processes separately, studies have shown that they do not occur in isolation. The histological classification of tumors has shown that those high-risk meningiomas often have the following characteristics: abundant blood vessels, increased nuclear mitosis, increased cell density, loss of tumor inherent structure, blurred basement membrane, and cerebral invasion or metastasis. In the final subsection, we also summarized the chromosomal abnormalities associated with these recurrent or progressive meningiomas, but research on the key biological pathways and their characteristics is still limited. We briefly compared the latest classification of meningiomas based on DNA methylation with the WHO grade and showed that the DNA methylation classification provides a more current prognosis, which requires further confirmation. Because of the complex and subtle changes caused by genetic abnormalities or other undetected factors, the precise mechanism underlying the pathology of meningiomas remains an enigma. Therefore, an

TABLE 2 | Overview of different classifications of meningiomas in latest studies.

DNA Methylation Classification (MC)	WHO Grade	Possible Biological Group
MC Benign 1 (Mc ben-1)	Grade I/II	immunogenic
MC Benign 2 (Mc ben-2)	Grade I	benign <i>NF2</i> wild-type
MC Benign 3 (Mc ben-3)	Grade I/II	hypermetabolic
MC intermediate A (Mc int-A)	Grade I/II	proliferative
MC intermediate B (Mc int-B)	Grade II/III	
MC malignant (Mc mal) (115)	Grade II/III	(12)

in-depth understanding of the development of recurrent and progressive meningiomas is further required to block the disease process and improve the prognosis of the disease.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication. WP, JZ and QL were responsible for the

conception of the idea, and manuscript preparation; MY and LZ primarily created the figure and tables; PW and JZ prepared and revised the manuscript.

FUNDING

This work was supported by grants from the National Natural Science Foundation (81901527) and Natural Science Foundation of Chongqing (cstc2021jcyj-msxmX0862).

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