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Review Article

Treating NF2 inactive mutation in meningiomas

Alauddin Syaifulanwar[1], Oktri Yetta Wimarti[1], Siti Ronelda[1], Soraya[1], Anastasya Hutapea[2], Andrea Valentino[3] and Darmawi[4*]

[1]Master Program in Biomedical sciences, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia;
[2]Bachelor Program in Medicine, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia;
[3]Department of Neurosurgery, Arifin Achmad General Hospital, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia;
[4]Department of Histology, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia.

*Corresponding author: darmawi@lecturer.unri.ac.id

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Corresponding author
Author Name
darmawi@lecturer.unri.ac.id

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Abstract

Meningioma is the most prevalent adult brain tumor with frequent somatic deletion of neurofibromatosis 2 (NF2). NF2 mutation in meningiomas tend to be relapsed which is limited in treatment option. Thus, personalized treatment for these circumstances is essential. The purpose of this literature review describes how the current development of NF2 mutation treatment approach in meningiomas. Targeting mTOR signaling using MLN3651 combine with selumetinib is one of a potential option for NF2 inactivation meningiomas. A novel therapeutic approach by inhibit EPH receptor signaling. There was also another option to treat NF2 meningiomas using demethylation drugs.

Keywords: Meningioma, Mutation, NF2, Treatment

Introduction

Meningioma, the most prevalent kind of primary brain tumor, reported around 30% of all recently diagnosed central nervous system (CNS) tumors, 90% of them as benign and 10% as malignant. National Program of Cancer Registries (NPCR) supplied information on 373,388 primary brain and other CNS cancers identified between 2010 and 2014. Meningiomas incidence are increase with age, with a median age of 66 years old. Study shows that females have 2.33 and 1.12 incidence rates of benign and malignant meningiomas, respectively. Higher-grade meningiomas in children had a higher recurrence rate and lower mortality. Blacks had 1.18 and 1.52 incidence ratios of benign and malignant meningiomas compared to Whites, respectively. Studies also found 2–3% of autopsies revealed incidental meningiomas.[1,2]

Etiology or risk factor of meningiomas including ionizing radiation, obesity, occupational (pesticide or herbicide), diet, allergies, hormones, cytogenetic and familial syndrome. In cytogenetic explained that 1q, 9q, 12q, 15q, 17q, and 20q were gained, while 1p, 4p, 6q, 9p 10, 14q, 18q, and 22q were lost. Studies show that 80% of meningiomas identified the loss of chromosome 22q, which contains the neurofibromatosis type 2 (NF2) gene.[2,3]

Meningiomas usually start with NF2 gene mutations and chromosomal 22q deletion. As tumor grade rises, more progression-associated molecular abnormalities are revealed, although most of the key genes are still unknown.[4]

NF2 is a tumor suppressor. A numerous of CNS disorder, is caused by NF2 loss of function mutations or deletions. NF2 causes bilateral vestibular schwannomas. NF2 patients might develop schwannomas on various cranial and peripheral nerves, meningiomas, and ependymomas.[5]

Studies suggested that MLN3651, a small molecule drug that inhibits Raf/MEK/ERK (Rapidly Accelerated Fibrosarcoma/ Mitogen-activated protein kinases/ Extracellular Signal-Regulated Kinase) activity additively, combined with selumetinib could be an option for NF2 deletion meningiomas.[6] New mTOR mechanistic target of rapamycin (mTOR)-inhibiting chemotherapies may treat recurrent meningiomas. Neoplasia requires mTOR-supported redox homeostasis. mTORC1 complex kinase inhibits

autophagosome components such Unc-51-like kinase 1 (ULK1) and Beclin.[7] TRAF7-KLF4 molecular cross-talk is a first step toward meningioma treatment.[8] Considering evidence in recent preclinical trials (in vitro and in vivo) show panobinostat and –HDAC inhibitors combination direct cell death and anti-tumor immunity in meningiomas.[9]

In this review, NF2 inactivation specifically refers to the loss of NF2 function due to genetic mutations, including nonsense mutations, frameshifts, and loss of heterozygosity. The aim of this literature review is to discuss NF2 loss in meningioma and how the current development of NF2 inactivation mutation meningioma treatment. Since surgical treatment of meningioma carries a lot of risks and recurrences still occur. Our review is limited to the latest medical treatments and epigenetic therapies.

Meningioma

Definition and Anatomical Location

Meningiomas, tumors that arise from meningeal epithelium and can originate in the brain or spinal cord.[10] There are 3 layers of the meninges, namely the dura mater, arachnoid, and pia mater. Meningiomas are dural-based malignancies that most frequently develop in the brain and, less frequently, the spinal cord. Rare cases develop as pulmonary or intraventricular malignancies.

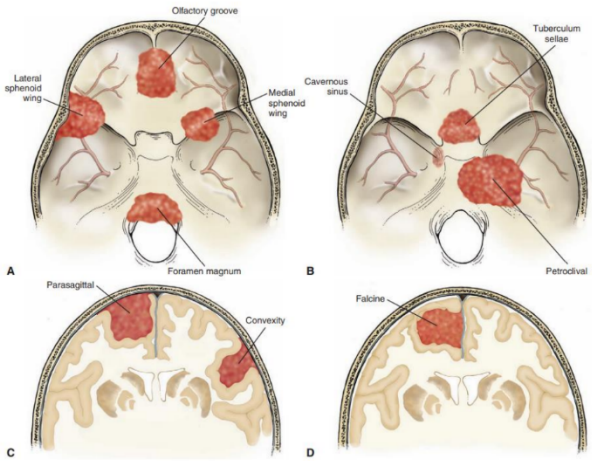


Figure 1. Common locations of tumor growth in relation to the adjacent skull, brain, and dural reflections (A–D)[12]

Meningiomas are typically extra-axial intracranial tumors. The sagittal sinus is frequently tightly surrounded by these tumors, which occur in the falcine and parasagittal regions in around half of cases. The base of the skull is where most of the leftovers are located. Meningiomas in the posterior fossa and, specifically, the ventricular area is quite infrequent. However, compared to meningiomas in adults, children's meningiomas are more frequently infratentorial, intraventricular, or intraparenchymal. Up to 25% of pediatric meningioma cases are linked to NF2.[11]

The majority of spinal meningiomas are laterally located, subdural, and firmly attached to the dura, all in close proximity to the spinal nerve roots. The most frequent location is the cervical spine, which is followed by the thoracic spine. In the lumbar area, meningiomas are uncommon. Spinal meningiomas have a startlingly feminine predominance.[11]

The scalp, epidermis, connective tissue covering the head and neck, the lung, the mediastinum, the peripheral nerve plexus and ganglia, the salivary gland, the jaw, and other unusual places have all been reported to harbor meningiomas outside the central nervous system (CNS). It is uncommon for primary meningiomas to develop in the bone, and they must be distinguished from meningiomas with osseous invasion.[13]

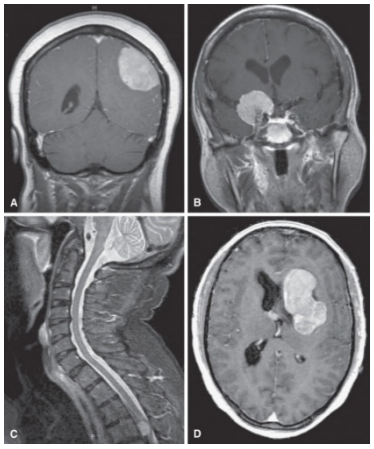


Figure 2. Frequent meningioma locations and presentations on MRI[12]

Causes

The cause of meningiomas is unknown. Radiation exposure is related to it. The genetic change described is the loss of a chromosome 22, usually involved in tumor growth inhibition. It Seen in approximately 50% of patients with the mutation in the neurofibromatosis type 2 (NF-2) gene.[14] Meningiomas also often have other Platelet Growth Factor Copy (PDFGR) and epidermal growth factor receptor (EGFR), which can promote the growth of these tumors. Different kinds genes associated with meningiomas include DAL1, SMO, AKT1, TRAF7 and mTORC1.[13]

Hormones have interacted with meningioma receptors such as progesterone, androgens, etc. Usually estrogen. Both in men and women, expression of progesterone is most commonly found in benign meningiomas. Although the exact role of hormones in growth and development of meningioma has not yet

been identified, researchers have found meningiomas are observed to occasionally grow faster during pregnancy period.[15]

Clinical Manifestations

Depending on the position of the tumor, patients usually present with clinical signs of increased intracranial pressure, seizures, and paresis.[11] Smaller meningiomas frequently stay asymptomatic throughout life because they are slow-growing tumors. Some of these asymptomatic tumors may have thick calcifications or ossifications. Larger, more symptomatic tumors experience local compression and peritumoral edema, which cause symptoms. The most frequent early symptoms are headache and newly developing seizures. The brain and spinal cord are compressed and irritated locally, causing the local manifestations, which result in focal neurologic symptoms and signs. The clinical picture frequently includes hydrocephalus for the uncommon malignancies that develop in the ventricles.[4]

It can be difficult to operate on tumors that develop in the cranial base because they have a propensity to penetrate the nearby osseous and non-osseous tissue. A wide range of symptoms, including cranial nerve palsy, sinus and orbital involvement problems, dental issues, and lumps in the forehead, could result from an invasion of the cranial base and surrounding structures. Although cranial base meningiomas are more likely to recur, this is likely due to the difficulties of performing a complete surgical excision rather than the biologic makeup of these tumors. Recurrence is more frequent in tumors in the anterior visual pathway, such as those that develop along the optic nerve. The sinonasal tract can also reveal extracranial meningiomas, which need to be separated from expansions from intracranial primary.[11]

After complete resection, benign meningiomas have a low chance of recurrence (~10%). However, atypical and anaplastic meningiomas have a greater possibility of recurrence thanks to their aggressive characteristics (respectively 29-52% and 50-94%).[16] Patients with anaplastic meningiomas had a median survival of less than two years in one research. One of the key elements of a good prognosis appears to be gross complete resection.[4]

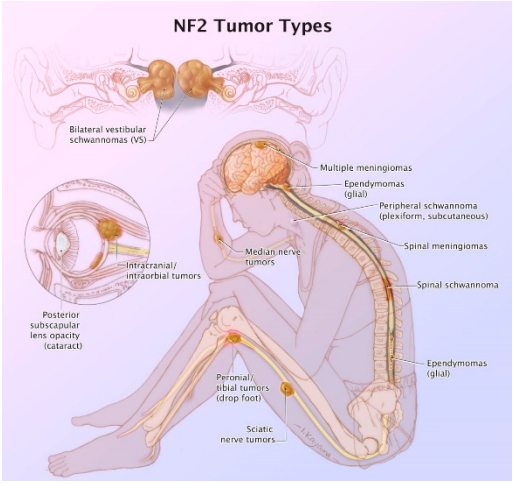
Grades of Meningiomas

Meningiomas are classified into three grades according to their characteristics. Meningioma subtypes vary by grade. To help identify subtypes based on the location and features, molecular testing is performed.[17]

1. Grade I meningiomas are the most prevalent type and classified into low grade tumor. This implies that the tumor cells grow slowly.
2. Grade II atypical meningiomas are mid-grade tumors. This means that the tumors are more likely to recur after being removed. The subtypes include choroid and clear cell meningiomas. Grade III anaplastic meningiomas are malignant (cancerous). This suggests they're rapidly growing tumors. There are two forms of meningiomas, papillary and rhabdoid.

Correlation of NF2 and meningioma

The tumor suppressor gene NF2 is located on chromosome 22 and has 17 exons with two splicing isoforms. There are 595 amino acid proteins encoded by NF2, which is called Merlin (moesin-ezrin-radixin-like protein).[18] Merlin is a tumor suppressor protein associated with incidence of benign tumors of the nervous system. Mutation and/or inactivation of the NF2 gene causes Neurofibromatosis type 2, a disorder



that is an autosomal dominant cancer that triggers

Figure 3. NF2 tumor types

the development of the nervous system tumors including bilateral schwannomas, meningioma, and ependymoma. **Figure 3** shows some of the tumors of the nervous system that can be caused by disorder of NF2.[18]

Ezrin/Radixin/Moesin (ERM) of the cytoskeleton-membrane junction protein is a member of the merlin family with puzzling roles, although it has been shown to stabilize the cytoskeleton membrane interface via suppressing signals involving the PI3kinase/Akt, Raf/MEK/ERK, and mTOR signaling pathways.[19] Click or tap here to enter text.Merlin, a cytoskeleton scaffolding protein, connects actin filaments, transmembrane receptors, and intracellular signaling to regulate essential pathways that control

proliferation and survival, including the hippo pathway, mammalian target of rapamycin (mTOR)/ Phosphoinositide 3-kinase (PI3K)/AKT pathway, and receptor tyrosine kinases (RTKs) **Figure 4.**[20]

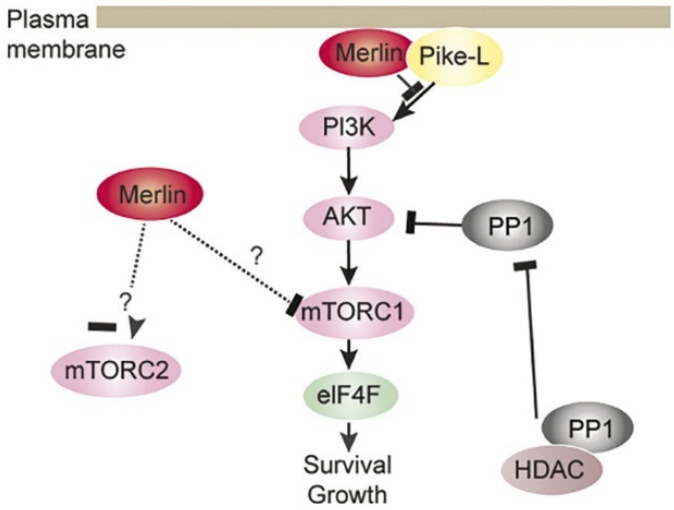


Figure 4. signaling pathways inhibited by merlin

NF2 is a rare autosomal dominant disease, the incidence of which is 1 in 33,000 births, it is due to biallelic inactivation of NF2.[21,22] Onset of symptoms is usually at age 20 years with bilateral vestibular schwannomas as a feature and the main definitive diagnostic criterion of NF2 as much as 90%, meningioma is the next most frequently identified tumor in approximately 50% of patients.[23–25] In cases of meningioma associated with NF2, 45- 58% intracranial meningioma, 20% spinal meningioma and in general they are WHO grade 1 benign tumors and slow growth. Currently, meningiomas in NF2 patients are frequently multiple, contributing to morbidity and mortality significantly.[26–28]

The most common types of mutations in the NF2 gene are nonsense mutations (39%) and frameshift (27%).[29] Multiple and recurrent meningiomas are associated with nonsense mutations and frame shifts that cleave protein.[30] Surgical specimens (tumor tissue) are important objects for detecting mutations.[28,31] On histological examination of tumor tissue in patients with multiple meningioma, it was found that NF2 inactivation was an early event before becoming a specific histopathological subtype. In studies of sporadic meningioma, NF2 inactivation by somatic mutation, epigenetic inactivation, or loss of the chr22q allelic was found in up to 60% of cases. This shows that the loss of NF2 is important in the occurrence of meningioma tumors.[4,32,33]

Molecular Mechanism

NF2 is the gene that encodes Merlin. Merlin, a member of the ERM (Ezrin-radixin-moesin) protein family, is an NF2-encoded protein with tumor-suppressive effects. Merlin has three structural components: an N-terminal FERM domain (1-300 residues), a middle α-helical region, and a C-terminal tail.[34] Merlin (Moesin-ezrin-radixin-like protein), a tumor suppressor protein, is known to function in a closed conformation that is critical in its tumor suppressor activity. This closed conformation is maintained by intramolecular interactions within the N-terminal and C-terminal FERM domains. The closed conformation allows Merlin to regulate various cellular events, including transcription, translation, ubiquitination, and miRNA biosynthesis, many of which are mediated through the Hippo and mTOR signaling pathways.[34] In the closed conformation, Merlin's C-terminal tail attaches to its own FERM domain which will create structural autoinhibition. When angiomotin (AMOT), a cell contact regulatory protein, binds to FERM, it removes the autoinhibitor tail, allowing LATS1/2 to bind to merlin. LATS1/2 is a kinase that, when active, phosphorylates or adds phosphate to its target protein, YAP/TAZ.[35] However, due to the lack of NF2, merlin fails to stabilize the ST1/2-SAV1-LATS1/2 complex, preventing the phosphorylation and activation of LATS1/2. The inactive LATS1/2 is then unable to phosphorylate Yes-associated protein/ transcriptional coactivator with PDZ-binding motif (YAP/TAZ). This failure of phosphorylation leads to the absence of deactivation of YAP/TAZ. YAP/TAZ, which is a transcriptional coactivator, will eventually enter the nucleus and activate pro-growth genes and cause uncontrolled tissue growth. This is called hippo pathway failure. In addition, in the nucleus, merlin also inhibits the activity of a ubiquitin ligase complex called *CRL4^{DCAF1}*. This complex (CRL4^{DCAF1}) has the ability to inactivate or degrade growth suppressor proteins and can suppress LATS1/2 activity indirectly so that when there is a fault in merlin present and active in the cell nucleus, CRL4^{DCAF1} will activate and suppress LATS1/2.[36]

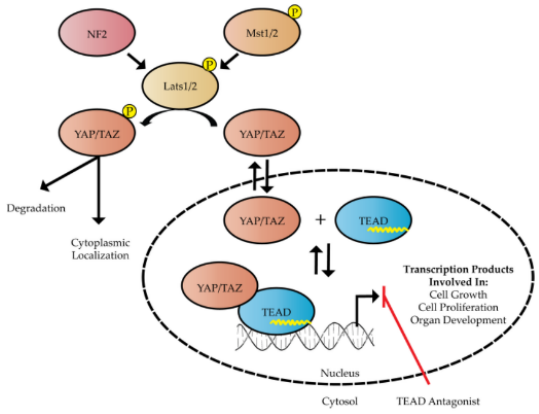


Figure 5. The Hippo signaling pathway[37]

There is also Mtor, another pathway that plays a role. Tuberous Sclerosis Complex (TSC1/2) are proteins that form a complex to inhibit mTORC1 via suppressing Ras homolog enriched in brain (Rheb), a GTPase that has the main role of activating mTORC1 that will work in cells for growth and fat synthesis. Merlin directly binds and stabilizes the TSC1/2 complex so that as long as merlin is active, mTORC1 is suppressed. If merlin cannot function properly, then TSC1/2 becomes unstable so that Rheb becomes freely active which results in mTORC1 becoming hyperactive. mTORC1 is the main regulator of metabolism so that the hyperactivity of mTORC1 will cause high metabolism, such as increased glycolysis and lipid synthesis, and promote cell growth and division.[38]

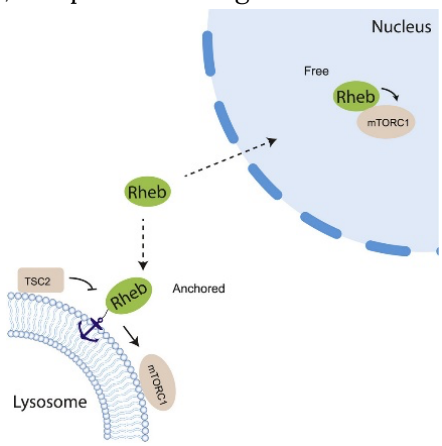


Figure 6. mTORC1 and Rheb[39]

Treatment

mTOR inhibitors impact meningioma tumor formation by activating the PI3K/Akt and Merlin protein pathways. Activating mTORC1 inhibits autophagosome components Beklin and ULK1. Neoplasia also affects redox homeostasis via mTOR.[7] The WHO classifies meningiomas as grade I (benign), II, or III (malignant). Meningiomas account for most of England's 70,000 annual brain tumor cases. NHS England reported 2000 meningioma surgeries. Many patients choose radiation over surgery because of its hazards.[7]

Surgery, radiation, and chemotherapy are the first treatments for grade II and III malignant neoplasms with considerable metastases. Meningiomas have several chemotherapeutic options, including mTOR inhibitors.[7] Furthermore, Histone deacetylase inhibitors (HDACi), an epigenome regulator, enhance oHSV's anti-cancer benefits in human MM models IOMM-Lee (NF2 wild-type) and CH157 (NF2 mutant). Trichostatin A and Panobinostat, at sub-micromolar concentrations, significantly boosted oHSV G47 infection and dissemination in MM cells in vitro.[9]

NF2, or MERLIN, inhibits meningioma tumor growth. Merlin deficiency enhances tumor-promoting mTOR activity. Merlin inhibited mTOR activation via the ubiquitin ligase CTLA4. Meningiomas grow when NF2, which inhibits mTOR, is deleted. Thus, mTOR inhibitors may treat meningioma in vitro. Redox homeostasis and mTOR inhibitors. Redox regulation requires mTOR. mTORC1/mTORC2 activation activates macroautophagy and redox homeostasis enzymes. Redox homeostasis causes cancers. Therefore, mTOR therapy must consider macroautophagy inhibition. SIROLIMIUS and TEMSIROLIMUS mTOR inhibitor studies in mice injected with WHO category III meningioma cell line. Injection was subarachnoid. mTOR inhibitors improved cell survival and proliferation in this study. Western blot showed a particular response to mTORC1 inhibition.[7]

In glioblastoma, it is known that mTORC1 triggers hypermethylation of H3K27 hypermethylation so it is necessary to consider treatment to prevent DNA methylation. Both Azacitidine and decitabine are new drugs that function by inhibiting DNA methyltransferase. New generation medicine, azacitidine and decitabine, work by preventing DNA methylation from doing its job.[7]

Several studies have shown that mTOR and FAK inhibitors are more selective against nf2-inactive molecular damage, while bevacizumab is more symptomatic (anti-edema and anti-angiogenesis). mTOR inhibitors that work by reducing cell proliferation and growth by suppressing protein synthesis and excessive metabolism due to nf2 inactivity are potential therapies to become basic therapy. However, dual mTORC1/2 inhibitors (e.g., AZD2014) show superior efficacy compared to mTORC1-specific agents in preclinical models.[49] On the other hand, FAK inhibitors decrease cell adhesion and increased mechanotransduction signaling due to loss of merlin's control over FAK still requires further research on clinical effectiveness.[50] FAK inhibitors demonstrated limited efficacy in NF2-altered tumors (3% objective response rate). Clinical studies show mTOR inhibitors and FAK inhibitors have side effects that are tolerable to patients, but grade 3 adverse events occurred.

Meanwhile, VEGF inhibitors reduce oedema and tumour volume by targeting VEGF-driven angiogenesis but does not restore merlin function. [51] The effectiveness of each class of therapy depends on the heterogeneity of the tumour and its grade. Combination therapies are often more effective. Preclinical data suggest FAK inhibition works best in combination with PI3K/mTOR inhibitors to block compensatory pathways.[5]

Current Treatment

Table 1. Meningioma mTOR inhibitor publications (complete) Meningioma mTOR inhibitor in vitro research[40–42]

Study Title	Drug	Publication Date	NTC Number	Targeted Therapies
mTORC1 Inhibitors Suppress Meningioma Growth in Mouse Models (A.)	Temsirolimus	March 2013	N/A	mTORC1 inhibitor
Everolimus Effectively Blocks Pulmonary Metastases from Meningioma (B.)	Everolimus	September 2015	N/A	mTORC1 inhibitor
A Phase II Trial of Bevacizumab and Everolimus as Treatment for Patients with Refractory, Progressive Intracranial Meningioma (C.)	Everolimus Bevacizumab	June 2016	NCT00972335	mTORC1 inhibitor and VEGF targeted drugs
Everolimus and Octreotide for Patients with Recurrent Meningioma: Results from the Phase II CEVOREM Trial (D.)	Everolimus Octreotide	February 2020	NCT02333565	mTORC1 inhibitor and SSTR2 inhibitor

mTORC1: mechanistic Target of Rapamycin Complex 1

VEGF: Vascular Endothelial Growth Factor

SSTR2: Somatostatin Receptor Type 2

Table 2. The comparison between mTOR inhibitors, FAK inhibitors, VEGF-targeted drugs

Therapy Category	Drugs	Target site	Pros	Cons
mTORC Inhibitors	Everolimus, Vistusertib (AZD2014)	mTORC1	Combination with PI3K inhibitors could potentially improve response.[43] In Grade 1 meningiomas, PFS-6 achieved 83%.[44]	In phase II clinical trials, vistusertib achieved PFS-6 in only 33% of grade 2/3 meningiomas.[44] mTORC1 inhibitors may increase mTORC2 activity, potentially hindering their effectiveness.[45] mTOR inhibitors can cause a variety of side effects, including nausea, diarrhea, hypophosphatemia, fatigue, and skin issues like acne-like dermatitis and rash.[45]
FAK Inhibitors	GSK2256098	FAK	High effectiveness where PFS-6 83% at grade 1.[46] Mostly it causes grade 1-2 side effects (e.g. proteinuria, pain) and overall was well tolerated.[46]	PFS-6 33% at grade 2/3.[46] -Low objective response (only 3% partial response).[46]
VEGF-targeted drugs	Bevacizumab	VEGF/ VEGFR	Tumor stabilization in 43.8-86% of patients in retrospective studies.[47] Potential combination with everolimus or other therapies.[42]	Risk of side effects (hypertension, proteinuria, and a spectrum of glomerular endothelial injury).[48]

PI3K: Phosphoinositide 3-kinase

PFS-6: Progression-Free Survival at 6 months

FAK: Focal Adhesion Kinase

VEGF/VEGFR: Vascular Endothelial Growth Factor/VEGF Receptors

Table 3. Experimental therapies targeting NF2-deficient meningiomas[45,46,53–55]

Study	Drug	Study Type	Mechanism	Result
The dual mTORC1/2 inhibitor vistusertib towards neurofibromatosis 2 patients for progressive or symptomatic meningiomas (2023)[45]	Vistusertib	Phase II clinical trial	mTORC1/2 dual inhibitors	Vistusertib successfully maintained tumor stability in many NF2 patients. 78% of participants experienced grade 3/4 adverse events, necessitating the development of better dosing regimens to improve tolerability.
Focal Adhesion Kinase Inhibition in meningiomas with somatic NF2 mutations (2022)[46]	GSK2256098	Phase II clinical trial	FAK inhibitor	FAK inhibition with GSK2256098 shows promising activity in meningiomas with NF2 mutations, particularly in prolonging progression-free time. The treatment is relatively safe and could be a new systemic therapeutic option for progressive or recurrent meningiomas with NF2 mutations.
Lapatinib's effect on meningioma growth in neurofibromatosis type 2 adults (2018) [53]	Lapatinib	Phase II clinical trial	EGFR/ HER2 inhibitor	Meningioma tumor growth was slower during treatment with lapatinib compared to the no-treatment period (p=0.0033). Lapatinib has good intratumoral penetration in extra-axial tumors such as meningiomas. However, further prospective studies are needed to test the effectiveness of lapatinib in NF2-related progressive meningiomas.
Inhibition of proteasomal pathway as a potential treatment for meningioma and schwannoma with NF2-associated (2023)[54]	ixazomib/MLN9708, pevonedistat/MLN4924, and TAK-243/MLN7243	Preclinical study	UPP inhibitor	Ixazomib is already FDA approved for multiple myeloma, easing the transition to clinical trials for NF2. The antitumor effect is also stronger than mTOR pathway inhibitors (e.g. rapamycin) which are only cytostatic. However, further evaluation is needed to address tumor heterogeneity and long-term toxicity.
Group I Paks as target for therapy in NF2-deficient meningioma. (2015)[55]	Frax597, 716 and 1036	Preclinical study	PAK inhibitors	PAK inhibitors might be useful agents in treating NF2-deficient meningiomas. Combination with other pathway inhibitors (e.g. PI3K/Akt) may be required to overcome resistance in malignant tumors

EGFR/ ErbB2: Epidermal Growth Factor Receptor/ Erb-b2 receptor tyrosine kinase 2

UPP: Ubiquitin–proteasome pathway

PAK: p21-Activated Kinase

Various experimental therapies targeting nf2 have been conducted **Table 3.** Thanks to the complexity of signalling pathways and tumour heterogeneity, combination therapies that target multiple pathways at once, such as combinations of mTOR and VEGF or FAK and VEGF inhibitors, have the potential to improve treatment effectiveness and overcome resistance. In clinical practice, treatment approaches should be personalized based on the tumour grade, location, and molecular characteristics of the patient to maximize the benefits of therapy while minimizing the risk of side effects. Today, Anti-VEGF and mTOR inhibitors are the most used and probably the most active drugs in aggressive meningiomas.[56]

Future Perspectives

Alternative treatments have not yet been investigated for meningioma that target the mTOR inhibition. Lycopene, a natural antioxidant, may be beneficial in the current unknown of the molecular process the formation of meningioma. To further prevent proliferation, one might target the mTOR inhibition by using epigenetic processes, such as DNA methylation using Azacitidine and Decitabine. Lot of active kinases are targets for dasatinib which is kinase inhibitor that has been approved by FDA. Combination therapy with mTORC1/mTORC2 inhibitors and might be potential for NF2-deficient MN treatment.[7]

HDACi therapy increased intratumoral oHSV replication and its ability to control human MM xenografts in vivo growth. Suggests additional translational research into the combination approach of HDACi and oHSV for the treatment of malignant meningioma. Preclinically that pan-HDACis enhance virus entrance and replication, improving MM oHSV treatment. HDACis and G47 are clinically used, therefore this finding can be used quickly. Future study should also explore this combo approach under immunocompetent condition as HDACis have been found to influence both innate and adoptive immunity.[9]

On the other side, targeting specific gene in cancer cells with genetic alteration has been investigated, known as synthetic lethality where mutations in two or more genes, when combined, cause cell death, while a mutation in just one of those genes alone does not. Research has identified a gene that is synthetically lethal with NF2. G6PD and ACSL3 have been identified as synthetic lethal partners with NF2 schwann cells.[61] Research on gastric cancer shows that inhibition of YAP which is overactivated because NF2 inactive and Bcl-2 family proteins can result in synthetic lethality that can prevent drug resistance and metastasis.[58] Synthetic lethality indeed is a promising approach for treating NF2 driven cancers by utilising the vulnerabilities of cells with NF2 mutation to kill them effectively.

Conclusion

In an in vitro study, minimally toxic, sub-micromolar concentrations of panHDACi, Trichostatin A, and Panobinostat, significantly increased oHSV G47 infectability and dissemination in malignant meningioma, resulting in increased oHSV-mediated target cell death at low multiplicity of infection (MOI). This suggests the need for clinical trials of HDACi in malignant meningioma. alive HDACi and oHSV specifically modify mRNA processing and splicing modules to fight malignant meningioma, according to transcriptomics. HDACi controlled intratumoral oHSV replication and MM xenograft growth. HDACi-oHSV combo therapy for malignant meningioma should be translated.[9]

NF2, or MERLIN, inhibits meningioma tumor growth. Merlin deficiency enhances tumor-promoting mTOR activity. Merlin inhibited mTOR activation via the ubiquitin ligase CTLA4. Meningiomas grow when NF2, which inhibits mTOR, is deleted. Thus, mTOR inhibitors may treat meningioma in vitro. Redox homeostasis and mTOR inhibitors. Redox regulation requires mTOR. mTORC1/mTORC2 activation activates macroautophagy and redox homeostasis enzymes. Redox homeostasis causes cancers. Therefore, mTOR therapy must consider macroautophagy inhibition. SIROLIMIUS and TEMSIROLIMUS mTOR inhibitor studies in mice injected with WHO category III meningioma cell line. Injection was subarachnoid. mTOR inhibitors improved cell survival and proliferation in this study. Western blot showed a particular response to mTORC1 inhibition.[7]

MEK or BRAF are the latest and should be studied preclinically and clinically in meningioma loss NF2. These inhibitors may impair KLF4's tumor-controlling capacity. KLF4 and TRAF7 meningioma patients have received MEK or BRAF.[8] Future research should focus in identifying novel synthetic lethal targets and optimizing combination therapies based on molecular profiling to enhance therapeutic outcomes. As our understanding of NF2-associated signaling pathways deepens, these targeted approaches may offer more effective personalized treatment and improving patient's prognosis.

Ethics approval

Not required.

Acknowledgments

Not applicable.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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