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REVIEW ARTICLE

Brain-invasive meningiomas: molecular mechanisms and potential therapeutic options

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Abstract

Meningiomas are the most commonly diagnosed benign intracranial adult tumors. Subsets of meningiomas that present with extensive invasion into surrounding brain areas have high recurrence rates, resulting in difficulties for complete resection, substantially increased mortality of patients, and are therapeutically challenging for neurosurgeons. Exciting new data have provided insights into the understanding of the molecular machinery of invasion. Moreover, clinical trials for several novel approaches have been launched. Here, we will highlight the mechanisms which govern brain invasion and new promising therapeutic approaches for brain-invasive meningiomas, including pharmacological approaches targeting three major aspects of tumor cell invasion: extracellular matrix degradation, cell adhesion, and growth factors, as well as other innovative treatments such as immunotherapy, hormone therapy, Tumor Treating Fields, and biodegradable copolymers (wafers), impregnated chemotherapy. Those ongoing studies can offer more diversified possibilities of potential treatments for brain-invasive meningiomas, and help to increase the survival benefits for patients.

Keywords Meningiomas · Brain invasion · Molecular mechanism · Target therapy · New strategies

Abbreviations

WHO	World Health Organization
SPARC	Osteonectin or BM-40
GFAP	Glial fibrillary acidic protein
EMA	Epithelial membrane antigen
ECM	Extracellular matrix
BM	Basement membrane
HSPG	Heparin sulfate proteoglycans
MMPs	Matrix metalloproteinases
HPSE	Heparanase
TIMPs	Inhibitors of matrix metalloproteinases
PFS	Progression-free survival
uPA	Urokinase plasminogen
uPAR	Urokinase plasminogen receptor
PAI	Plasminogen activator inhibitor
HGF	Hepatocyte growth factor
PDGF	Platelet-derived growth factor
EGF	Epidermal growth factor
TGF-α	Transforming growth factor-α
VEGF	Vascular endothelial growth factor
MAPK	Mitogen-activated protein kinase
PI3K	Phosphatidylinositol-3-kinase
CTLA-4	Cytotoxic T lymphocyte antigen 4
PD-1/ PD-L1	Programmed death 1/programmed death-ligand 1
HRT	Hormone replacement therapy
ALK	Anaplastic lymphoma kinase

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Introduction

Meningiomas are primary brain tumors that originate from meningothelial (arachnoid) cells [1] and the proportion in all intracranial tumors exceeds 35% [2]. The World Health Organization (WHO) has defined three meningioma subtypes based on the number of mitotic figures and malignant

degree: benign, atypical, and anaplastic, and account for 70–80%, 5–20%, and 1–3%, respectively [3]. Benign meningiomas usually do not disrupt the surrounding brain structures. Therefore, complete surgical resection is the preferred treatment for the vast majority of these meningiomas. However, even in benign cases, meningiomas have high recurrence rates, even after curative surgical treatment [4]. It is documented that recurrence rates of benign meningiomas can be up to 20%, even after Simpson I resections, and atypical and anaplastic tumor grades can have recurrence rates of up to 40% and 80%, respectively [5]. The most important factors affecting the recurrence of meningiomas are tumor grade, the extent of surgical resection, and invasion of adjacent brain tissue [6, 7]. Meningiomas with brain invasion generally show obvious edema of brain tissue around the tumor in T2 weighted MRI, and the tumor demonstrates the ability to circumvolute vessels or break through the arachnoid under the microscope during surgery (Fig. 1). Consequences of such a brain-invasion include neurological compromise and a further decrease in the possibility of total surgical resection. The latest classification by WHO of brain tumors proposed brain invasion as an unattached standard for atypia and therefore guide diagnosis and treatment for meningioma [3].

Despite invasion stated explicitly as neoplastic tissue within the adjacent brain, and no separating tissue layers exist in the latest edition [3], there are other evaluating criteria for brain invasion. Brain-invasive meningioma was first defined in the WHO classification in 1993, and its definition was rather vague, partially including [8] or excluding, [9] tumor cells growing along with the Virchow-Robin spaces. Owing to the contributions by Perry et al. [10], a more accurate definition of invasive growth was illustrated as tumor cells invading adjacent brain tissue without separating the connective tissue layer. However, sometimes the surgical specimens used to assess invasion lacked an infiltrative interface with the brain; therefore, Rempel et al. [11] suggested SPARC (secreted protein, acidic and rich in cysteine) as a sign of brain-invasive meningioma. Beyond that, staining for GFAP (glial fibrillary acidic protein), CD44, and EMA (epithelial membrane antigen) were shown to increase the sensitivity of detecting brain invasions [12, 13]. Moreover, some studies further described the pattern of meningioma infiltrative growth: (1) diffuse growth (single cells diffuse into brain tissue) [14, 15]; (2) nests/cluster-like (islands of tumor cells) [14–16]; and (3) finger-like/tongue-like tumor expansion into the surrounding brain [13, 14, 16]. Interestingly, infiltration also exhibits gender-specific patterns [14]. Based on previous results, Brokinkel et al. [12] recently recommended a more systematic and accurate detection standard for brain invasion in meningiomas, which contains pre-, intra-, and post-operative methods and should be indicated in communications between neurosurgeons and neuropathologists.

For such invasive meningiomas, gross total resections are not always possible. Meanwhile, adjuvant irradiation strategy in invasive meningiomas has only been investigated in a few studies and has not shown promising prognostic effect yet [12]. In 2014, a study reported by Sun et al. [17] revealed no significant prognostic impacts for radiation

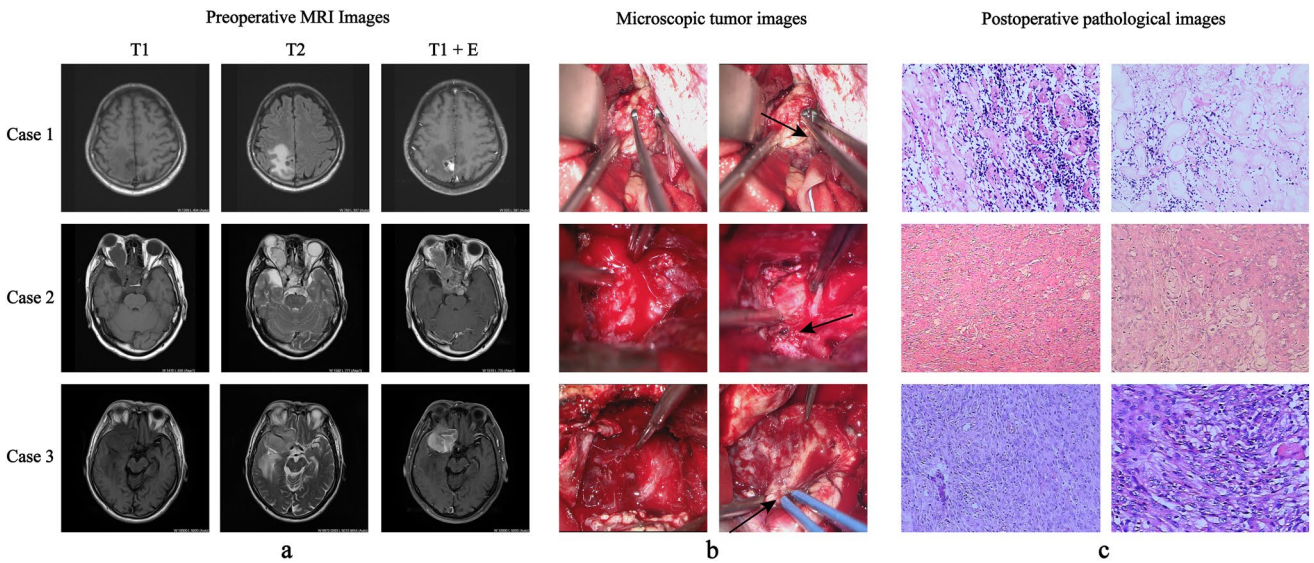

Fig. 1 Clinical cases of meningioma exhibiting biological behavior of brain invasion. **a** Magnetic resonance imaging (MRI) of brain-invasive meningiomas demonstrating vanishment of interface with the brain tissue and marked surrounding edema. **b** Microscopic images of brain-invasive meningiomas during the surgery. Black arrows highlight the site where the tumors penetrate the arachnoid interface and invade the normal brain tissues. **c** Pathological images of brain-invasive meningiomas under different magnification

therapy in totally resected atypical meningiomas. Consistently, in a larger cohort of 50 patients, whether received radiation therapy or stereotactic radiosurgery for residual meningioma, there is a much higher recurrence risk in the brain-invasive meningioma group [18]. Moreover, atypical meningiomas with spontaneous necrosis appear to be resistant to radiotherapy [18]. Thus, it is essential to review the underlying molecular mechanisms of brain-invasive meningioma tumor cells and describe the current understanding of target treatment options and other promising approaches for brain-invasive meningiomas.

Molecular targets and related agents for brain-invasive meningiomas

After undergoing surgical resection and radiotherapy, patients who relapse with brain-invasive meningiomas have limited therapeutic choices. Next, some critical molecules and related drugs that have potential actions against brain-invasive meningiomas will be reviewed.

Brain invasion of meningioma involving interactions between meningioma cells, normal brain stromal cells, the extracellular matrix (ECM), and basement membranes (BM), which is considered a three-step process, initially degradation of ECM/BM, and tumor cells migration, finally promoting adhesion of meningioma cells to resident cells with the help of growth factors and blood-vessel formation [19, 20], leading to local brain invasion (Fig. 2). Thus, mediators of the invasive behavior of meningioma tumor cells mainly focus on tissue-degrading enzymes, cell adhesion molecules, and various growth factors, which promote tumor proliferation and angiogenesis.

Extracellular matrix degradation

Degradation of the ECM/BM is thought to be one of the most important determinants of tumor cell invasion [21]. ECM/BM are rigid structures formed from macromolecules, such as type IV collagen, laminin, entactin, nidogen, fibronectin, and heparin sulfate proteoglycans (HSPG). Proteases, including matrix metalloproteinases (MMPs), serine proteases, cathepsins, and heparanase (HPSE), have the capability of breaking down basal membranes and connective tissue [22–24]. Therefore, such enzymes play crucial roles in the process of meningioma invasive growth [25].

MMPs

MMPs are lysosomal endopeptidases involved in ECM degradation [26]. MMPs have been grouped into the following four broad categories based on their substrate specificity: (I) interstitial collagenases (MMP-1, MMP-8, and MMP-13) that degrade fibrillary collagens; (II) type IV collagenases (MMP-2 and MMP-9) that degrade the basement membrane collagens gelatin and elastin; (III) stromelysins (MMP-3, MMP-10, and MMP-11) that degrade proteoglycans, fibronectin, laminin, gelatin, and the globular proteins

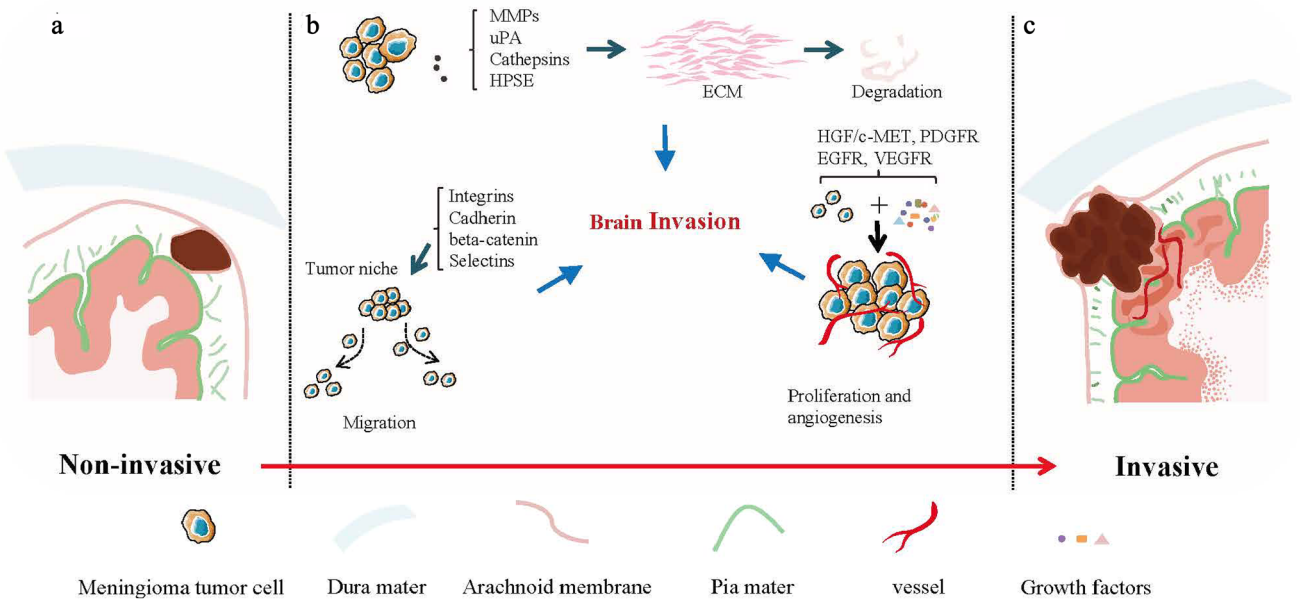

Fig. 2 Meningioma brain invasion is considered a three-step process that requires various kinds of proteases to degrade the ECM, adhesion molecules to promote tumor cell migration to resident cells, and different growth factors and neovascularization to feed and support meningioma tumor cells, leading to local brain invasion

of type IV collagens; and (IV) membrane-type MMPs (MMP-14, MMP-15, MMP-16, and MMP-17) that contain a unique transmembrane domain in their carboxyl-terminus that localizes these MMPs to the cell surface [27]. There are natural inhibitors of MMPs, inhibitors of matrix metalloproteinases (TIMPs), which form a complex with the active centers of MMPs and control their activities. Specifically, TIMP-1 inhibits MMP-9, whereas TIMP-2 controls MMP-2. Importantly, MMP-2 and MMP-9 are found to be expressed in a broad spectrum of meningiomas and represent valuable prognostic factors in predicting higher risk recurrence in totally resected meningiomas [28, 29]. Recently, Jalali et al. [28] demonstrated that MMP-16 modulates meningioma invasion by positively regulating MMP-2. MMP-3 is positively correlated with meningiomas having an aggressive character [30]. Besides, RNA interference (RNAi)-mediated targeting of MMP-9 significantly regressed cell invasion and orthotopic meningioma formation [31, 32]. Taken together, the results show the potential of MMP inhibitors as a promising therapy for invasive meningioma, and the synthesis of a wide-spectrum inhibitor of MMPs is urgently needed.

The urokinase plasminogen (uPA)-uPA receptor (uPAR) system

The 55-kDa serine protease uPA consists of two disulfide bridges linked to polypeptides. It can be converted from an inactive precursor into an active form by the actions of various proteases, including plasmin, cathepsins B or L [33]. Active uPA interact with receptor uPAR, subsequently requires transmembrane co-receptors for signaling transduction. Integrins family are one of those essential co-receptors [34, 35]. As a result, uPA-uPAR can efficiently convert plasminogen to active plasmin [34]. Plasmin is essential for the degradation of ECM in direct and indirect ways. Additionally, uPA is known to exert additional activities, including the promotion of cellular migration, proliferation, and alteration of cellular adhesive properties [34].

uPA is expressed in many tumor types, including breast, lung, glioblastoma, prostate, and esophageal squamous cell carcinomas [36–39]. It is documented that synthetic inhibitors target uPA could efficiently inhibit the metastasis of prostate and mammary carcinoma cells [40, 41]. Regulation of uPA is achieved at many levels, including at least two types of fast-acting specific inhibitors, plasminogen activator inhibitor (PAI)-1 and PAI-2. A report by Kandenwein et al. [42] showed that the expression of uPA may be controlled, in part, by promoter methylation and is correlated with pathological meningiomas. Importantly, uPA and uPAR interference by RNAi led to the inhibition of intracranial meningioma formation in a mouse model [43]. Based on these studies, low-molecular-weight inhibitors, which target the uPA-uPAR-PAI-1 system, should be considered as treatment options for invasive meningiomas.

Lysosomal cysteine proteinases

Lysosomal cysteine proteinases are comprised of a large family of papain-like enzymes [44]. Schmitt et al. [45] proposed a proteolytic cascade by cysteine proteases, which starts with the activation of the lysosomal enzymes cathepsin D and cysteine cathepsins B and L, subsequently activating cell membrane-associated pro-urokinase, inducing the extracellular release of plasmin from plasminogen to finally activate various types of MMPs and degrade collagen and other basal lamina proteins. It has been proved that the progression of brain tumors strongly correlated with the high expression of cathepsins B, L, and H [46, 47]. Three types of endogenous inhibitors control their activity: stefins, cystatins, and kininogens [48]. Generally, stefins (stefins A and B) predominantly act intracellularly [47], whereas cystatins (cystatins C) and kininogens act extracellularly [49]. The balance between these inhibitors and cysteine cathepsins seems to be highly relevant and may serve as biomarkers for tumor progression. In brain tumors, the down-regulation of total inhibitory activity of cystatins has been observed and takes responsibility for early meningioma recurrence. Thus, it seems to especially safeguard brain tissues [50]. Consistently, cathepsin B and L are highly expressed in invasive types of benign meningiomas and are considered as diagnostic markers for invasive meningiomas [51]. Collectively, the use of cysteine protease inhibitors may lead to more informed therapeutic strategies in the future.

Heparin sulfate proteoglycans (HSPG) and heparanases (HPSE)

Invasion by meningioma tumor cells is affected by the microenvironment, including components of the ECM/BM, such as HSPG, which is composed of a core protein to which repeating disaccharide units have been added. The specific structures of heparin sulfate chains are achieved through several enzymatic steps that create highly charged, sulfated micro-domains, and are secreted as entities into the ECM or intracellular secretory vesicles [52, 53]. A multitude of growth factors and chemokines bind to HPSG, regulating biological processes, and modulating the adhesion and spread of tumor cells [54]. HPSE is an endo-β-D-glucuronidase that cleaves heparin sulfate chains of HSPG at specific sites, into 5–7 kD sized fragments [55]. Dario Marchetti proposed that HPSE acts as a cellular switch from a non-invasive to invasive phenotype [56]. Indeed, overexpression of HPSE has been found in several human cancers and positively correlates with more extensive tumor invasion and metastasis [57, 58]. Using PG545, a heparanase

inhibitor or a glycopolymer of HPSE efficiently reduced tumor cell invasion and metastasis [54, 57]. Another heparanase, M402-necuparanib, is currently under phase II trial investigation in pancreatic cancer [59]. The compound roneparstat has been positively completed in a phase I study with dexamethasone in patients with advanced multiple myeloma [60]. Taken together, HPSE could be a novel therapeutic target for invasive brain tumors. However, the expression of HPSE and its functions on brain invasion in meningiomas still need to be defined, and whether inhibitors of HPSE have any effect on invasive meningiomas is largely unknown.

Cell adhesion molecules

The attachment of cells to their surroundings is important in determining cell shape, proper cell function, and tissue integrity. Cell adhesion is selectively regulated by cell adhesion molecules leading to migration and rearrangement of cell types. According to their migration properties and primary amino acid sequences, four major classes of adhesion molecules have been defined: integrins [61], cadherins [62], immunoglobulin superfamily [63], and selectins [64].

Integrins and their inhibitor, cilengitide

Integrins are cell surface adhesion molecules important for many cellular features, including proliferation and migration. Integrins are composed of different, non-covalently associated α and β chains. These subunits associate to yield a wide variety of heterodimers. Recently, much interest has focused on the role of integrins in carcinomas [65–67]. Previous studies have indicated that each histologic meningioma subtype has a specific spectrum of integrin expression, especially αVβ3 and αVβ5 integrins [68], which contribute to invasive growth of meningiomas [69].

Cilengitide is a pentapeptide that targets αVβ3, αVβ5, and αVβ1 integrins by mimicking the Arg-Gly-Asp (RGD)-binding site [70, 71], which has been conducted in phase I, II, and III clinical trials to evaluate therapeutic effects in cancers [72–75]. Wilisch-Neumann et. al. [76] explored the effects of cilengitide in meningioma cell lines and mouse models and found inhibition of brain invasion in mice after administration of cilengitide.

E-cadherin/β-catenin signaling pathways

Epithelial cadherin (E-cadherin) belongs to the cadherin family, it is a cell-surface glycoprotein that is vital for calcium-dependent cell–cell adhesion and structural rigidity [77, 78]. The extracellular amino-terminus forms a ‘‘zipper-like’’ structure which can act as a tight cell junction. And the intracellular part indirectly associates with cytoskeletal components at cell–cell junctions via catenin [78]. β-catenin, one of the four types of catenins, is a multifunctional protein [77] and forms the E-cadherin/catenin complex [79]. Disruption of this junction will result in diverse disorders, including loose cell-to-cell contacts, and loss of contact inhibition, which are tightly related to tumor invasion [78, 80]. A study conducted by Keiyu et al. revealed that E-cadherin and β-catenin expression closely correlated with grading criteria for meningiomas [81]. Similarly, Ahmed et al. showed that high β-catenin expression was linked to the low incidences of brain invasion and recurrence. Taken together, the E-cadherin/catenin complex could be potential therapeutic targets for meningioma treatment [82].

Selectins

The selectin family represents a group of carbohydrate-binding type I membrane glycoproteins. There are three members, E-, P-, and L-selectin [83]. E-selectin secretion is activated following local stimulation by endothelia of skin and bone marrow and subsequently induced by inflammatory cytokines [84]. P-selectins are stored in alpha granules of the platelet. Through exocytosis, they translocate to the cell surface of activated endothelial cells and platelets [85]. L-selectins are expressed on granulocytes, monocytes, and the majority of lymphocytes and leukocytes [86]. The aforementioned selectins function by interacting with the selectin binding ligand, namely P-selectin glycoprotein ligand-1, which is expressed on the microvilli of activated leukocytes.

Selectins mainly correlate with binding, rotation, and extravasation of activated leukocytes, which commonly take place on the endothelium and also in inflammation reactions [86]. Additionally, some recent studies have implied that selectins could help cancer cells adhere to the endothelium and recruit leukocytes to promote the progression and metastasis of various types of cancer [85, 87]. Consistent with this, a lack of L-selectin was shown to inhibit metastasis [87], and inhibition of P-selectin, which mediates the interaction of thrombocytes and endothelium, significantly reduced metastasis by down-regulating the thrombi assembly [88]. Notably, Atukeren et al. [89] recently evaluated selectins expression in meningiomas and found that all three selectins display higher expression levels in meningiomas compared to control brain tissues, suggesting that selectins are possibly involved in the pathological mechanism of meningioma. Further clinical and experimental studies are needed to demonstrate these current findings.

Growth factors

Growth factors play a seminal role in the brain invasion process, including the promotion of migratory, proliferative, and angiogenesis responses in meningioma cells. Thus, hepatocyte growth factor (HGF), platelet-derived growth

factor (PDGF), epidermal growth factor (EGF), transforming growth factor-α (TGF-α), and vascular endothelial growth factor (VEGF), and relevant inhibitors are all reviewed in the next section (Fig. 3).

HGF/c-MET signaling pathways

HGF is a multifunctional protein secreted by mesenchymal cells and has a strong mitogenic effect on hepatocytes. HGF consists of a heavy chain (60 kD) with four domains and a light chain (32 kD). It binds to its tyrosine-kinase receptor (RTK), which is a product of the proto-oncogene c-MET. Mature c-MET is structurally distinct from most other RTKs and exists as a heterodimer containing an extra-cellular α chain and a transmembrane β chain. Once activated by HGF binding, c-MET is auto-phosphorylated and recruits adaptor proteins, activating multiple downstream effector proteins and signaling cascades [90].

Dysregulation of the HGF/c-MET signaling pathway has been known to induce tumor cell proliferation, motility, and invasion in several human cancers, including breast, lung, and hepatocellular carcinomas [91–93] and has recently attracted considerable attention. This pathway is widely expressed in human brain tumors, such as gliomas, meningiomas, and schwannomas [94–96], and a study has reported that 3 out of 17 c-MET positive meningiomas exhibited brain invasion activity [95]. In the last decades, a big effort has been made to develop related inhibitors and monoclonal antibodies through preclinical, phase I, II, or III clinical trials [90, 97–99]. As of yet, there are unfortunately no clinical trials focusing on meningiomas. Given our recent knowledge about HGF/c-MET in cancer cells, future clinical trials focusing on anti-HGF/c-MET agents should take into account whether brain-invasive meningiomas can benefit from these treatments.

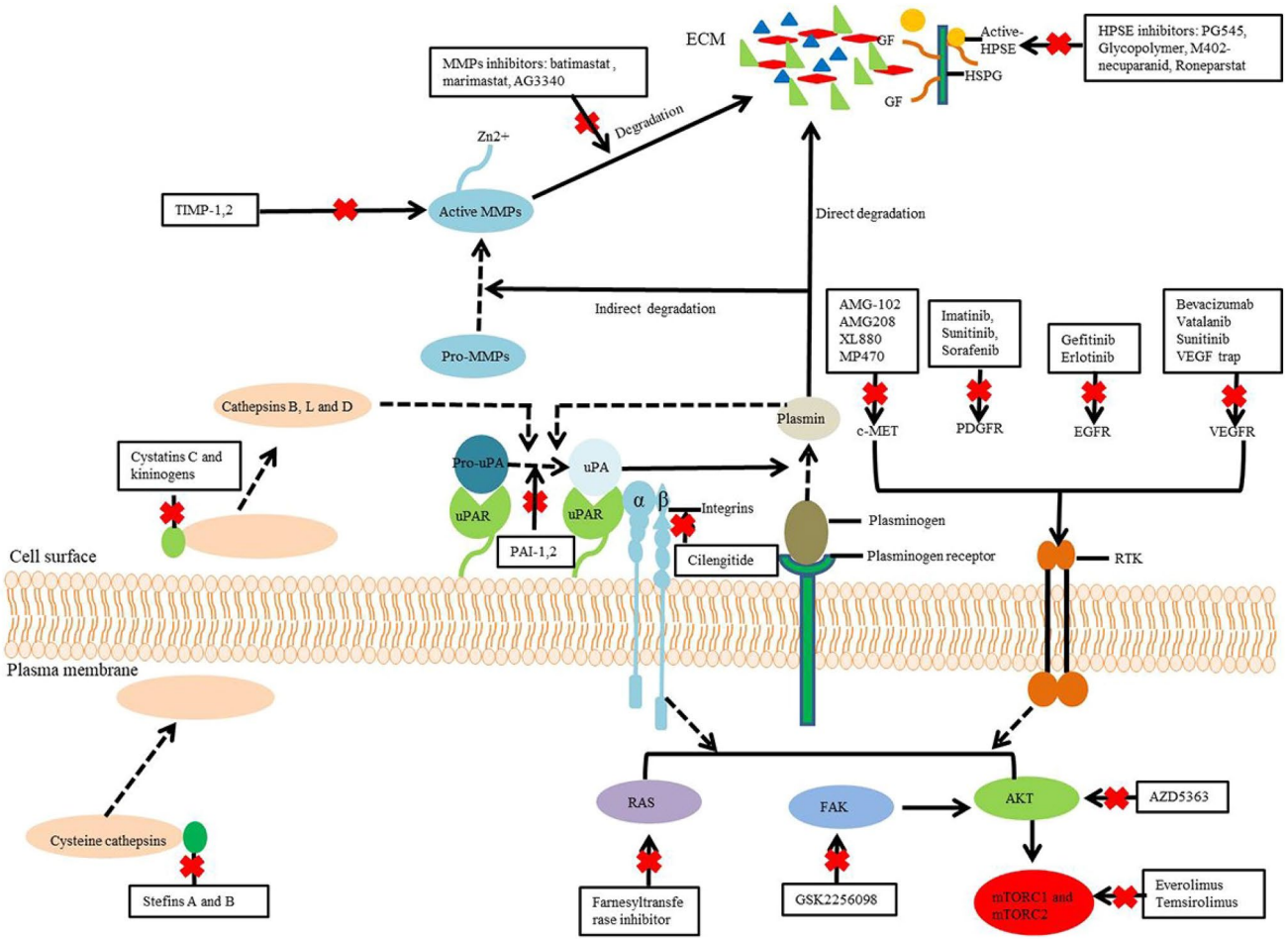

Fig. 3 Selected signaling pathways in meningiomas and molecular targets for drug therapy. *ECM* the extracellular matrix, *HSPG* heparin sulfate proteoglycans, *HPSE* heparanase, *MMPs* matrix metalloproteinases, *TIMP* inhibitors of matrix metalloproteinases, *uPA/uPAR* urokinase plasminogen activator/receptor, *PAI* plasminogen activator inhibitor, *HGF* hepatocyte growth factor, *PDGF/R* Platelet-derived growth factor/receptor, *EGF/R* epidermal growth factor/receptor, *VEGF/R* vascular endothelial growth factor/receptor

PDGF and EGF receptors

PDGF act as a proliferation driver in normal development and multiple cancers [100–102]. Increasing evidence of the key role of PDGF in meningioma growth has been reported [103–105]. All histological grades of meningiomas express the PDGF ligands AA and BB, Interestingly, only PDGF-β-R receptor was found, which predominantly binds to PDGF-BB. PDGF-BB has been shown to stimulate meningioma growth and activate MAPK and induce c-Fos expression. Conversely, anti-PDGF-BB restrains cell growth [104].

Most meningiomas express both *EGF* and *TGF-α* mRNAs [106, 107]. Up-regulated TGF-α activity in meningioma cells and tumor specimens has been proved to correlate with aggressive growth [108]. Meanwhile, over 60% of meningiomas highly expressed EGF receptor (EGFR) [109]. EGF or TGF-α activate their receptors, which promotes the proliferation of meningioma cells in in vitro study [108]. These findings suggest that EGFR activation by autocrine or paracrine mechanisms in human meningiomas may promote tumor growth.

Signal transduction from activated tyrosine kinase receptors, including PDGFR and EGFR, is mediated in part via Ras/Raf/MAPK and PI3K pathways [107], indicating that tyrosine kinase inhibitors may be effective against meningiomas. Imatinib is an oral tyrosine kinase inhibitor, which targets the Bcr-Abl, PDGFR, and c-Kit receptors. Meningiomas often overexpress PDGFR-α and β and are potential targets for imatinib treatment. Moreover, imatinib increases chemo- and radio-sensitivities of different tumor cells in culture, such as glioblastoma cells, soft tissue sarcomas, and leukemic cells [110–112], suggesting that imatinib may enhance the activity of other chemotherapeutic agents used to treat brain tumors. Thus, the combination of imatinib and hydroxyurea has been investigated in two phases II trials to test their efficacy in progressive meningiomas [113]. In 2018, data from phase II clinical trials suggest that lapatinib, a dual EGFR/ErbB2 small molecular kinase inhibitor, might have growth-inhibiting effects on meningiomas in NF-2 patients [114]. Although no definite conclusions due to the limited number of patients, well-designed and prospective clinical trials are urgently needed for the therapeutic management of invasive meningiomas. Similarly, recent single-arm phase II studies on the EGFR inhibitors gefitinib (NABTC 00-01) and erlotinib (NABTC 01-03) proved no significant activity against recurrent meningiomas [115].

VEGF/VEGFR and inhibitors

Invasive meningiomas cannot expand beyond the cerebral-pial interface without an adequate blood supply. As meningiomas are rich in blood vessels, their blood supply is predominantly derived from both the external carotid artery and cerebral pial vessels [116]. High expression of VEGF and VEGF receptor-1 was found in meningiomas [117] and was associated with the extent of peritumoral brain edema [118]. A study by Lamszus et al. [119] showed a strong and consistent correlation between VEGF content and meningioma grade, indicating that treating invasive meningiomas may benefit from anti-angiogenic therapy.

Bevacizumab is the anti-VEGF antibody that has been utilized and improved the survival for several malignancies including colorectal, lung, breast, and glioblastomas [120, 121]. To date, bevacizumab has been examined in several retrospective analyses and two phase-II trials involving patients with refractory meningiomas [122]. Generally, these results show promise for patients with recurrent meningioma. Of note, bevacizumab has several important side effects such as high blood pressure, hemorrhage, proteinuria, and colitis. Encouraged by previous results, some researchers have also assessed the efficacy of VEGF inhibitors in patients with relapsed meningiomas. The wide-spectrum tyrosine kinase inhibitor sunitinib, which can target VEGFR, PDGFR, and several other oncogenic pathways, is currently being used in clinical practice for several cancers. This agent was studied in a phase II trial of 36 patients with grade II and III meningiomas who had multiple recurrences and were heavily pretreated [123]. The calculated PFS-6 was 42%. However, toxicity was a significant factor, as four patients developed intratumoral hemorrhages, one of which was fatal. Another two patients developed thrombotic microangiopathy. Further exploration of the role of VEGF/VEGFR inhibitors in invasive meningiomas seems warranted. Hopefully, larger prospective studies of bevacizumab and other VEGF/VEGFR inhibitors will be feasible for this indication in the near future. These agents have the potential to join the list of therapeutic options for treating brain-invasive meningiomas.

Other promising treatment for brain-invasive meningiomas

Immunotherapy for brain-invasive meningiomas

The complex association between the immunology and malignant tumorigenesis has shown huge potential on various types of cancer management such as metastatic melanoma, which have been promisingly identified as sensitive and tolerated to inhibitors of immune checkpoint pathways cytotoxic T lymphocyte antigen 4 (CTLA-4), and programmed death 1 (PD-1)/PD-ligand 1 (PD-L1). This immunotherapeutic approach has been approved by the U.S. Food and Drug Administration [124]. While it currently remains largely unknown about the immune microenvironment in meningioma, immunotherapy possesses perspectival application for managing meningiomas.

A recent report by Du et al. demonstrated the significant reduction of infiltrating T lymphocytes in anaplastic meningiomas, such as CD4 + and CD8 + T cells with PD-1 expressed, which are considered inclined to invade peripheral brain tissue [125]. Additionally, they detected PD-L1 expression in meningioma at either protein or gene levels, and the expression was higher in anaplastic cases [125]. Their study however failed to detect a significant link between PD-L1 levels and survival outcomes due to their cohort was mostly composed of low-grade meningiomas which barely exhibited brain invasion. The prognostic significance of PD-L1 in meningiomas has been investigated to identify the correlation of PD-L1 expression and the infiltrating immune cell population and suggested that PD-L1 possibly plays an important biologic role in the aggressive phenotype of higher-grade meningiomas. Besides, current clinical trials testing anti-PD1 drugs pembrolizumab and nivolumab in recurrent or residual high-grade meningiomas are undergoing [126]. Thus, immunotherapeutic strategies such as checkpoint inhibition, or targeting mesothelin through vaccines/engineered T cells have the potential to be utilized as clinical medication in PD-L1 overexpressing brain-invasive meningiomas (Fig. 4a).

Hormone therapy

According to the epidemiologic evidence, the incidence of meningioma is commonly higher among females, especially when pregnancy and breast cancer occur [127, 128]. So regulation of meningioma growth and development by a sexual hormone is defined. Progesterone and estrogen, which are antagonistic to each other, function in the modulatory mechanism. During hormone replacement therapy (HRT) for some patients in menopause, estrogen-only HRT, but not estrogen + progesterone HRT increased the risk of suffering meningioma according to a large scale clinical study of

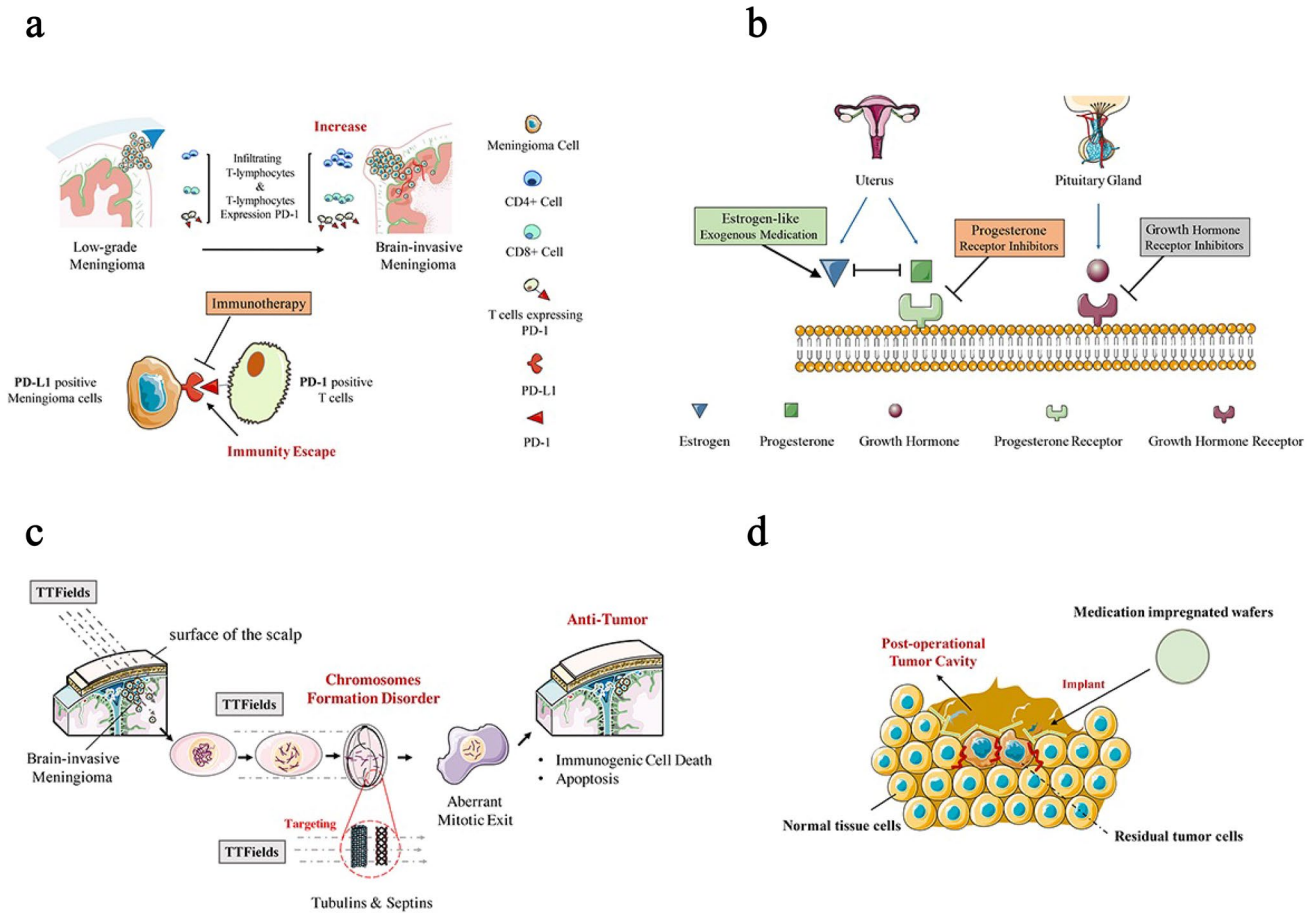

Fig. 4 Schematic overview of other promising treatments for brain-invasive meningiomas. **a** current immunotherapy strategy in meningioma, anti-PD1 drugs pembrolizumab, and nivolumab are undergoing clinical trials in recurrent or residual high-grade meningiomas. **b** hormone replacement in the treatment of brain-invasive meningiomas. **c** Tumor treating fields are identified to disrupt the mitotic process in dividing meningioma cells which leads to violent membrane blebbing, subsequently induces immunogenic cell death. **d** schematic illustration of potential biodegradable copolymers (wafers) impregnated chemotherapy for brain-invasive meningioma

women [129–131]; HRT without supplementing oral contraceptive also play a role in meningioma formation [132].

Progesterone receptor is detected in 58–83% of meningiomas, while estrogen receptor is only reported in 0–8% of this disease [133]. The high expression rate of the progesterone receptor provides a potential therapeutic target for growth inhibition of meningiomas. This concept is supported by a phase II clinical study showing modest clinical regression of meningiomas by blocking progesterone receptors with the anti-progestational agent mifepristone [134]. However, the recent double-blind phase III clinical trial by Ji et al. [135] proved that mifepristone failed to control the unresectable meningioma. The role of the antiandrogenic drug in controlling meningioma is presenting controversial and in need of further evidence to clarify their potential effect [136]. As the antagonist of progesterone, estrogen-like exogenous exposures are associated with a lower risk of meningioma in men [137].

Studies also demonstrate that the status of the GH/IGF-1 axis is significantly associated with the progression rate of meningiomas. Blockade of the GH receptor on the Growth of the tumor cells can be inhibited in vitro by blocking the

Table 1 Selected papers predicting/demonstrating the benefit of targeting/chemotherapy in patient with meningioma (Part I)

Type of trial	Pertinent findings	Author/Year/Reference	Trial number
Phase II clinical trial	***Lapatinib*** has growth-inhibitory effects on progressive meningiomas in NF2 patients	Osorio et al./2018/[114]	NCT00973739
Phase II clinical trial	The combination of ***everolimus*** and ***bevacizumab*** is well-tolerated and produces stable disease in patients with recurrent meningioma	Shih et al./2016/[145]	NCT00972335
Phase II clinical trial	No firm conclusions can be drawn about the combination of ***imatinib*** and ***HU***	Mazza et al./2016/[113]	NCT01125046, NCT00972335
Phase I/II clinical trial	No effect of ***HU*** or ***verapamil*** on meningioma recurrence, PFS, and in vivo tumor burden reduction. Drug delivery to the tumor may be a major limitation	Karsy et al./2016/[146]	NCT00706810
Phase II clinical trial	***(90)Y-DOTATOC*** and ***(177)Lu-DOTATOC*** are promising tools for treating progressive unresectable meningioma	Marincek et al./2016/[147]	N.A
Retrospective study	Study shows a considerable response in patients with WHO grade II and III meningioma treated with ***bevacizumab***	Furtner et al./2016/[148]	N.A
Phase III randomized clinical trial	Long-term administration of ***mifepristone*** is well tolerated but has no impact on patients with unresectable meningioma	Ji et al./2015/[135]	N.A
Phase II clinical trial	***Pasireotide LAR*** has limited activity in recurrent meningiomas	Norden et al./2015/[149]	N.A
Phase II clinical trial	***Sunitinib*** is active in recurrent atypical/malignant meningioma patients	Kaley et al./2015/[123]	NCT01125046
Phase II clinical trial	***Y-DOTATOC*** may represent a promising second- or third- line therapeutic option for complex meningiomas	Gerster-Gillieron et al./2015/[150]	N.A
Phase II clinical trial	The study failed to provide evidence to support the use of monthly long-acting ***somatostatin analogue*** schedule in recurrent high-grade meningiomas	Simo et al./2014/[151]	N.A
Phase II clinical trial	Patients with surgery and radiation refractory recurrent meningiomas treated with ***PTK787/ ZK 222,584*** show elevated PFS-6 and median PFS	Raizer et al./2014/[152]	NCT 00,348,790
Phase II clinical trial	***Imatinib*** plus ***hydroxyurea*** is well tolerated among patients with meningioma but has modest antitumor activity for this indication	Reardon et al./2012/[153]	N.A
Retrospective study	Study shows a significant response to ***bevacizumab*** in patients with atypical or anaplastic meningioma	Nayak et al./2012/[154]	N.A
Retrospective study	Study suggests ***bevacizumab*** activity in recurrent or refractory meningioma	Lou et al./2012/[155]	N.A

NF2 neurofibromatosis type 2, *HU* hydroxyurea, *LAR* long-acting Release, *PTK787/ZK 22,584*: 1-[4-chloroanilino]-4-[4-pyridylmethyl] phthalazine succinate, *PFS* progression-free survival

GH receptor [138]. The antitumor effect of a kind of GH receptor antagonist pegvisomant against intracranial meningiomas has been demonstrated in animal models [139]. But the clinical trial of the GH receptors' anti-meningioma effect is still lacking. For the correlation between hormone and growth of meningioma, and unsatisfied clinical outcomes of hormone therapy on regressing meningioma, more studies of other hormone receptor inhibitors and the exogenous hormone-like supplement treatment are urgent for providing a novel avenue to curing meningioma (Fig. 4b).

Future perspectives

Brain invasion in meningiomas is correlated with a poor prognosis and an increased risk of recurrence. Once brain invasion has occurred, the therapeutic options for treating meningiomas include surgical resection, radiotherapy, and chemotherapy. The location and biological features of the tumor may limit total resectBesidesition, meningiomas are usually not very sensitive to radiotherapy, and conventional chemotherapy remains controversial. Thus, treating patients with brain-invasive meningiomas, particularly after surgery and radiotherapy, represents an unmet need in neuro-oncology. In this article, we reviewed various aspects of brain invasion in meningiomas, molecular mechanisms of invasion and related targeting agents, and other promising strategies that may use as potential approaches to directly treat brain invasion.

Brain invasion is considered a multiple-step process with several factors involved, such as meningioma tumor cells, microenvironment resident cells, extracellular matrix components, tissue-degrading enzymes, cell adhesion molecules, and various growth factors and receptors. The establishment of meningioma cell lines [140–142] and recent animal models [143] will surely provide a good opportunity to explore the molecular mechanisms involved in invasion and design novel therapeutic approaches to prevent repeat surgeries and radiotherapy. Since meningiomas are derived from arachnoidal cells of the leptomeningeal layer, many agents that have failed for other brain tumors due to the low permeability of the blood–brain barrier may be effective for meningiomas.

Table 2 Selected papers predicting/demonstrating the benefit of targeting/chemotherapy in patient with meningioma (Part II)

Type of trial	Pertinent findings	Author/Year/Reference	Trial number
Phase II clinical trial	Study of ***subcutaneous octreotide*** in adults with recurrent or progressive meningioma	Johnson et al./2011/[156]	NCT00813592
Phase II clinical trial	***Erlotinib*** or ***gefitinib*** in patients with recurrent meningioma when Phase II clinical trial	Norden et al./2010/[115]	N.A
Phase II clinical trial	***Imatinib mesylate*** activity for treating recurrent meningioma	Wen et al./2009/[157]	N.A
Phase I clinical trial	***PRRT*** with ***(90)Y-DOTATOC*** can interfere with the growth of meningiomas	Bartolomei et al./2009/[158]	N.A
Phase II clinical trial	Treatment with ***IFN-alpha*** for recurrent meningiomas is tolerated moderately well and modestly effective	Chamberlain and Glantz/2008/[159]	N.A
Phase II clinical trial	***Somatostatin analogues*** may offer a novel, relatively nontoxic alternative treatment for recurrent meningiomas	Chamberlain et al./2007/[160]	N.A
Phase I clinical trial	Minor regression of meningioma that can result in significant clinical benefit is suggested in the male and premenopausal female subgroups of patients treat with ***mifepristone***	Grunberg et al./2006/[134]	N.A
Phase I clinical trial	***Hydroxyurea*** treatment is of marginal efficacy for meningioma	Fuentes et al./2004/[161]	N.A
Phase I clinical trial	***Hydroxyurea*** has not shown effectiveness in the treatment of non-resectable slow-growing meningiomas	Loven et al./2004/[162]	N.A
Phase II clinical trial	No recurrent meningioma patient demonstrated a neuroradiographic complete or partial response to ***TMZ***	Chamberlain et al./2004/[163]	N.A
Phase I clinical trial	***Hydroxyurea*** arrests progression of unresectable or recurrent benign meningiomas	Mason et al./2002/[164]	N.A
Phase II clinical trial	***IFN-alpha*** seemed to be an effective oncostatic drug for meningioma	Muhr et al./2001/[165]	N.A
Prospective study	***Hydroxyurea*** for treatment of unresectable and recurrent meningiomas: decrease in the size of meningiomas	Schrell et al./1997/[166]	N.A
Phase I clinical trial	***IFN-alpha*** is effective in the treatment of recurrent malignant meningiomas	Kaba et al./1997/[167]	N.A
Phase II clinical trial	A definite recommendation for the use of ***tamoxifen*** in refractory meningiomas cannot be made	Goodwin et al./1993/[168]	N.A

PRRT peptide receptor radionuclide therapy, *IFN-alpha* interferon alpha, *TMZ* temozolomide

Based on previous results, the number of potential molecular targets, molecular inhibitors, and drug combinations have increased dramatically. However, the selection of the most promising candidates or their combinations for clinical trials is becoming particularly important. It is now established that targeted therapies are active only in the tumor subsets which feature oncogenic activation of targets, as documented by the impressive efficacy of BRAF inhibitors in BRAF-mutant melanomas and anaplastic lymphoma kinase (ALK) inhibitors in *ALK*-translocated non-small cell lung cancers [144]. Since the molecular pathogenesis of meningiomas and the critical molecular changes driving the brain-invasion of these tumors are still poorly understood, the molecular targeting cores remain to be elucidated. Here, we reviewed the most promising brain invasion targets and related agents (Fig. 3) and described reports predicting or demonstrating the benefits of clinical trials in patients with invasive meningiomas (Tables 1, 2). In the near future, more preclinical studies and clinical trials targeting extracellular matrix degradation enzymes (such as MMPs, uPA-uPAR, lysosomal cysteine, HGF/c-MET), cell adhesion molecules (such as integrins, E-cadherin/β-catenin) and various growth factors (such as EGF/EGFR, TGF-α, PDGF/PDGFR, VEGF/VEGFR) should be conducted to determine the efficiency of related inhibitors for brain-invasive meningiomas. If some of these options show promise, can we further functionally predict whether a meningioma patient will be sensitive to related inhibitors before treatment? For those brain-invasive meningiomas without a predominant genetic marker, a wide-spectrum inhibitor that targets several important signaling pathways may be needed or combined with other approaches including immunotherapy and hormone therapy.

Conclusion

Despite excellent outcomes from surgery and radiotherapy in most meningioma cases, there remains a small subset of patients with brain-invasive meningioma who are refractory to conventional therapies. It is of great importance to identify alternative therapies for these patients. Understanding the crucial mechanisms of brain invasion will promote the development of more effective targeted molecular agents. Moreover, the success of these potential targeted agents and therapeutic options may offer an opportunity to improve the therapeutic strategies for brain-invasive meningiomas.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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