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Brain Pathology

INVITED REVIEW

Molecular neuropathology of brain-invasive meningiomas

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Abstract

Invasion of brain tissue by meningiomas has been identified as one key factor for meningioma recurrence. The identification of meningioma tumor tissue surrounded by brain tissue in neurosurgical samples has been touted as a criterion for atypical meningioma (CNS WHO grade 2), but is only rarely seen in the absence of other high-grade features, with brain-invasive otherwise benign (BIOB) meningiomas remaining controversial. While post-surgery irradiation therapy might be initiated in brain-invasive meningiomas to prevent recurrences, specific treatment approaches targeting key molecules involved in the invasive process are not established. Here we have compiled the current knowledge about mechanisms supporting brain tissue invasion by meningiomas and summarize preclinical models studying targeted therapies with potential inhibitory effects.

KEYWORDS
brain meningioma interface, invasion, meningioma

1 | INTRODUCTION

As one of the hallmarks of cancer, cellular invasion and migration facilitate progression and metastasis in a variety of cancers. The underlying cellular mechanisms for this phenomenon have been subject of extensive research and hold promise to yield future therapeutic options [1]. While metastasis of meningiomas is extremely rare [2, 3], tissue invasion is common and has wide implications for the treatment and clinical course of these tumors. More aggressive growth patterns, the predisposition for recurrence, and worse prognosis led to the acceptance of brain invasion as a stand-alone grading criterion for atypical grade 2 meningioma in 2016 [4]. Nevertheless, the significance of this finding in BIOB meningiomas remains unclear [5]. Whereas some studies show a higher frequency of recurrences in such cases, other do not; this discrepancy is likely, in part, because most brain-invasive meningiomas already show other high-grade features, but also because histologic brain invasion is not always uniformly defined and/or interpreted among pathologists and investigators [6–15].

While the clinical impact of brain invasion has been reported widely, the actual molecular mechanisms involved in migration and invasion of meningioma are less apparent in the literature. Since the understanding of these concepts is critical for the development of tailored therapeutic approaches for invasive meningioma [16], this review pursues the goal of providing an overview of the cellular components and molecular mechanisms involved.

Niklas von Spreckelsen and Christoph Kesseler contributed equally to this work.

2 | MATERIALS AND METHODS

A systematic search was performed in both the Embase and PubMed databases. Using the Emtree/MeSH terms, "meningioma AND invasion" as well as "meningioma AND migration" were searched. Results were merged and conference abstracts as well as non-English articles removed. The remaining titles and abstracts were then screened for relevance to this review and 224 sources were selected for detailed review. For the corresponding PRISMA flow chart [17], see Figure S1.

3 | GENERAL FEATURES OF CELL INVASION AND MIGRATION

Invading cells rely on an armamentarium of programs and signaling pathways to migrate along or invade given structures. For an in-depth understanding of general cellular migratory mechanisms, we refer the reader to several excellent previously published reviews [18–20]. In brief, these mechanisms can involve migrational patterns, cytoskeletal dynamics, cell-cell, and cell-extra cellular matrix (ECM) adhesion properties, partial digestion of the ECM through proteolytic activity, as well as production of chemokines and growth factors. The interplay of all these cellular pathways determines if and how a given cell or a cell complex invades adjacent tissue.

The detailed mechanisms involved in these processes are dependent on the tumor type and the tissue composition and can result in local invasion in continuity (e.g., breast cancer), clustered invasion detached from the primary tumor, or single-cell migration (e.g., melanoma) resulting in metastases [21]. Different molecular modulators have been implicated to enhance invasion/cancer cell migration in a variety of cancers. Growth factors such as HGF (prostate cancer) [22], FGF-2/FGFR4 (colorectal cancer) [23], TGFβ (NSCLC, gastric cancer, metastatic breast cancer, prostate cancer, etc.) [24], VEGF (prostate cancer, glioblastoma) [25] and chemokines i.e. IL-6 (head and neck cancer, ovarian cancer, bone metastasis), and CXCL12/CXCR4 (prostate cancer, mammary adenocarcinoma) all have been shown to drive invasion in the named specific cancer types [26]. Similarly, cytoskeletal organization and adhesion systems have been shown to play a vital part in tumor cell invasion from melanoma, colon, breast, and lung cancers [27].

In meningioma, the invasion is local and collective and, in contrast to gliomas or metastatic malignancies [28, 29], meningiomas do not necessarily follow existing neuronal or vascular structures. Therefore, a unique combination of molecular factors supporting meningioma invasion into the brain can be assumed.

The structure critical for supporting or preventing brain invasion is the so called "brain-meningioma interface." First classified into four categories by Nakasu et al. in 1989 (smooth, lobular, finger-like expansion and invasive) it has since been subject to a vast amount of studies into invasive growth of meningiomas [30]. The different invasion types (bone invasion, perivascular growth along the Virchow-robin-spaces and direct brain invasion, Figure 1) and the existence of a peritumoral "capsule" composed of hyperplastic arachnoid trabeculae, determine whether tumors can be surgically removed without violating the adjacent pia or nervous tissue [31]. The factors determining invasive growth patterns on the cellular level are diverse and subject of this review.

3.1 | Cytoskeleton alterations

The cytoskeleton plays a central role in cell migration. Fluctuating cytoskeletal polymerization at different edges of the cell allow for the formation of cell protrusions (lamellipodia and/or filopodia) (Figure 2A–D) [32, 33]. This enables the cell to migrate by protruding one edge

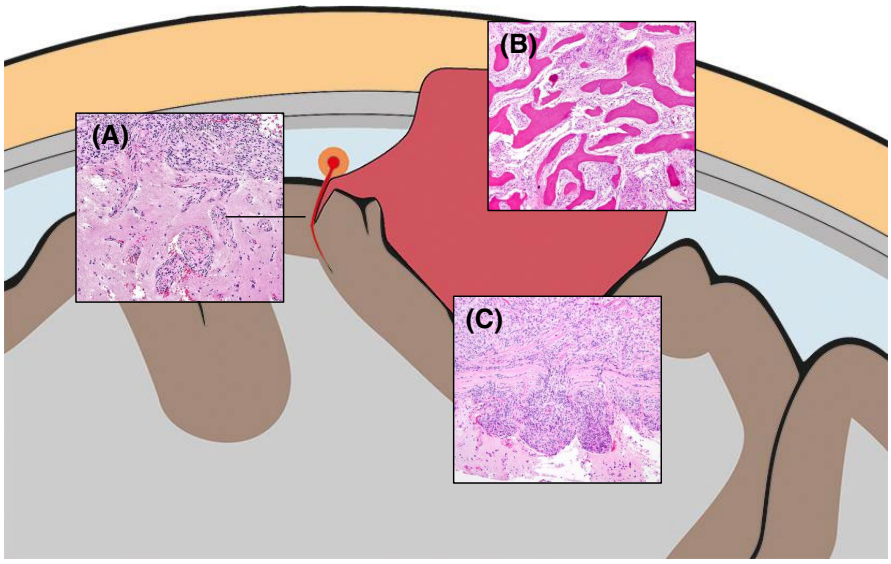

FIGURE 1 Schematic summary of structures with potential involvement in meningioma tumor invasion. (A) invasion along the perivascular Virchow-Robin space, (B) bone invasion, (C) brain invasion

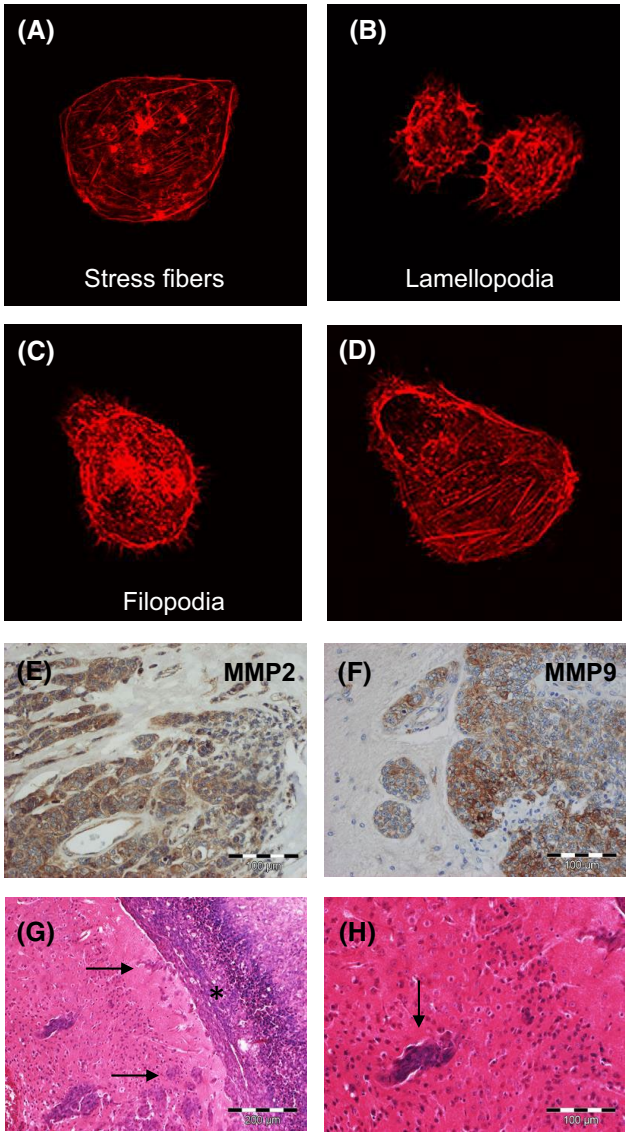

FIGURE 2 Molecular neuropathology of invasive meningiomas. (A–D) Confocal imaging of IOMM-Lee meningioma cells showing morphological cell changes associated with single-cell invasion (A: stress fibers, B: lamellopodia, C: filopodia, D: combination of all three mechanisms). (E and F) Invasive meningiomas show upregulation of matrix metalloproteinases at the brain invasion front (E: MMP2, F: MMP9). (G and H) IOMM-Lee cell invasion in orthotopic mouse models. (G) Mouse IOMM-Lee xenografts with tumor formation (*) and several island-like invasion (arrow). (H) Perivascular meningioma cell spreading in the IOMM-Lee xenograft model

and retracting the other. The polymerization processes are influenced by several factors often interacting with actin and are directly involved in cytoskeletal migration [34]. In the context of meningiomas, only a few studies have focused on cytoskeletal alterations and their relation to invasion. Phosphorylated vimentin (an intermediate filament) has been shown to be a marker for non-infiltrative tumor types [35]. Immunohistochemical (IHC) staining for cortactin and fascin-1, both involved in actin remodeling, revealed higher expression levels in high-grade meningiomas [36, 37]. In a functional study investigating transgelin (TAGLN), downregulation of this actin-binding protein reduced invasion, while its overexpression promoted invasion of high-grade meningioma [38, 39].

A prominent factor interacting with actin in meningioma is the tumor suppressor gene *NF2* with its gene product merlin. *NF2* alterations are found in about half of sporadic meningiomas [40, 41]. However, the organization of the actin cytoskeleton by merlin seems to be independent from its tumor suppressor function [42].

Another key component for regulating cytoskeletal arrangements are the Rho family GTPases. As a target of many signaling cascades involved in migration they act as molecular switches controlling the formation of lamellipodia and filopodia [43]. In invasive meningioma, aberrant hypermethylation of DLC1, a GTPase-activating protein with tumor suppressor activity, can lead to increased Rho activity and consequently to an increased invasive potential [44]. Vav3, a guanine nucleotide exchange factor for Rho family GTPases, has been shown to be upregulated in invasive meningiomas [45]. These data suggest that upregulation of Rho-driven cytoskeletal rearrangements seems to play a role in the invasiveness of meningioma.

3.2 | Cell-cell and cell-extracellular matrix interactions

Adhering and reacting to surrounding cells and the extracellular matrix (ECM) is a second vital requirement for migration and invasion. The proteins directly involved in this process are mainly cell surface adaptors and receptors for mechanotransduction and signaling [19]. Integrins and cadherins are the most reported protein families in this context.

Integrins are versatile heterodimeric surface receptors of which each subtype can bind certain surrounding molecules or scaffolds. When bound to an extracellular ligand they mediate mechanotransduction to the cytoskeleton through different adaptor proteins and can therefore serve as an anchor and/or support cell motility. In meningioma, it has been demonstrated that integrins are widely expressed in a subtype and grading-dependent manner [46]. The integrins αvβ1, αvβ3, αvβ5 have been directly implicated in invasion [47–50]. Integrins seem to provide a reasonable target for specific anti-invasive therapy in meningioma, with two studies reporting promising results using preclinical orthotopic mouse meningioma models [50, 51].

The cadherin family consists of surface-bound glycoproteins. These calcium-dependent molecules play a vital role in the formation of adhesion-junctions, interact with the cytoskeleton through catenin, and directly influence signaling pathways [52]. The loss of E-cadherin and switch to N-cadherin is part of the epithelial to mesenchymal transition (EMT), a dynamic process resulting in increased motility and invasiveness of a given cancer cell [53]. Accordingly, several studies have attempted

to correlate E-cadherin expression with WHO grade and invasiveness, but the reported results are ambiguous. Some datasets provided a significant correlation between low E-cadherin levels and higher WHO grade [54, 55], while others failed to find an association [56–59]. Another important protein closely tied to E-cadherin is β-catenin. As an integral part of adherens junctions, it contributes to tight cell adhesions, but in addition plays a large role in the Wnt signaling pathway. Catenin expression in meningioma correlates inversely with WHO grade, recurrence, and invasion [55, 60, 61].

Further regulation of these cell-cell and cell-ECM interactions is mediated through the density-enhanced phosphatase-1 (DEP-1, CD148). While this has been shown for other cancers [62], Peterman et al. showed that DEP-1 inhibits motility, invasion and DEP-1 deficiency results in reduced cell-matrix adhesion and enhanced cell motility specifically in meningioma cells [63].

Other molecules known to be involved in adhesion regulation in meningioma whose expression levels seem to correlate with invasion and WHO grade include osteopontin, periostin (ligand for CD44), and I-CAM1 (CD54) [36, 37, 54, 64, 65].Another protein that is well established in the context of tumor cell invasion in other cancers but with a unclear role in meningioma is CD44. As a critical membrane-bound proteoglycan for promigratory signaling and mechanotransduction in other cancers, in meningioma the expression seems to be correlated with invasion and WHO grade in some studies [64, 66, 67]. Interestingly, a paucity of CD44 expression in meningiomas (in contrast to gliomas) has been attributed to a non-infiltrative phenotype [68]. However, most of the studies related to adhesion molecules in meningioma are based on immunohistochemical evaluation of human tumor samples, while in-depth functional studies using meningioma cells are scarce. The correlations of the above-mentioned factors with invasive potential in meningioma are summarized in Tables 1 and 2.

4 | ECM, ITS COMPONENTS AND ENZYMATIC ALTERATIONS

Just as a change in receptor status can alter cell adhesion properties, changes of the ECM have been implicated in determining invasive growth patterns [69]. While Rooprai et al. showed that different ECM proteins like collagen IV, laminin, vitronectin and fibronectin cause different invasion patterns in vitro, their expression levels in meningioma tissues do not correlate with WHO grades, with the exception of laminin γ1 which seems to be more prevalent in WHO grade 3 tumors [70–72]. Conflicting results are reported on secreted protein, acidic and rich in cysteine (SPARC). As a basement membrane protein involved in cell–ECM interaction, the majority of studies have found increased expression level in invasive meningioma [45, 73–75]. However, when specifically looking at the adjacent basement membrane in brain-invasive meningiomas, Schittenhelm et al. did not observe a correlation of meningioma invasion and SPARC expression [76]. Moreover, the immunoexpression of SPARC was reported to be independent from WHO grade and invasion recently [77].

The role of growth factors and their receptors in relation to meningioma invasion is unclear so far. While growth factors such as VEGF, EGF, bFGF, TGF-β1 and HGF/SF have been implicated in tumor progression and invasion in other cancers [78], in meningioma only VEGF expression seems to correlate with WHO grade and none are increasingly expressed in invasive meningiomas [79, 80]. While exogenous addition of growth factors such as TGF-β, PDGF, and VEGF can trigger increased invasion in vitro, they seem to play a secondary role in meningioma invasion in vivo [63, 81, 82].

4.1 | Interplay of proteases and their inhibitors

As a broad cluster of enzymes, proteases are able to degrade a large part of ECM components and/or different receptors. Their expression levels and the interplay with their inhibitors have been shown to play a prominent role in cancer invasion [83].

One of the three prominent groups of proteases involved in meningioma invasion are the metalloproteinases (MMPs) (Figure 2E,F). A mismatch of MMP expression and their inhibitory counterparts, so called tissue inhibitors of metalloproteinases (TIMPS), can

TABLE 1 Cytoskeletal factors and their impact on invasion in meningioma

Protein	Impact on invasion	Experimental approach	Reference
Phosphorylated Vimentin	Negative correlation	SELDI-TOF Mass. Spec.	[35]
Cortactin	Positive correlation	IHC	[36, 37]
Fascin-1	Positive correlation	IHC	[37]
Transgelin	Increases invasion	Cell culture	[38, 39]
hypermethylated DLC1	Increases invasion	Cell culture	[44]
Vav3	Positive correlation	IHC	[45]

Abbreviation: IHC, immunohistochemistry.

TABLE 2 Relevant proteins involved in cell–cell, cell–ECM interactions, and invasion

Protein	Impact on invasion	Experimental approach	Reference
Integrins αvβ1, αvβ3, αvβ5	Increases invasion, inhibition reduces invasion	Cell culture In vivo IHC	[47–50]
Cadherin E/N	Conflicting data positive and negative correlation reported	IHC	[54–59]
β-catenin	Negative correlation	IHC	[55, 60, 61]
DEP-1	Decreases invasion	Cell culture In vivo	[63]
Osteopontin	Positive correlation	IHC	[36, 37, 64]
Periostin	Positive correlation	IHC	[65]
ICAM1 (CD54)	Positive correlation	IHC	[54]
CD44	Positive correlation	IHC	[54, 64, 66–68]

Abbreviation: IHC, immunohistochemistry.

lead to increased migration and invasion. In meningioma invasion, MMP-9 seems to play the most prominent role. Several studies show that increased MMP-9 expression in meningioma correlates with invasive growth, and downregulation results in inhibition of cell migration and invasion in vitro [84–88].

Similar effects with increased expression levels resulting in invasion and recurrence were shown for MMP-16 [89] or MMP-11 [90] Data on the role of MMP-1 and MMP-2 and the MMP inhibitors TIMP1 and 2 are partially contradicting and overall seem to play a more complex, context-dependent role. While Nordqvist et al. saw no correlation of MMP-2 mRNA levels and tumor invasiveness, Okuducu et al. found an increased immunohistochemical MMP-2 expression in invasive meningioma [31, 57, 70, 85, 86, 91–93].

Besides MMPs, cathepsins are another group involved in ECM degradation. Cathepsins are lysosomal cysteine proteases, which are found to be upregulated in invasive meningiomas as well as astrocytomas. Namely cathepsin B and L were shown to correlate with invasiveness and recurrence and targeted inhibition of cathepsin B reduced migration and invasion in vitro [88, 94, 95]. Inversely, the expression levels of the cysteine proteinase inhibitors (CPIs) stefin A, B, and cystatin C were downregulated in invasive tissue, whereas silencing of stefin B increased invasion [94–96].

An important third type of protease involved in meningioma invasion is the urokinase-type plasminogen activator (uPA). Coupled with its high affinity receptor, urokinase plasminogen activator receptor (uPAR), uPA activates plasmin and triggers a proteolytic cascade in its vicinity known to facilitate metastasis and cancer progression. This also seems to hold true in aggressive meningiomas. High uPA/uPAR levels and uPA activity are found in invasive meningiomas and their knockdown leaves cells less invasive and migratory [92, 97, 98]. The most relevant modulation in the ECM by invasive meningioma therefore seems to be related to enzymatic alterations (Table 3).

5 | TRANSCRIPTION FACTORS AND SIGNALING

All of the above-mentioned processes are regulated partly through transcription factors and modification of signaling pathways. As in other cancers, the PI3K/AKT pathway has been implicated in meningiomas, with involvement in cell-cell and cell-ECM interaction through integrin signaling [65, 99], in the regulation of cytoskeletal integrity [38] and the interplay of proteases and their inhibitors, specifically MMP-9 [88]. Similarly, the focal adhesion kinase (FAK) and its broad downstream effects have been shown to influence migration and invasion after activation through integrins, growth factors, and other ECM components [50, 51, 71, 88, 100, 101]. Other pathways involved include the mitogen-activated protein kinase (MAPK) [88, 99] and the Hippo pathways [102]. While comprehensive pathway analyses with respect to invasion in meningioma are currently lacking, there are individual transcription factors shown to significantly alter or at least correlate with invasion and migration. Among other targets, protein C-ets-1 (Ets-1) positively regulates MMP-2 and MMP-9 and uPA expression and levels of Ets-1 have correlated with both malignancy and invasiveness in meningioma without implicating one specific pathway [86, 97]. The transcription factors Kruppel-like-factor 4 (KLF4) and Retinoblastoma protein-interacting zinc-finger gene 1 (RIZ1) both reduce tumor growth, motility, and invasion while the high mobility group nucleosome binding domain 5 (HMGN5) and forkhead box protein M1 (FOXM1) propagate invasive growth of the given meningioma [103–107].

In addition to transcription factors, micro RNAs (mi-RNAs) have recently been shown to play a role in invasion of meningiomas through post-transcriptional modification. Mi-RNAs regulate translational processes by targeting mRNAs for cleavage or translational repression [108]. In the context of meningioma, miR145, Let-7d,

TABLE 3 Relevant ECM components and enzymes involved in meningioma invasion

Protein	Impact on invasion	Experimental approach	Reference
SPARC	Conflicting data positive and no correlation reported	IHC Cell culture	[45, 73–77]
VEGF, TFG-b, PDFG	Exogenous addition triggers invasion, no correlation with invasiveness in clinical samples	IHC Cell culture In vivo	[63, 79–82]
MMP-1,2/TIMP 1, 2	Conflicting data likely complex/context dependent	ISH IHC Zymography	[31, 57, 70, 85, 86, 91–93]
MMP-9	Correlates with and increases invasion	ISH IHC Cell culture	[84–88]
MMP-11	Correlates with invasion	IHC	[90]
MMP-16	Correlates with and increases invasion	IHC Cell culture In vivo	[89]
Cathepsin L	Correlates with invasion	IHC Cell culture	[94, 95]
Cathepsin B	Correlates with invasion, inhibition reduces invasion	IHC Cell culture	[88, 94, 95]
Stefin A	Negative correlation with invasion	IHC Cell culture	[96]
Stefin B	Negative correlation with invasion, silencing increases invasion	IHC Cell culture	[96]
Cystatin C	Negative correlation with invasion	IHC Cell culture	[96]
uPA/uPAR	Correlates with invasion, knockdown decreases invasion	IHC Zymography Cell culture In vivo	[92, 97, 98]

Abbreviation: IHC, immunohistochemistry.

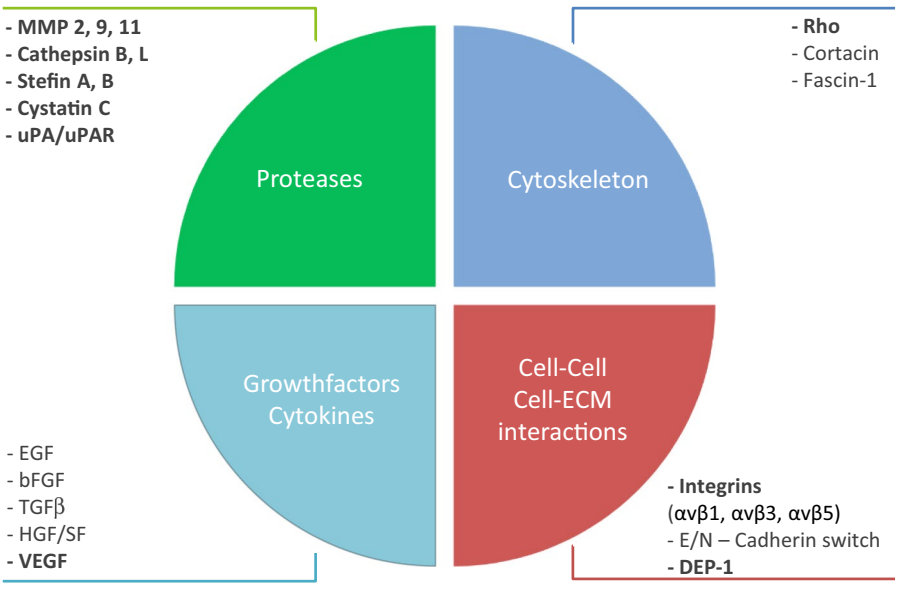

FIGURE 3 Summary of molecular mechanisms acting in meningioma cell invasion

miR-18a, and miR-200a were all shown to negatively regulate proliferation and invasion [109–111].

In summary, until now there has been no comprehensive pathway analyses investigating meningioma invasion. Those involved are likely to include PI3K/AKT, FAK, MAPK, and Hippo pathways. Several single transcription factors have been implicated to contribute to invasion, part of which induce MMP-2 and MMP-9 (Ets-1) and therefore underline the importance of enzymatic ECM alteration in the invasion of meningiomas.

Figure 3 summarizes the different aspects of molecular mechanisms driving meningioma invasion.

6 | IN VIVO MODELS FOR MENINGIOMA INVASION

In order to identify key drivers of meningioma cell invasion, it is mandatory to have systems at hand enabling the specific modification of a given factor, and studying the interaction between meningioma cells and brain tissue. Unfortunately, the availability of such experimental systems is limited so far. Few groups have used classical orthotopic xenograft models with implantation of meningioma cells at convexity or skull base. While in most studies, the focus has been on overall survival or unraveling of positive drug effects on meningioma cell growth [112], only occasionally has the combination of modified cells, treatment, and analysis of brain invasion been acknowledged [50, 51, 109, 113] (Figure 2G,H). An interesting model to monitor brain invasion in mice by handheld confocal microcopy offers a nice opportunity to study the dynamics of brain invasion in mice [114]. Another exciting approach recently published is the establishment of organoid models, either patient-derived or based on established meningioma cell lines [115]. Sophisticated co-culture models studying the interaction between meningioma cells and astrocytes/neurons to elucidate the dynamics acting at the brain–meningioma interface are lacking so far.

7 | SUMMARY

Meningioma represents a unique type of intracranial tumor with both mesenchymal and epithelial features, and beside the pure tumor proliferation/growth, the capacity to invade surrounding structures with the potential consequence of worse clinical outcome represents a process which is not well understood so far. While the mechanisms of epithelial-to-mesenchymal transition well known to participate in cancer cell invasion are less likely to be relevant in meningioma, the remodeling and modification of extracellular matrix proteins seem to be the dominating feature. However, the available data are limited because the majority of studies have used correlative approaches linking invasiveness with different proteins in vitro or analyzing human meningioma samples for expression. To characterize such a complex mechanism, more sophisticated methods than previously used are necessary to capture intratumoral differences that may arise due to different migratory programs. Simple immunohistochemical approaches and collective protein expression analysis might not sufficiently elucidate the diverse local intratumoral expression dynamics. Single cell analyses and better models of invasion might help in future studies.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTION

Niklas von Spreckelsen: literature search, writing, artwork. Christoph Kesseler: literature search, figures. Benjamin Brokinkel: literature search, proofreading. Arie Perry: figures, proofreading. Roland Goldbrunner: proofreading. Christian Mawrin: concept, figures, writing, proofreading.

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FIGURE S1 Flowchart for literature screening

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