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EXPERIMENTAL RESEARCH

Proteins involved in regulating bone invasion in skull base meningiomas

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Abstract
Background Bone invasive skull base meningiomas are a subset of meningiomas that present a unique clinical challenge due to brain and neural structure involvement and limitations in complete surgical resection, resulting in higher recurrence and need for repeat surgery. To date, the pathogenesis of meningioma bone invasion has not been investigated. We investigated immunoexpression of proteins implicated in bone invasion in other tumor types to establish their involvement in meningioma bone invasion.
Methods Retrospective review of our database identified bone invasive meningiomas operated on at our institution over the past 20 years. Using high-throughput tissue microarray (TMA), we established the expression profile of osteopontin (OPN), matrix metalloproteinase-2 (MMP2), and integrin beta-1 (ITGB1). Differential expression in tumor cell and vasculature was evaluated and comparisons were made between meningioma anatomical locations.
Results MMP2, OPN, and ITGB1 immunoreactivity was cytoplasmic in tumor and/or endothelial cells. Noninvasive transbasal meningiomas exhibited higher vascular endothelial cell MMP2 immunoexpression compared to invasive meningiomas. We found higher expression levels of OPN and ITGB1 in bone invasive transbasal compared to noninvasive meningiomas. Strong vascular ITGB1 expression extending from the endothelium through the media and into the adventitia was found in a subset of meningiomas.
Conclusions We have demonstrated that key proteins are differentially expressed in bone invasive meningiomas and that the anatomical location of bone invasion is a key determinant of expression pattern of MMP1, OPN, and ITGB1. This data provides initial insights into the pathophysiology of bone invasion in meningiomas and identifies factors that can be pursued as potential therapeutic targets.

Keywords Bone invasion · Integrins · Matrix metalloproteinase · Meningioma · Osteopontin · Transbasal meningioma

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Introduction

Meningiomas are dural-based intracranial neoplasms that are thought to arise from arachnoid cap cells. The majority of meningiomas are benign tumors with only approximately 5 % exhibiting features of malignancy [2]. The World Health Organization (WHO) classifies meningiomas into three grades, with grade I comprising 90 % of the tumors and exhibiting benign histopathological features, grade II showing atypical features, and grade III having anaplastic or malignant features [39]. Histopathological features associated with aggressive behavior include increased cell density, a higher nuclear-to-cytoplasmic ratio, a sheet-like growth pattern, prominent nucleoli, elevated mitotic index, and necrosis. The presence of brain invasion is a feature considered to predict aggressive clinical behavior and recurrence, and is more recently used as a diagnostic criterion for WHO grade II designation [39].

A subset of meningiomas invade bone, create significant hyperostosis, and infiltrate adjacent neural and soft tissue structures [2, 5, 34]. In such cases, the proportion of the tumor growing in the bone and soft tissues can in fact be much larger than the intradural component, suggesting preferential bony tropism. Bone invasion is not factored into the WHO criterion for grading of meningiomas, however, the extent of bone invasion can bear directly on the clinical behavior of meningiomas, and more importantly, patient outcome. Bone-invasive skull base meningiomas pose a specific clinical challenge, as incomplete tumor resection carries both an increased risk of compromise of vital vascular and neural structures in addition to the risk of recurrence.

To date, there have been no studies that focus on the pathophysiology of bone invasion and bone tropism in meningiomas. Integrins, OPN, and MMPs are thought to play key regulatory roles in bone invasion and osteolytic metastasis in other tumors such as breast, prostate, and lung [7–9, 13–15, 20, 22, 32, 50]; however, what role, if any, these molecules play in the bony tropism of meningiomas is not known. As a first step toward understanding the molecular mechanisms of bone invasion, we focused our study on distinct clinical subpopulations of skull base meningiomas that exhibit characteristic bone tropism. Based on clinical, radiological, and surgical characteristics, we defined two categories of skull base bone-invasive meningiomas: spheno-orbital and transbasal anterior skull base meningiomas, with their control counterparts being sphenoid wing and noninvasive anterior skull base meningiomas, respectively. We used TMA to analyze the expression profile of MMP2, OPN, and ITGB1 in these tumors.

Materials and methods

Tumor samples

Following institutional research ethics board approval, we reviewed a database of all surgically resected meningiomas from the past 20 years at our institution. Radiological and surgical criteria were used to select bone-invasive spheno-orbital or transbasal anterior skull base tumors and their control counterparts, sphenoid wing and noninvasive anterior skull base meningiomas, respectively. We chose to study only WHO grade I meningiomas to avoid bias due to tumor grade. Demographic data representing bone-invading and noninvading skull base meningiomas are summarized in Table 1.

TMA construction

Stained slides and formalin-fixed, paraffin-embedded, tissue specimens were obtained from our archives, and original diagnoses were reviewed by neuropathology (SC). Regions of representative tumor were identified on the slides and the corresponding areas of tissue circled on paraffin blocks. TMA construction was performed with a semi-automated tissue arrayer (Pathology Devices, Westminster, MD, USA) using a 1.5-mm coring needle. The sample cores were embedded in a single paraffin block. A control hematoxylin and eosin (H&E) stain was performed and the cores were reviewed by neuropathology for tumor integrity.

Immunohistochemistry

Formalin-fixed paraffin-embedded sections of 4μm were dewaxed in xylene and brought down to water through graded ethanol solutions. Antigen retrieval was achieved by incubation in citrate buffer of pH 6.0 for 15 min. Endogenous peroxidase and biotin activities were blocked with 3 % hydrogen peroxide and an avidin/biotin blocking kit, respectively. Nonspecific reactivity was blocked by incubation with 10 % normal goat serum. Tissue was incubated at room temperature with corresponding antibodies (ITGB1, Abcam; OPN, Lab Vision; MMP2, Lab Vision, and CD31, Lab Vision) with previously optimized concentrations. This was followed by incubation with a biotinylated secondary antibody (Vector labs, Burlingame, CA, USA) for 30 min and horseradish peroxidase-conjugated Ultra Streptavidin labeling reagent (ID Labs, London, ON) for 30 min. After washing in Tris buffered solution (TBS), color development

Table 1 Demographic data representing meningiomas in the present study

Meningioma location	*n*	Female	Male	Age	Follow-up (months)	Mass effect	Seizure	Diplopia	Visual acuity
Spheno-orbital invasive	8	6	2	48.3	31 (2–68)	8 (100 %)	1 (13 %)	1 (13 %)	3 (38 %)
Sphenoid wing noninvasive	18	13	5	55.4	33 (0–71)	17 (94 %)	5 (28 %)	1 (6 %)	4 (22 %)
Transbasal invasive	10	6	4	53.4	90 (0–212)	10 (100 %)	2 (20 %)	2 (20 %)	5 (10 %)
Transbasal noninvasive	23	16	7	42.5	28 (0–194)	22 (96 %)	7 (30 %)	2 (9 %)	8 (35 %)
All invasive	18	12	6	56.8	52 (0–212)	21 (100 %)	3 (14 %)	3 (14 %)	8 (38 %)
All noninvasive	41	29	12	49	30.5 (0–194)	39 (95 %)	12 (29 %)	3 (7 %)	12 (29 %)
Total	59	41	18	52.9	41.3	60 (97 %)	15 (24 %)	6 (10 %)	20 (32 %)

was done with NovaRed solution (Vector Labs Cat# SK-4800). Counterstaining was performed with Mayer's hematoxylin. The slides were then dehydrated in graded ethanol solutions, cleared in xylene, and mounted in Permount (Fisher, Pittsburg, PA, USA, cat# SP15-500).

Microscopy and analysis

The slides were scanned and visualized using the MIRAX digital slide scanning application (Carl Zeiss MicroImaging GmbH, Jena, Germany). The immunohistochemical expression of OPN, ITGB1, and MMP-2 were semi-quantitatively scored for intensity and percentage of immunoreactive cells. Intensity was graded from 0 to 2 (0: none, 1: mild/moderate, 2: strong), and percentage was scored from 0 to 3 (0: none, 1: <25 %, 2: 25–50 %, 3: >50 %). The intensity and percentage scores were then combined to produce a composite immunoscore [36]. Where there was more than one specimen available, an average of the immunoscores for the specimens was calculated.

Statistical analysis

Student's t test assuming unequal variances was used to evaluate differences between groups. A p value of <0.05 was assumed to be significant.

Results

Clinicopathological correlations

Patient demographics and clinical information including pattern of tumor invasion, presenting symptoms, pathological grade, radiological data, and follow-up information was recorded as summarized in Table 1. No differences were found in patient age, sex, meningioma progression, or pathological grade between the two skull base bone-invasive meningioma groups and their control counterparts.

Immunohistochemical analysis of MMP2, OPN, and ITGB1

MMP2

MMP2 was expressed to a variable degree in tumor cell cytoplasm and the immunoscores of MMP2 tumor expression showed no significant difference between spheno-orbital tumors and the control sphenoid wing tumors and between transbasal and anterior skull base control meningiomas (Table 2). MMP2 expression within tumor vessels was restricted to the endothelium and did not involve the media or adventitia (Table 2). There was significantly lower vascular immunoexpression by bone-invasive transbasal tumors compared to control anterior skull base (p=0.004 one-tailed) (Fig. 1a, b).

OPN

OPN was expressed to a variable degree in tumor cell cytoplasms with the majority of tumors showing only low levels of expression. The immunoscores of OPN in tumor cells showed no significant difference between spheno-orbital tumors and the control sphenoid wing tumors and between transbasal and anterior skull base control meningiomas (Table 2). Vessels demonstrated OPN immunoreactivity, found within the vascular media not the intima or adventitia (Fig. 1d). While statistical comparisons of invasive spheno-orbital vascular to controls failed to reach significance (Table 2), the comparison of invasive transbasal vascular staining to controls demonstrated a significantly greater immunoscore for OPN in the invasive group of tumors (p=0.037 one-tailed) (Table 2).

ITGB1

ITGB1 was expressed to a variable degree within the cytoplasm of tumor cells. The immunoscore of ITGB1 expression within tumor cells showed no significant difference between spheno-orbital tumors and the control sphenoid wing tumors (Table 2). However, there was significantly

Table 2 Immunohistochemical (IHC) staining scores (mean ± SD) of MMP2, OPN, and ITGB1 in ISB (invasive skull base), NISB (noninvasive skull base), IS (invasive sphenoid wing), and NIS (noninvasive sphenoid wing) meningiomas

	Tumor					Vessel				
IHC stain	ISB Mean ± SD	NISB Mean ± SD		IS Mean ± SD	NIS Mean ± SD	ISB Mean ± SD	NISB Mean ± SD		IS Mean ± SD	NIS Mean ± SD
MMP2	1.8±3.9	2.5±1.8		1.6±0.6	1.4±1.9	4±8	6±0 *	p=0.004	6±0	5.2±3.2
OPN	2.3±7.6	1.7±3.7		2.4±3.8	2.4±6.5	4.3±6.2	2.3±4.3 *	p=0.037	4.2±5.8	3.67±6.4
ITGB1	4.6±6.2	2.5±5.5 *	p=0.035	2.6±4.6	4.2±6.1	5.3±1.5	5±3		4.2±5.8	5.5±2.3

Asterisk (*) indicates statistically significant differences

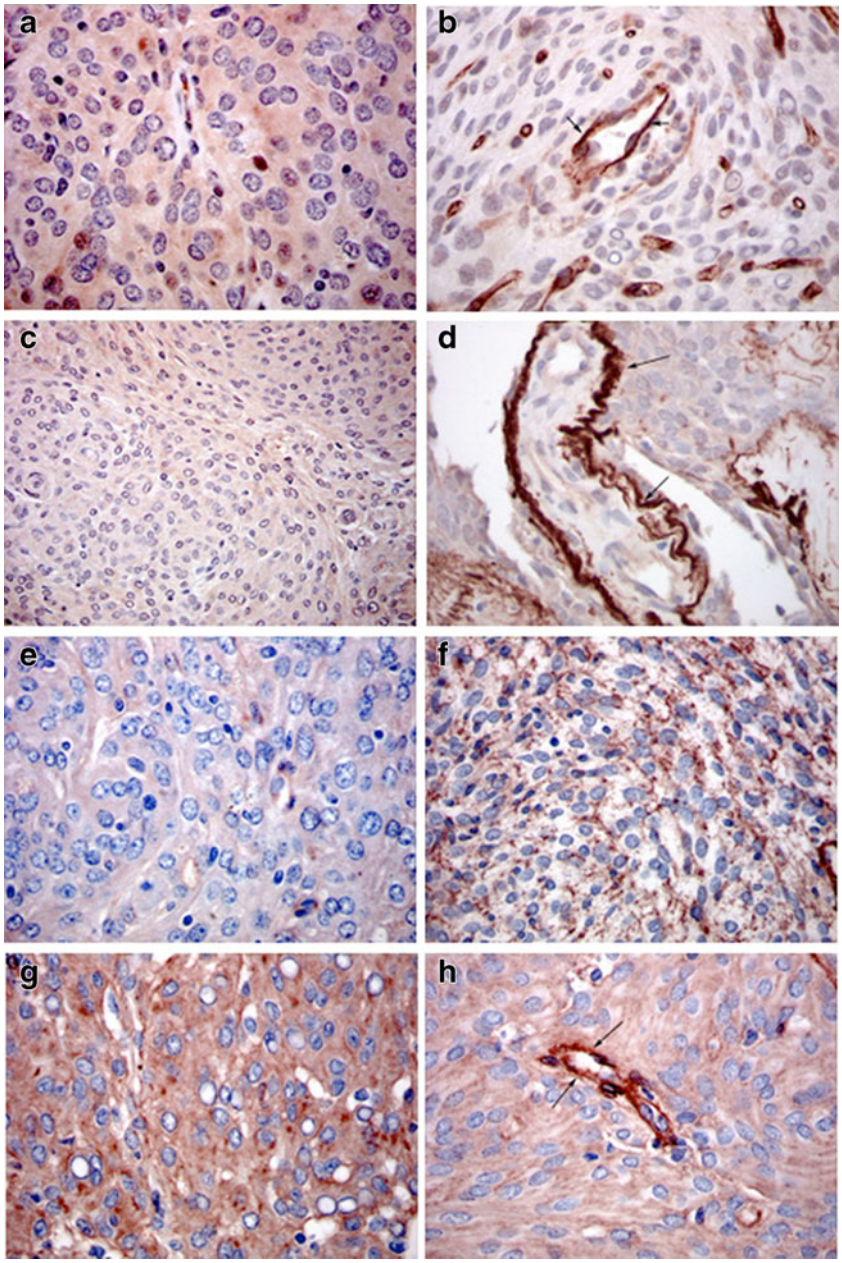

Fig. 1 Immunohistochemical expression of MMP2, OPN, and ITGB1 in bone invasive and noninvasive meningiomas (original magnification ×400). **a** Low vascular MMP immunoexpression in a bone-invading transbasal meningioma. **b** High vascular MMP immunoreactivity in a noninvading skull base meningioma. The *arrows* indicate vascular immunostaining. **c** Low vascular OPN immunoexpression in a noninvading skull base meningioma. **d** High vascular OPN immunopositivity in a bone-invading transbasal meningioma. The *arrows* indicate vascular immunostaining. **e** Low tumoral ITGB1 immunoreactivity in a noninvading skull base meningioma. **f** High tumoral ITGB1 immunoexpression in a bone-invading transbasal meningioma. **g** Low vascular ITGB1 immunopositivity in a noninvading skull base meningioma. **h** High vascular ITGB1 immunoreactivity in a bone-invading transbasal meningioma in multiple layers extending from the endothelium through the media and into the adventitia. The *arrows* indicate vascular immunostaining

greater ITGB1 expression by invasive transbasal tumor cells over anterior skull base controls (p = 0.035 one-tailed) (Fig. 1e, f). Vessels within the tumor demonstrated high levels of ITGB1 in multiple layers extending from the endothelium through the media and into the adventitia (Fig. 1h). Nonetheless, immunoscores showed no difference between the vascular expression of either spheno-orbital or transbasal tumors and their respective controls (Table 2).

Discussion

Meningiomas make up approximately a one-fourth of all intracranial tumors and the WHO identifies 12 distinct histopathological subtypes [2, 12]. The molecular mechanisms of tumor growth and malignant progression are poorly understood and research results have been discordant. This is in part due to the fact that meningiomas are a large heterogeneous group of tumors classified histologically without a molecular or genetic basis [29]. Focusing on studying specific clinical subclasses of meningiomas, as we have done with bone invasion, can potentially help eliminate the heterogeneity in the studies and improve our understanding of the biology of meningiomas. We examined the differential expression profile of MMP2, OPN, and ITGB1 in two subclasses of bone-invasive meningiomas, spheno-orbital and transbasal anterior skull base, and established a distinct anatomical basis to the expression profile of these known bone-modulating factors.

MMP2

MMPs are a family of zinc-dependent peptidases that mediate degradation of extracellular matrix components. MMPs are implicated in tumor cell growth, invasion, and metastasis [11]. The biological role and functional contribution of MMPs is complex and their role in meningiomas is far from established. Previous studies have focused on establishing the role of MMP2 in meningiomas, in particular as it relates to tumor recurrence, brain invasion, and peritumoral edema, and the data is conflicting [10, 19, 21, 23, 24, 26, 28–31, 48]. Though some studies found higher MMP2 expression levels in recurrent meningiomas [28, 48], others have found no association between meningioma grade and MMP2 levels [29]. No correlation between MMP2 expression level and brain-invasive potential of meningiomas has been found to date [23, 24, 26]. Studies focused on the predictive potential of MMP2 on meningioma peritumoral edema have been contradictory, with Paek et al. [30] suggesting a positive association, whereas Panagopolous et al. [31] noted no such association. Yet Jaalinoja et al. [19] found no MMP-2 expression in benign meningiomas altogether.

MMP2 expression has been shown to vary with different meningioma histological subtypes [12, 37]. Rooprai et al. [37] reported the weakest MMP2 expression in meningothelial meningiomas, with the fibroblastic subtype exhibiting the strongest MMP2 expression. Fevre-Montange, using microarray analysis of fibroblastic and meningothelial meningiomas, found MMP2 to be one of the three signature genes that distinguished fibroblastic meningiomas, with the other two signature factors being tenascin and fibulin-1 (FBLN1) [12]. However, others have found no association between meningioma subtype and MMP2 immunoexpression [28, 48]. The variability in results of MMP2 is in part due to meningiomas being a large heterogeneous group of tumors, classified histologically without a molecular or genetic basis and in part due to lack of uniformity in methodology, including use of antibodies and immunohistochemical scoring methods [33].

We found no difference in MMP2 expression between bone-invasive and noninvasive skull base meningiomas by tumor cells. There is, however, a distinct upregulation in vascular expression of MMP2 in noninvasive anterior skull base meningiomas compared to transbasal bone invasive skull base meningiomas. This elevated vascular MMP2 was not seen in the spheno-orbital group, suggesting that anatomical location of bone invasion is an important determinant of proteins involved in regulating their growth, vascular proliferation, and potentially osteolytic activity. Despite the popular assumption that MMPs promote tumor invasion and growth, a recent study revealed that MMP2 overexpression in astrocytoma cells inhibited tumor growth and increased vascular destabilization [44]. The investigators hypothesized that MMP2 may target the activity of other pro- and antiproliferative factors, thereby inhibiting tumor cell proliferation in vivo [44]. Our findings of higher vascular MMP2 expression in noninvasive meningiomas could potentially point towards an inhibitory role for this matrix metalloproteinase in bone invasion through vascular destabilization.

OPN

OPN has been implicated in bone invasion in a number of cancer types and other intracranial tumors [45]. A recent study has proposed OPN expression as a negative prognostic indicator for recurrence of WHO grade I meningiomas [42] during a mean follow-up of 23 nonrecurrent and 9 recurrent meningiomas. As WHO classification does not include bone invasion as one of the criteria, it is unclear from this study if the higher recurrence rate was associated with bone invasion. Recently, Barresi et al. [3] noted OPN expression in psammoma bodies and calcifications, but also within noncalcified nonpsammomatous neoplastic cells of osteoblastic meningiomas, which are benign indolent tumors, suggesting that the findings of Tseng et al. in regard to OPN as a potential negative prognostic indicator should be interpreted with caution [46].

Several studies support the role of OPN in promotion of bone invasion in other tumor types [1, 3, 4, 6, 7, 15–18, 20, 22, 25, 27, 38, 40, 41, 47, 49, 51]. First, OPN is shown to increase bone resorption by osteoclasts in breast carcinomas [22]. Equally, serum OPN levels and immunoexpression are higher in breast tumors metastasized to the bone, with antisense inhibition of OPN in human breast cancer cells attenuating osteolytic metastasis [25, 38]. As well, melanoma cells with OPN expression have a higher rate of lung and bone metastasis when injected into wild-type mice compared to OPN-deficient mice [38, 40].

In the present study, similar to MMP2, OPN expression by tumor cells was not different in bone-invasive meningiomas; however, a significant increase in vascular expression of OPN was seen in transbasal anterior skull base bone-invasive meningiomas. These results, taken together with the MMP2 results, point to bone remodeling being a highly vascular-dependent process and variable based on the anatomical location of meningiomas.

ITGB1

Integrins are shown to mediate bone metastasis and osteoclast activity in neoplasms of breast and prostate [4, 32, 35, 41, 43, 47, 50]. They mediate the adhesion of osteoclasts to bone matrix in breast cancer, thereby stimulating the release of lysosomal enzymes that trigger bone collagen degradation [47].

In our study, ITGB1 was the only one of three factors that had a significantly higher expression in tumor cells of transbasal bone-invasive skull base versus anterior skull base

noninvasive meningiomas. However, similar to MMP2 and OPN, there was no difference in expression in spheno-orbital bone-invasive meningiomas. Once again, these results support the significance of anatomical location governing the difference in biology of transbasal bone invasion versus spheno-orbital meningiomas. Of note is the striking vascular ITGB1 expression found in invasive as well as noninvasive meningiomas, independent of tumor location. ITGB1 stained multiple vascular layers extending from the endothelium through the media and into the adventitia, compared to OPN, which stained only the endothelial cells and MMP2 that stained only the vascular media.

Previous studies focusing on ITGB1 expression in meningiomas are limited to date [4]. Bello et al. [27] found higher ITGB1 expression in atypical and malignant meningioma vasculature as well as tumor cells compared to benign meningiomas. It was noted that tumor vascular ITGB1 immunopositivity was localized to endothelial cells. ITGB1 was also found in vessels present in peritumoral brain tissue, suggesting ITGB1 expression in activated vasculature surrounding tumor tissue, as normal brain tissue is not known to express ITGB1. The significance of ITGB1-mediated pathways was also suggested by the strong correlation between the expression of ITGB1 and vitronectin, an ITGB1-specific ligand required for its activity and promotion of cell migration [27]. This high expression level of ITGB1 in meningiomas makes it a potentially suitable therapeutic target for treatment of unresectable meningiomas.

Conclusions

This study provides initial insights into the expression profile of proteins involved in bone invasion in skull base bone-invasive meningiomas. Of the three factors investigated, MMP2, OPN, and ITGB1, ITGB1 in transbasal anterior skull base bone-invasive meningiomas was the only factor found to be significantly upregulated. Furthermore, transbasal meningiomas demonstrate significantly higher levels of OPN and ITGB1 expression in the tumor vasculature, suggesting a vascular-dependent role for bone invasion in this subset of meningiomas. None of the factors demonstrated significant difference between spheno-orbital bone invasive and their control sphenoid wing meningiomas, whether cytoplasmic or vascular. Our results strongly suggest that the molecular regulators of bone tropism, osteolytic activity, and vascular remodeling of meningiomas is dependent on anatomical location, with transbasal anterior skull base meningiomas showing a distinct differential expression pattern compared to spheno-orbital meningiomas.

Conflicts of interest None.

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