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ORIGINAL ARTICLE

Expression levels of β-catenin and galectin-3 in meningioma and their effect on brain invasion and recurrence: a tissue microarray study

Rehab Allah Ahmed, Abdelhadi M Shebl, Hany Onsy Habashy
Department of Pathology, Mansoura University, Faculty of Medicine, Mansoura DK 35516, Egypt

ABSTRACT

Objective: Meningiomas are neoplasms that arise from the meninges of the central nervous system (CNS). They constitute about 25.6% of CNS tumors diagnosed in Egypt. Some morphological variants of meningiomas display aggressive behavior, leading to brain-invasive growth pattern. Although meningiomas are usually treated by complete surgical excision, the risk of postoperative recurrence remains. Hence, additional biomarkers for predicting aggressive behavior must be discovered. This study aims to explore the clinical and biological relevance of the protein expression levels of β-catenin and galectine-3 in meningioma and to understand the pathobiology of this neoplasm.

Methods: This retrospective study was carried out on 153 cases of meningioma by using tissue microarrays and immunohistochemistry for β-catenin and galectine-3.

Results: High β-catenin expression was significantly associated with transitional and meningiotheliomatous meningiomas, low tumor grade, low recurrence rate, and low incidence of brain invasion. Meanwhile, high galectin-3 expression was associated with brain invasion, recurrence, high tumor grade, and tumor type. Logistic regression analysis indicated that among all variables included in the model, β-catenin and galactin-3 expression levels were significant predictors of tumor recurrence ($P<0.001$).

Conclusions: Galectin-3 and β-catenin are involved in meningioma recurrence but not in brain invasion. These molecules could be important potential therapeutic targets and predictors for meningiomas.

KEYWORDS Immunohistochemistry; meningioma; recurrence; brain invasion; galectin-3 and β-catenin

Introduction

Meningiomas are neoplasms that arise from the meninges of the central nervous system (CNS)[1,2]. Meningiomas constitute 24%–30% of primary intracranial tumors in the USA[3] and 25.6% of CNS tumors in Egypt[4]. Growing meningiomas cause pressure on but do not invade the surrounding brain structures because these tumors are often bound by the pial–glial basement membrane[5]. However, some morphological variants of meningiomas display aggressive behavior, leading to brain-invasive growth pattern[6,7]. These variants are characterized by inward projections of tumor into the adjacent brain tissues without an intervening dura and reactive astrocytosis in the adjoining brain tissues and are considered as grade 2 based on the 2016 WHO classification[1,5,6].

Correspondence to: Rehab Allah Ahmed
E-mail: rehaballah1975@gmail.com
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Complete surgical excision is the preferred treatment for meningiomas, but the risk of postoperative recurrence remains[2]. The most important factors affecting the recurrence of meningiomas are tumor grade, invasion of the surrounding brain tissues, and extent of surgical resection[6,8].

Scholars have studied various biomarkers with predictive and prognostic values for the recurrence and brain invasiveness of meningiomas. These biomarkers include Ki67, Her-2, matrix metalloproteinases, galectin-3, E-cadherin, and β-catenin[6,9,10].

β-catenin, one of the four types of catenins, is attached to the cytoplasmic terminal of E-cadherin to form a complex. The deregulation of β-catenin leads to cellular discohesion and changes in cell morphology[10] and commonly occurs in gastric, colon, and hepatocellular tumors[11,12].

Galectin-3, a member of the family of β-galactoside lectins[13], regulates the cell-to-cell and cell-to-matrix interaction by promoting the adherence of tumor cells to the extracellular matrix and endothelium[14,15]. Galectin-3 also controls cancer metastasis[16], but the underlying mechanism remains unclear[17]. Galectin-3 is expressed in some CNS

tumors, such as astrocytomas and meningiomas[18,19], and in papillary thyroid carcinomas[20]. Galectin-3 regulates the expression and nuclear accumulation of β-catenin and activates the Wnt signaling pathway by regulating the phosphorylation of glycogen synthase kinase-3 beta through the PI3K/AKT pathway in colon cancer cells[21].

To the best of our knowledge, no studies have examined the concurrent expression of β-catenin and galectin-3 in meningiomas. The present study aims to evaluate the expression of these biomarkers in meningiomas through immunohistochemistry (IHC) analysis and determine their association with pathological type and grade, brain invasion, and postoperative recurrence.

Materials and methods

This retrospective study was conducted on 153 patients diagnosed with meningioma in the Faculty of Medicine, Mansoura University, Egypt, between January 2010 and December 2015. Operative specimens were collected through total, near-total, or subtotal excision. All studied cases were reported as meningioma in the official pathology reports. This study was approved by Mansoura faculty of medicine, pathology department.

Demographic data (age and sex), clinical data (primary tumor site and tumor recurrence following either complete or incomplete excision and determined by CT or MRI studies), and pathological data (histological type and presence of brain invasion) were obtained from the files of the Pathology Department. Sections stained by H&E were retrieved from the archive of the pathology laboratory and reviewed carefully for proper assessment of brain invasion. The infiltration of meningiomas into Robin–Virchow spaces was not considered brain invasion[5]. The retrieved slides were reexamined to revise the tumor type and grade according to the 2016 WHO classification[1]. Paraffin-embedded tissue blocks with the most representative microscopic slide were selected for tissue microarray analysis. The tissue microarray blocks were constructed through mechanical pencil tip method[22].

The H&E-stained section of each tissue microarray block was examined to ensure adequacy of the prepared blocks. The other sections were mounted on positively charged slides with 3–4 μm thickness for immunohistochemical studies.

Immunohistochemical staining

The prepared sections were deparaffinized using xylene and rehydrated in descending grades of alcohol to water. Antigens were retrieved using 0.01 M citric acid buffer (pH 6.0) and heated in a microwave oven for 10 minutes. The sections were then incubated in 3% H_2O_2 for 5 minutes to block endogenous peroxidase and washed with distilled water. The sections were added with mouse monoclonal anti-human antibodies against β-catenin (clone; 12F7, 1:500 dilution) and galectin-3 (clone A3A12, 1:100 dilution) antigens (Abcam, Cambridge, UK). Positive controls were examined with each run of immunohistochemical staining by using an adenocarcinoma of the colon for β-catenin and normal colonic mucosa for galectin-3. The antibodies were incubated at room temperature for 1 hour. Immunostaining was conducted by mouse- and rabbit-specific HRP/DAB (ab64264) detection IHC kit (Abcam, Cambridge, UK) according to the manufacturer's protocols. DAB was then added to the sections for visualization of the immunoreaction. Mayer hematoxylin was used to counterstain the slides. In each run of immunostaining, a negative control was examined by omitting the primary antibody.

Immunostaining evaluation

The immunostaining intensity of β-catenin was examined under the highest power of a light microscope and scored as 0 (no expression), 1 (yellowish), 2 (imperial yellow), and 3 (brown). The percentage of the stained cells was scored as 0 (<5%), 1 (5%–10%), 2 (11%–50%), 3 (51%–80%), 4 (>80%). The two scores were then multiplied, obtaining values ranging from 0 to 12, and classified as follows: 0 (–), 1–3 (+), 4–6 (++), and >6 (+++). β-catenin was considered to be expressed if it is located in the cytoplasm, membrane, or perinuclear granules[10].

The staining pattern of galectin-3 expression is either cytoplasmic or nuclear and scored according to the percentage of the stained tumor cells: – (<10%), + (10%–25%), ++ (26%–50%), and +++ (>50%)[23].

Statistical analysis

Data were analyzed using the SPSS program version 16 (Inc., Chicago, IL, USA). Fisher's exact and Chi-square probability tests were used to examine the association between the different clinicopathological variables and the protein expression of β-catenin and galectin-3. The association between the different clinicopathological parameters and the protein expression of β-catenin and galectin-3 was also studied using binary logistic regression models with Hosmer–Lemeshow goodness-of-fit. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using brain invasion or recurrence as dependent variable.

Results

Patients' characteristics

A total of 153 patients diagnosed with meningioma were included in this study. The patients were aged from 6 to 80 years (mean±SD: 47.58±13.92) and were mostly female (73.9%). About 64% of the tumors were located within the hemisphere, and 26.1% of the tumors were located in the skull base. The most prevalent histological types were transitional and meningiotheliomatous meningiomas. About 12% of the cases were classified as grade 2 meningiomas, and only 2% were categorized as malignant variants. Twenty cases were positive for recurrence, and 22 cases showed brain invasion (**Table 1**).

Table 1 Clinicopathological characteristics of 153 meningioma cases

Variables	*n* (%)
Age, years	
Ranging from 6 to 80 years (mean±SD)	47.58±13.92
<30	22 (14.4)
>30	131 (85.6)
Gender	
Male	40 (26.1)
Female	113 (73.9)
Location	
Hemispheric	99 (64.7)
Skull base	40 (26.1)
Spinal	14 (9.2)
Histologic type	
Transitional	60 (39.2)
Meningiotheliomatous	41 (26.8)
Psammomatous	12 (7.8)
Fibroblastic	11 (7.2)
Atypical	18 (11.8)
Microcystic	3 (2)
Metaplastic	2 (1.3)
Angiomatous	3 (2)
Malignant	3 (2)
Histologic grade	
Grade 1	131 (85.6)
Grade 2	19 (12.4)
Grade 3	3 (2)
Recurrence	
No	133 (86.9)
Yes	20 (13.1)
Brain invasion	
No	131 (85.6)
Yes	22 (14.4)

Correlation of protein expression with other clinicopathological variables

β-catenin was expressed in 115 (75.1%) meningioma cases (**Figure 1**). High β-catenin expression was significantly associated with transitional and meningiotheliomatous meningiomas, low tumor grade, low recurrence rate, and low incidence of brain invasion (**Table 2**).

Galectin-3 was expressed in 147 (96.07%) cases (**Figure 2**). High galectin-3 expression was associated with brain invasion, tumor recurrence, high tumor grade, and atypical and malignant meningiomas (**Table 3**).

Spearman correlation analysis of galectin-3 and β-catenin showed a negative correlation with mild significance (P = 0.021).

Multivariate logistic regression analysis

The variables included in the models were age, sex, site, tumor type, tumor grade, and expression markers. Of these variables, β-catenin and galectin-3 expression levels were significant predictors of tumor recurrence but not of brain invasion. **Tables 4** and **5** show the predictors of brain

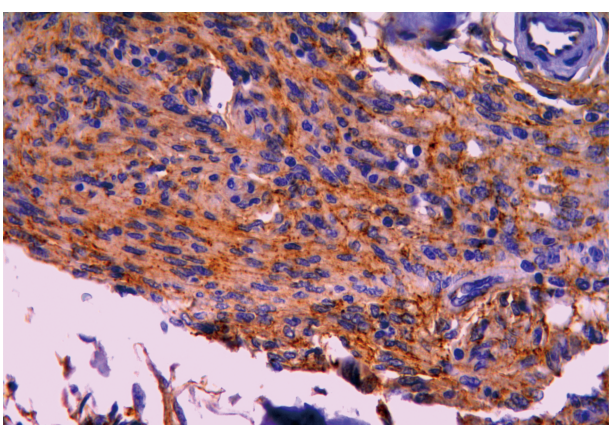

Figure 1 Transitional meningioma showing strong membranous, cytoplasmic, and perinuclear granular expression of β-catenin (IHC staining, 400×).

Table 2 Relation of β-catenin expression to other clinicopathological variables

Variables	β-catenin expression, *n* (%)				χ^2	*P*
	0	+	++	+++		
Age, years					2.379	0.498
<30	3 (13.6)	3 (13.7)	15 (68.2)	1 (4.5)		
>30	35 (26.7)	17 (12.9)	69 (52.6)	10 (7.6)		
Gender					0.727	0.867
Female	27 (23.8)	14 (12.3)	63 (55.7)	9 (7.9)		
Male	11 (27.5)	6 (15.0)	21 (52.5)	2 (5.0)		
Location					4.971	0.548
Hemispheric	29 (29.2)	13 (13.1)	50 (50.5)	7 (7.0)		
Skull base	8 (20.0)	4 (10.0)	25 (62.5)	3 (7.5)		
Spinal	1 (7.2)	3 (21.4)	9 (64.3)	1 (7.1)		
Histologic type					60.234	<0.001
Transitional	5 (8.3)	8 (13.3)	42 (70.0)	5 (8.3)		
Meningotheliomatous	11 (26.8)	1 (2.4)	24 (58.5)	5 (12.1)		
Psammomatous	3 (25.0)	0	8 (66.6)	1 (8.4)		
Fibroblastic	3 (27.3)	5 (45.4)	3 (27.3)	0		
Atypical	11 (61.1)	5 (27.8)	2 (11.1)	0		
Microcystic	1 (33.3)	0	2 (66.7)	0		
Metaplastic	1 (50.0)	0	1 (50.0)	0		
Angiomatous	0	1 (33.3)	2 (66.7)	0		
Malignant	3 (100.0)	0	0	0		
Histologic grade					40.522	<0.001
Grade 1	23 (17.5)	14 (10.7)	83 (63.4)	11 (8.4)		
Grade 2	12 (63.1)	6 (31.5)	1 (52.6)	0		
Grade 3	3 (100.0)	0	0	0		
Recurrence					21.798	<0.001
No	27 (20.3)	14 (10.5)	81 (60.9)	11 (8.2)		
Yes	11 (55.0)	6 (30.0)	3 (15.0)	0		
Brain invasion					37.116	<0.001
No	23 (17.6)	14 (10.7)	83 (63.4)	11 (8.4)		
Yes	15 (68.2)	6 (27.3)	1 (4.5)	0		

invasion and recurrence, respectively, determined using multivariate logistic regression models.

Discussion

Although a large majority of meningiomas are classified as benign, their tissue morphologies and treatment outcomes greatly vary[24]. Patients with invasive meningiomas require postoperative follow-u and adjuvant radiotherapy to increase their survival rate. Hence, assessing brain invasion through microscopic evaluation is important. However, in some instances, this method is difficult to perform on H&E-stained

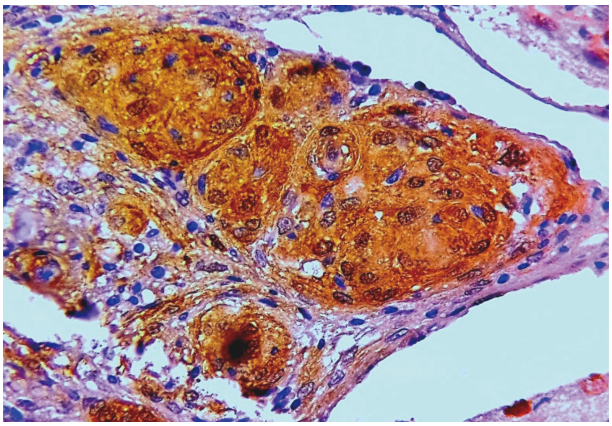

Figure 2 Meningotheliomatous meningioma showing strong cytoplasmic and nuclear expression of galectin-3 (IHC staining, 400×).

sections. In this regard, additional sections stained by immunohistochemical markers must be examined[2,6,9].

Altered β-catenin expression has been identified in several human malignancies, such as gastric, colon, hepatocellular carcinomas, and meningiomas[10-12]. The occurrence and development of meningiomas are due to intracellular adhesion mediated by E-cadherin and β-catenin[25-27].

In this study, the expression level of β-catenin was low in high-grade and aggressive tumors and in cases with brain invasion and tumor recurrence. Similarly, studies that examined cases with similar clinical criteria and pathological grades[10,28] showed that the decreased number of cell adhesion molecules was associated with enhanced tumor cell proliferation and might contribute to the invasive ability of meningioma.

Ide et al.[29] stated that the percentages of nuclear β-catenin are high in anaplastic meningiomas. The high expression of N-cadherin and the nuclear localization of β-catenin may be involved in the progression of anaplastic meningiomas. However, opposite results were obtained in the present study. The discrepancy in the findings could be due to the type of meningiomas studied. Ide et al.[29] tested their biomarkers in canine meningiomas, whereas the present study evaluated human meningiomas. The two studies also employed different clones and techniques.

Zhou et al.[10] also tested the expression of adhesion molecules (E-cadherin and β-catenin) in pituitary adenoma. The expression of the two biomarkers was significantly down regulated, consistent with the present results.

Galectin-3 mediates cancer metastasis[17], but the underlying mechanism remains unclear[18]. Galectin-3 is expressed in some CNS tumors, such as astrocytoma and meningioma[16,20]. Hancq et al.[30] reported the high expression of galectin-3 in 64% of benign meningiomas (grade 1) and in 29% of atypical meningioma. However, the staining results were not significantly different between the two groups. Moreover, the expression galectin-3 was similar between recurrence *vs*. non recurrence group of grade 1 meningiomas[31].

Rodriguez et al.[32] reported no statistically significant difference between galectin-3 immunoreactivity and WHO grade. Galectin-3 was downregulated during the progression of colon cancer and breast carcinomas; as such, cancer cells can interact with laminin, thereby facilitating cancer invasion and metastases[33,34].

In this study, the moderate and strong expression of galectin-3 was prevalent among tumors presenting high grade, recurrence, atypical characteristics, and brain invasion. This finding contradicts those reported by Hancq et al.[30] and Rodriguez et al.[32].

Miyazaki et al.[35] reported the significant expression of galectin-3 in poorly differentiated carcinoma and tumor progression. This finding is similar to the present results but differs from those reported by Okada et al.[36]; in their study, patients with low immunoreactivity for galectin-3 had a low survival rate.

In this study, an inverse relation was found between the expression of β-catenin and galectin-3. However, Song et al.[21] reported that high galectin-3 expression increases the expression of β-catenin. The difference in the results can be attributed to the fact that galectin-3 exhibits other functions, in addition to its role in cell-to-cell and cell-to-matrix interactions as β-catenin prevents tumor spread[10,21].

In this study, galectin-3 overexpression was associated with tumor progression. Liu et al.[37] explained that galectin-3, similar to Bcl-2, exhibits anti-apoptotic activity, thereby promoting the survival of malignant cells.

Kim et al.[18] stated that galectin-3 induces the metastasis of gastric carcinoma by upregulating protease-activated receptor-1(PAR-1) and matrix metalloproteinase-1(MMP-1).

Honjo et al.[38] evaluated the cellular localization of galectin-3 and determined its expression in tongue carcinoma and normal tongue mucosa. The expression of nuclear galectin-3 decreased during the transformation to the malignant phenotype, whereas the expression of cytoplasmic galectin-3 increased. Baldus et al.[39] reported that nuclear galectin-3 reactivity was higher in diffuse-type cancers than in intestinal-type tumors. Nakahara et al.[40] explained the regular movement of galectin-3 between the cytoplasm and

Table 3 Relation of galactin-3 expression to other clinicopathological variables

Variables	Galectin-3 expression, *n* (%)				χ^2	*P*
	0	+	++	+++		
Age, years					1.636	0.651
<30	0	10 (45.5)	9 (40.9)	3 (13.6)		
>30	6 (4.5)	63 (48.1)	41 (31.2)	21 (16.2)		
Gender					3.846	0.279
Female	6 (5.3)	54 (47.7)	38 (33.6)	15 (13.2)		
Male	0	19 (47.5)	12 (3)	9 (22.5)		
Location					6.396	0.380
Hemispheric	3 (3.0)	42 (42.4)	36 (36.4)	18 (18.2)		
Skull base	3 (7.5)	22 (55.0)	10 (25.0)	5 (12.5)		
Spinal	0	9 (64.2)	4 (28.5)	1 (7.1)		
Histologic type					90.118	<0.001
Transitional	2 (3.3)	14 (23.3)	32 (53.3)	12 (20.0)		
Meningotheliomatous	1 (2.5)	34 (82.9)	5 (12.2)	1 (2.4)		
Psammomatous	2 (66.6)	1 (33.3)	0	0		
Fibroblastic	1 (9.1)	9 (81.8)	1 (9.1)	0		
Atypical	0	0	10 (55.6)	8 (44.4)		
Microcystic	0	3 (100)	0	0		
Metaplastic	0	1 (50)	0	1 (50.0)		
Angiomatous	0	2 (66.7)	0	1 (33.3)		
Malignant	0	2 (66.7)	0	1 (33.3)		
Histologic grade					35.823	<0.001
Grade 1	6 (4.6)	73 (55.7)	39 (29.8)	13 (9.9)		
Grade 2	0	0	9 (47.3)	10 (52.6)		
Grade 3	0	0	2 (66.6)	1 (33.4)		
Recurrence					35.618	<0.001
No	6 (4.5)	73 (54.8)	41 (30.8)	13 (9.7)		
Yes	0	0	9 (45.0)	11 (55.0)		
Brain invasion					39.384	<0.001
No	6 (4.6)	73 (55.7)	39 (29.8)	13 (9.9)		
Yes	0 (0)	0 (0)	11 (50.0)	11 (50.0)		

nucleus. The change in the localization of this protein suggests its anti-apoptotic action.

The differences in the results of studies regarding the association of galectin-3 with tumor progression and poor prognosis could be attributed to the differences in the number of studied cases, the type of the tested clones, the techniques used, and the cellular localization of galectin-3 (cytoplasmic *vs*. nuclear).

In this study, galectin-3 and β-catenin were significantly associated with brain invasion but were not independent predictors. Further research should be conducted to confirm this finding considering the few cases with brain invasion

Table 4 Multivariate logistic regression model for brain invasion of meningioma in relation to other parameters

Variables	*P*	Odds ratio	95% CI	
			Lower	Upper
Age	0.880	1.113	0.2750	4.504
Gender	0.788	1.162	0.390	3.462
Location	0.083	0.432	0.167	1.115
Histological type	0.458	1.124	0.825	1.532
Histological grade	0.586	0.615	0.106	3.549
β-catenin score	0.930	1.025	0.595	1.765
Galectin-3 score	0.309	0.687	0.333	1.418

Table 5 Multivariate logistic regression model for meningioma recurrence in relation to other parameters

Variables	*P*	Odds ratio	95% CI	
			Lower	Upper
Age	0.034	0.104	0.013	0.847
Gender	0.083	3.473	0.850	14.195
Location	0.248	0.367	0.067	2.013
Histological type	0.267	1.292	0.822	2.032
Histological grade	0.336	0.351	0.042	2.961
β-catenin score	0.003	0.183	0.059	0.568
Galectin-3 score	<0.001	13.646	3.774	49.341

employed in the present study or the presence of other molecular factors responsible for brain invasion.

In conclusion, galectin-3 and β-catenin are independent predictors of meningioma recurrence and are potential new targets for treatment of this malignancy. The precise action mechanisms of galectin-3 and β-catenin in meningiomas should be further investigated.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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