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Original Article

The expressions of TC1 (C8orf4) and β-catenin were correlated with the malignant phenotype of gliomas and meningiomas

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Abstract: TC1 (Thyroid cancer 1, C8orf4) can enhance the transcriptional activity of Wnt/β-catenin signaling pathway, and plays important role in tumor development. We investigated the correlations of TC1 and β-catenin in gliomas and meningiomas. The expressions of TC1 and β-catenin were examined in 86 gliomas and 75 meningiomas using immunohistochemistry method. The expression of TC1 was positive in 81 (81/86, 96.19%) gliomas and 69 (69/75, 92.00%) meningiomas, and correlated with the advanced WHO grade both in gliomas and meningiomas. The expression of β-catenin was positive in 63 (63/86, 73.26%) gliomas and 67 (67/75, 89.33%) meningiomas, and correlated with the advanced WHO grade of meningiomas. The expression of TC1 was positively correlated with the expression of β-catenin in gliomas or meningiomas, respectively. Moreover, the nuclear expression of TC1 was observed in 33 gliomas and 11 meningiomas. The nuclear expression rate of TC1 was significantly higher in gliomas than that in meningiomas. In conclusion, the expressions of TC1 and β-catenin were correlated with the malignant phenotype in both gliomas and meningiomas. TC1 may co-express with β-catenin, and promote the malignant transformation of gliomas and meningiomas.

Keywords: TC1, C8orf4, β-catenin, glioma, meningioma, wnt

Introduction

Meningioma and Glioma are two most common primary central nervous system (CNS) tumors in adults. Meningiomas account for more than one-third of all CNS tumors (35.8%) and are mostly non-malignant. Only a few meningiomas are malignant, which represent 1.6% of all malignant CNS tumors [1, 2]. Gliomas account for 28% of all CNS tumors and 80% of malignant tumors. The most common malignant subtype of gliomas is glioblastoma, which represents 45.2% of all malignant CNS tumors [1, 3].

Many signaling pathways participate in the development and malignant transformation of gliomas and meningiomas, such as Wnt signaling pathway [3-7]. The Wnt signaling pathway is involved in the de-defferentiation, proliferation, invasion and metastasis of malignant tumors, including lung cancers, liver cancers, colorectal cancers, ovarian cancers, and so on [8-14]. In normal cells, because the Wnt signal is weak, β-catenin is phosphorylated in a destruction complex that contains glycogen synthase kinase 3 (GSK3), adenomatous polyposis coli (APC), Axin, and casein kinase I (CKI), then degraded by an ubiquitin-mediated proteasomal pathway [15]. But, in tumor cells, β-catenin is abnormally accumulated, and forms a complex with T-cell factor/lymphoid enhancer factor (Tcf/Lef) in nucleus, which leads to the transcriptions of the Wnt target genes, such as cyclin D1, c-myc and MMP7 [3, 16, 17]. TC1 (Thyroid cancer 1, C8orf4), a novel activator of Wnt signaling pathway, up-regulates the β-catenin-mediated transcriptions by binding with Chibby. It relieves β-catenin from Chibby, promotes the formation of β-catenin-Tcf/Lef complex, and enhances the activity of Wnt signaling pathway [18, 19]. The high expression of TC1 was involved in the development of many tumors [12, 20-22].

Recently, more and more studies showed that the abnormal activation of Wnt signaling pathway promoted the progression of gliomas and meningiomas. The positive regulators of Wnt signaling pathway, such as Wnt1, Wnt3a, β-catenin and Frat1, were reported overexpressed in gliomas and promoted the development of gliomas [3, 23-26]. On the other hand, the inhibitors of Wnt signaling pathway, such as APC, Axin and GSK3β, were reduced or aberrant expressed in gliomas [27]. The expression level of β-catenin was found reversely correlated with the invasion status and WHO grade of meningiomas [28]. But, it was also reported that increased expression of β-catenin by down-regulating of miR-200a involved in cell proliferation in meningiomas and arachnoidal cells [29]. The role of β-catenin in gliomas and meningiomas still need to be confirmed. Although the high expression of TC1 was related to the progression of many tumors, such as thyroid cancer, ovarian cancer, lung cancer, oral cancer, and gastric cancer [12, 20-22], the expression and function of TC1 in CNS tumors was not investigated previously.

In this study, we for the first time examined the expression of TC1 in gliomas and meningiomas, and explored the correlations among the expressions of TC1, β-catenin and the clinicopathological factors of gliomas and meningiomas.

Materials and methods

Patients and tissue specimens

In this study, 86 glioma tissues and 75 meningioma tissues were obtained randomly from the patients that underwent surgery in the First Affiliated Hospital of China Medical University between 2010 and 2013. The glioma patients included in the study were 59 men and 27 women, and aged 9-73 years with a mean age of 42 years; the meningioma patients were 34 men and 41 women, and aged 27-74 years with a mean age of 47 years. The histological diagnosis and grade were assessed by examination of hematoxylin-eosin stained sections according to the classification system of the World Health Organization [30]. The gliomas were diagnosed as astrocytomas (n = 69, including 13 anaplastic astrocytomas and 16 glioblastomas), and oligodendrogliomas (n = 17, including 7 anaplastic oligodendrogliomas), and were classified as grade I (n = 11), grade II (n = 39), grade III (n = 20), and grade IV (n = 16). The meningiomas were also classified as grade I (n = 64), grade II (n = 7), and grade III (n = 4). The study was conducted according to the regulations of the institutional review boards at China Medical University.

Immunohistochemistry

All resected specimens were embedded in paraffin blocks after fixed with 10% neutral-buffered formalin. Tissue blocks were cut into 4-μm sections. After deparaffinized, rehydrated and antigen retrieval by pressure cooking in a PH 6 citrate buffer for 1.5 min, the sections were incubated with rabbit polyclonal anti-TC1 antibody (1:200; Santa Cruz Biotechnology Inc., CA) and mouse monoclonal anti-β-catenin antibody (610154; 1:200; BD Transduction Laboratories, KY) at 4°C overnight. Following this, the detection of antibodies was accomplished using the streptavidin-peroxidase method. Some slides were stained in the absence of primary antibodies and served as negative controls.

Evaluation of immunostaining

All the immunostained sections were evaluated by 2 investigators who were blinded to the clinical data. Five views per slide were randomly examined, and 100 tumor cells per view were observed at ×400 magnification. The positive rate of every case was obtained by calculating the percentage of positively stained cells in each section. Percentage scores were assigned as (1) 1-25%; (2) 26-50%; (3) 51-75%; and (4) 76-100%. The intensity of TC-1 or β-catenin staining was scored as 0, 1, 2 and 3 if negative, weak, moderate, or marked, respectively. Scores from each tumor sample were multiplied to give a final score of 0 to 12, and based on the scores, the tumors were finally determined as having negative (0), low (>0 and ≤6) or high (≥8) expression, respectively. When ≥10% of the tumor cells per section were stained in the nuclear regions, the sample was scored as having positive nuclear expression of TC1.

Statistical analysis

The Pearson Chi-Square test or the Likelihood-Ratio test was used to assay the correlations among the expression levels of TC1 and β-catenin and the clinicopathological factors of gliomas and meningiomas. P values less than 0.05 were considered statistically significant.

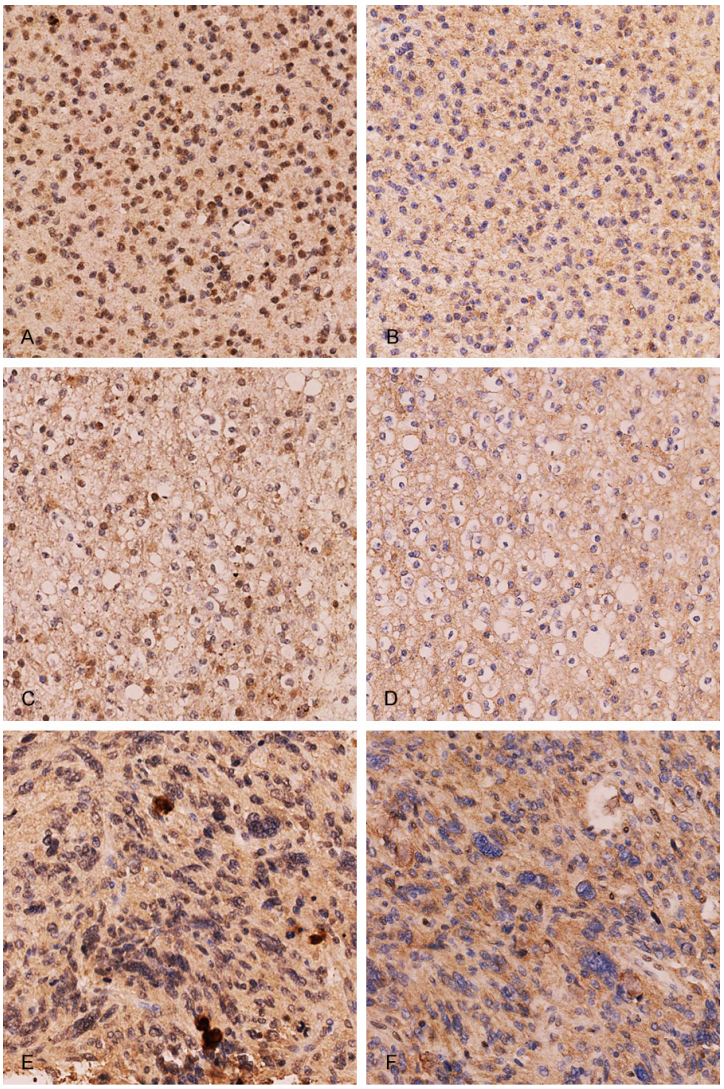

Figure 1. The expression of TC1 and β-catenin in representative glioma cases. In an astrocytoma case, the expression of TC1 was strong in the cytoplasm and nuclei of tumor cells (A); the expression of β-catenin was positive in cytoplasm (B). In an oligodendroglioma case, the expressions of TC1 (C) and β-catenin (D) were observed in cytoplasm, and the nuclear expression of TC1 was also displayed in some tumor cells. In a glioblastoma case, the expressions of TC1 (E) and β-catenin (F) were both strong in the cytoplasm of tumor cells.

Results

The expressions of TC1 and β-catenin were positively correlated with the malignant phenotype of gliomas

The expression of TC1 was observed in cytoplasm of gliomas. Some tumor cells also showed nuclear expression of TC1 (**Figure 1**). The expression of TC1 was positive in 81 cases of gliomas (81/86, 96.19%). The low and high expression rates were 27.91% (24/86) and 66.28% (57/86), respectively. Thirty-three cases of gliomas also displayed nuclear expression of TC1 (33/86, 38.37%). The cytoplasmic expression of TC1 was positively correlated with the advanced WHO grade (P = 0.041) of gliomas. Moreover, the cytoplasmic expression rate of TC1 in oligodendrogliomas was much higher than that in astrocytomas (P = 0.049). But, the cytoplasmic expression of TC1 was not correlated with the patients' sex (P = 0.356) and age (P = 0.212). The nuclear expression of TC1 was not correlated with the WHO grade (P = 0.297), histological subtype (P = 0.771), patients' sex (P = 0.3863) or age (P = 0.620) in gliomas (**Table 1**).

β-Catenin was positively expressed in 63 cases of gliomas (63/86, 73.26%). The low and high expression rates were 31.40% (27/86) and 41.86% (36/86), respectively (**Figure 1**). The expression rate of β-catenin in gliomas of WHO grade IV was much higher than that in gliomas of WHO grade II (P = 0.029). But, the expression of β-catenin was not correlated with the histological type (P = 0.173), patients' sex (P = 0.350), or age (P = 0.293) in gliomas (**Table 1**).

The expression of TC1 was positively correlated with the expression of β-catenin and the advanced WHO grade of meningiomas

The cytoplasmic expression of TC1 was positive in 69 cases of meningiomas (69/75, 92.00%). The low and high expression rates of TC1 were 37.33% (28/75) and 54.67% (41/75), respectively (**Figure 2**). Eleven cases (11/75, 14.67%) showed nuclear expression of TC1. The cytoplasmic expression of TC1 was positively correlated with the advanced WHO grade (P = 0.005), but was not correlated with the patients' sex (P = 0.732) or age (P = 0.295) of meningiomas. The nuclear expression of TC1 was also positively correlated with the WHO grade (P<0.001) of meningiomas (**Table 2**).

Table 1. The expression of TC1 and β-catenin in gliomas

	n	TC1 cytoplasmic expression				TC1 nuclear expression			β-catenin expression			
		Negative	Low	High	*P* value	Negative	Positive	*P* value	Negative	Low	High	*P* value
β-Catenin expression					0.011			0.001				
Negative	23	2	8	13		19	4					
Low	27	0	12	15		9	18					
High	36	3	4	29		25	11					
Sex					0.356			0.863				0.350
Male	59	2	16	41		36	23		18	16	25	
Female	27	3	8	16		17	10		5	11	11	
Age					0.212			0.620				0.293
<42	42	3	15	24		27	15		13	15	14	
≥42	44	2	9	33		26	18		10	12	22	
Histological type					0.049			0.771				0.173
Astrocytoma	69	5	22	42		42	27		21	22	26	
Oligodendroglioma	17	0	2	15		11	6		2	5	10	
WHO grade					0.041			0.297				0.089
I	11	0	7	4		9	2		5	4	2	0.029[a]
II	39	3	11	25		23	16		8	15	16	
III	20	0	4	16		10	10		4	7	9	
IV	16	2	2	12		11	5		6	1	9	

[a]The *P* value between WHO grade II and IV.

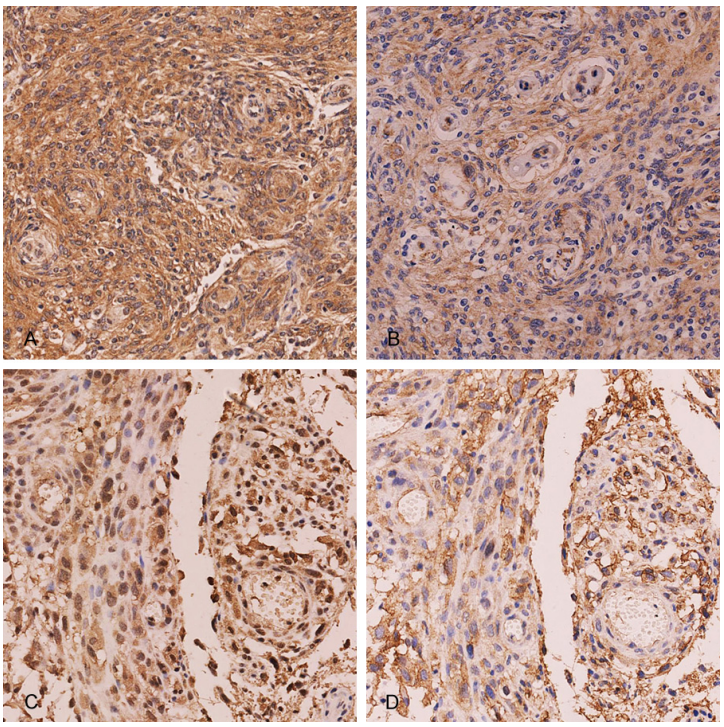

Figure 2. The expression of TC1 and β-catenin in representative meningioma cases. The expressions of TC1 (A) and β-catenin (B) were positive in a meningioma case. In an anaplastic meningioma case, the expression of TC1 was strong in the cytoplasm and nuclei of tumor cells (C); the expression of β-catenin was strong in the membranous-cytoplasmic region of tumor cells (D).

The expression of β-catenin was positive in 67 cases of meningiomas (67/75, 89.33%). The low and high expression rates of β-catenin were 44.00% (33/75) and 45.33% (34/75), respectively (**Figure 2**). The expression of β-catenin was not correlated with the WHO grade (P = 0.074), patients' sex (P = 0.452) or age (P = 0.184) in meningiomas.

The expression of TC1 was positively correlated with β-catenin expression

We further analyzed the relationship between the expression of TC1 and β-catenin in both gliomas and meningiomas. When put the glioma cases and meningioma cases together (n = 161), the cytoplasmic and nuclear expressions of TC1 were both positively correlated with the expression of β-catenin (P<0.001 and P = 0.005, respectively) (**Table 3**). When analyzed the glioma cases and meningioma cases respectively, we also

Table 2. The expression of TC1 and β-catenin in meningiomas

	n	TC1 cytoplasmic expression				TC1 nuclear expression			β-catenin expression			
		Negative	Low	High	*P* value	Negative	Positive	*P* value	Negative	Low	High	*P* value
β-Catenin expression					0.001			0.150				
Negative	8	2	4	2		8	0					
Low	33	0	18	15		26	7					
High	34	4	6	24		30	4					
Sex					0.732			0.507				0.452
Male	34	2	12	20		28	6		2	16	16	
Female	41	4	16	21		36	5		6	17	18	
Age					0.295			0.113				0.184
<47	37	4	16	17		34	3		4	20	13	
≥47	38	2	12	24		30	8		4	13	21	
WHO grade					0.005			<0.001				0.074
I	64	6	28	30		60	4		6	30	28	
II	7	0	0	7		0	7		0	3	4	
III	4	0	0	4		4	0		2	0	2	

Table 3. The correlations of TC1 and β-catenin in gliomas and meningiomas

	n	TC1 cytoplasmic expression				TC1 nuclear expression			β-catenin expression			
		Negative	Low	High	*P* value	Negative	Positive	*P* value	Negative	Low	High	*P* value
β-Catenin expression					<0.001			0.005				
Negative	31	4	12	15		27	4					
Low	60	0	30	30		35	25					
High	70	7	10	53		55	15					
Type					0.321			0.001				0.027
Gliomas	86	5	24	57		53	33		23	27	36	
Meningiomas	75	6	28	41		64	11		8	33	34	

achieved similar results. The cytoplasmic and nuclear expressions of TC1 were positively correlated with the expression of β-catenin (P = 0.011 and P = 0.001, respectively) in gliomas (**Table 1**). On the other hand, the cytoplasmic expression of TC1 was positively correlated with the expression of β-catenin in meningiomas (P = 0.001). But, the nuclear expression of TC1 was not correlated with β-catenin expression in meningiomas (P = 0.150) (**Table 2**).

The nuclear expression rate of TC1 was much higher in gliomas than that in meningiomas

We analyzed the difference of TC1 or β-catenin expression between gliomas and meningiomas. We found that the nuclear expression rate of TC1 in gliomas (33/86, 38.37%) was much higher than that in meningiomas (11/75, 14.67%) (P = 0.001). The expression level of β-catenin in gliomas wan much lower than that in meningiomas (P = 0.027) (**Table 3**).

Discussion

The Wnt signaling pathway plays important role in the de-defferentiation, proliferation, invasion and metastasis of malignant tumors [17]. The aberrant activation of Wnt signaling pathway were reported in many cancers, including CNS tumors, such as gliomas and meningiomas. The abnormal expression of many members of Wnt signaling pathway, including positive or negative regulators, such as Wnt1, Wnt3a, β-catenin, Frat1, APC, Axin and GSK3β, were examined and reported in these tumors [3, 23-29]. But, as a novel activator of Wnt signaling pathway, the expression and role of TC1 was not investigated in gliomas or meningiomas previously.

We for the first time examined the expression of TC1 in gliomas and meningiomas. We showed that the expression of TC1 was common in gliomas and meningiomas. The cyto-

plasmic expression of TC1 was positively correlated with the advanced WHO grade in both gliomas and meningiomas. Meanwhile, we observed the nuclear expression of TC1 in both gliomas (38.37%) and meningiomas (14.67%). The nuclear expression of TC1 was also correlated with the high WHO grade of meningiomas. These results demonstrated that the expression of TC1 involves in the malignant transformation and progression of gliomas and meningiomas.

It is believed that TC1 promotes the progression of cancers by up-regulating the activation of Wnt signaling pathway [19, 32]. So, we further investigated the correlation of TC1 and β-catenin in gliomas and meningiomas. Our data showed that the expression of TC1 was significantly correlated with the expression of β-catenin in both gliomas and meningiomas. It is indicated that TC1 can co-express with β-catenin, and may promote the malignant progression by enhancing the activation of Wnt signaling pathway in gliomas and meningiomas.

Interestingly, the nuclear expression rate of TC1 in gliomas was higher than that in meningiomas; and the expression level of β-catenin in gliomas wan lower than that in meningiomas. Examining the nuclear expression level of TC1 and the expression level of β-catenin might be useful to distinguish these two CNS tumors in some cases.

In conclusion, the expressions of TC1 and β-catenin were common, and correlated with the malignant phenotype in both gliomas and meningiomas. TC1 may co-express with β-catenin, enhance the activity of Wnt signaling pathway and promote the malignant transformation of gliomas and meningiomas.

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Disclosure of conflict of interest

None.

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