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Cortactin and Fascin-1 Correlate with WHO Grades in Primary Brain Tumors

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Cortactin and fascin-1 play important roles in tumor progression and invasion in several human cancers, but not yet clarified in primary brain tumors. To test the possible role of these two markers in primary brain tumors, we performed immunohistochemical analysis of cortactin and fascin-1 in 65 meningiomas and 61 astrocytomas among various World Health Organization (WHO) grades. The immunostain intensity of these tumors was scored on a scale of 0 (absence of staining), 1 (weak staining), 2 (moderate staining), and 3 (strong staining). Additionally, the percentage of tumor staining was also scored 0 (less than 5%), 1 (5% to less than 25%), 2 (25% to less than 50%), 3 (50% to less than 75%) and 4 (75% to 100%). The percentage score was multiplied by the corresponding intensity score to obtain immunostain scores ranging from 0 to 12. Only scant (less than 5%) or undetectable cortactin and fascin-1 expression were demonstrated in 5 normal brain tissues. Higher cortactin and fascin-1 immunostain scores were significantly correlated with more advanced WHO grades of meningiomas (P=0.041 and P=0.047). In astrocytomas, higher WHO grade tumors was significantly associated with fascin-1 immunostain scores (P=0.045), but not with cortactin scores (P=0.461). In conclusion, overexpression of cortactin and fascin-1 may have some influence on tumor progression and invasion in meningiomas and astrocytomas.

Key words: meningioma, astrocytoma, glioma, cortactin, fascin-1, WHO grades.

INTRODUCTION

Primary brain tumors (PBTs) are fatal, causing an annual 0.4% male and 0.3% female mortality rate in more developed countries.[1] Some molecular epidemiologic factors related to the development of PBTs have been identified, including mutative DNA damage, cell-cycle disarrangement, disorder metabolic and long-term inflammatory conditions.[2] Gliomas and meningiomas make up most PBTs.[3] Astrocytomas, the most common gliomas, are divided into 4 grades based on the histological criteria of the World Health Organization (WHO).[4] Similarly, there are 3 different histological grades of meningioma.[4] More advanced histological grades imply higher ability of tumor invasion, progression, and metastasis, which often lead to poorer prognosis.[5] However, the complexity of the histological structure and the discrepancy of judgement are the major challenges in making an accurate diagnosis. In addition, unlike other solid organs, the small amount of fragmented specimens of PBTs may raise the possibility of disorientation because of the restricted surgical space. The combined analyses of hematoxylin and eosin stain slides and proper immunohistochemical stains provide more information to effectively promote diagnostic accuracy in PBTs. Therefore, the development of new biomarkers may play some important roles in distinguishing high grade from low grade in astrocytomas and meningiomas.

Human cortactin is a p80/p85 multidomain F-actin binding protein that activates the actin-related 2/3 protein complex and neuronal Wiscott-Aldrich Syndrome protein to promote actin polymerization.[6] Down-regulation of cortactin not only decreases cell migration and invasion, but also enhances intercellular adhesion.[7] In recent studies, overexpression of cortactin has been found in several human cancers, including gastric adenocarcinomas[8], esophageal[9] and head and neck squamous cell carcinomas[10], breast carcinomas[11], as well as salivary gland adenoid cystic carcinomas.[12] However, the role of cortactin in astrocytomas and meningiomas is still vague. Otherwise, fascin families are groups of actin-binding proteins which contribute to cell motility and adhesion.[13]

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In human, the fascin-1 encoding gene locates at chromosome 7p22 and widely expresses in mesenchymal tissue and the developing nervous system.[14] Compared with the non-neoplastic lining epithelia of internal organs, the level of fascin-1 significantly increases in some human carcinomas, such as those from lung[15], breast[16], stomach[8], colon[17], pancreas[18,19] and urinary bladder.[20] Until now, only one paper in the English literature is available on the topic of fascin-1 expression in patients with glioblastoma multiforme.[21]

In this study, we tested the hypothesis that cortactin and fascin-1 may be related to tumor progression and invasion in meningiomas and gliomas. Our results demonstrated the trends of higher immunostain scores of these biomarkers correlated with more advanced WHO grade of meningiomas and most of gliomas.

MATERIALS AND METHODS

This study was approved by Institutional Review Board I of the Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No.: 1-101-05-011), Taipei, Taiwan. Paraffin-embedded tumor tissues were obtained and tissue microarray slides were constructed. The tissue microarray consisted of samples from 65 and 51 patients with various WHO grades of meningiomas and gliomas respectively. These included cases comprising 41 grade I, 18 grade II and 6 grade III meningiomas, as well as 4 pilocytic astrocytomas, 9 diffuse astrocytomas, 9 anaplastic astrocytomas, 15 glioblastoma multiformes, 6 gliosarcomas from the year of 1991 to 2005. We also selected 5 non-neoplastic brain tissues as the control group in this study. The histopathological differentiation of these brain tumors was determined according to the WHO criteria of tumor classification.

One core was taken from a selected area of each paraffin-embedded tumor tissue and tissue microarray slides were constructed. Each representative core in the tissue microarray slide was 2 mm in diameter and the pathological diagnosis in these cases was reviewed by at least two experienced pathologists. The tissue microarray slide showed uniform staining as the original paraffin-embedded specimens. None of these cases had ever received radiation or chemotherapy before surgery.

Immunohistochemistry

Tissue microarray sections were de-waxed in xylene, rehydrated in alcohol, and immersed in 3% hydrogen peroxide for 5 min to suppress endogenous peroxidase activity. Antigen retrieval was performed by heating (100^{o}C) each section for 30 min in 0.01 mol/L sodium citrate buffer (pH 6.0). After 3 rinses (each for 5 min in phosphate buffered saline [PBS]), sections were incubated for one hour at room temperature with a monoclonal mouse anti-human cortactin antibody (1:100, DAKO, Glostrup, Denmark) and a monoclonal mouse anti-human fascin-1 antibody (1:100, NeoMarkers, Fremont, U.S.A.) diluted in PBS respectively. After 3 washes (each for 5 min in PBS), sections were incubated with biotin-labeled secondary immunoglobulin (1:100, DAKO, Glostrup, Denmark) for 1h at room temperature. After 3 additional washes, peroxidase activity was developed with 3-amino-9-ethylcarbazole substrate chromogen (DAKO, Glostrup, Denmark) at room temperature.

For assessment of cortactin and fascin-1 expression, the intensity of cytoplasmic immunostaining was scored on a scale of 0 (absence of staining), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). The weak, moderate and strong cytoplasmic stainings were defined as the identification of microscopic expressions under the magnification of 40×, 20×, and 10× or 4× respectively. The percentage of tumor staining was also scored 0 (less than 5%), 1 (5% to less than 25%), 2 (25% to less than 50%), 3 (50% to less than 75%) and 4 (75% to 100%). The percentage score was multiplied by the corresponding intensity score to obtain immunostain scores ranging from 0 to 12. For these biomarkers analysis, tumors with < 5% cytoplasmic staining were considered as negative staining. In addition, we used normal gastric glandular epithelia as a negative control.[7]

Statistical analysis

The immunostain scores of cortactin and fascin-1 in normal brain tissue, meningiomas, and gliomas were compared with the negative control specimen. Statistical analysis was performed using Spearman's correlation test to analyze the relationships of immunostain scores with the WHO grading system.

RESULTS

Immunostain scores of cortactin and fascin-1 correlate with WHO grades in meningiomas

Of all the included meningioma cases, the average intensity and percentage scores of cortactin were 1.3 ± 0.7 and 2.5 ± 1.3 in grade I, 2.0 ± 0.6 and 2.7 ± 0.9 in grade II, 2.3 ± 0.5 and 2.8 ± 0.7 in grade III tumors, respectively. More advanced WHO grades of meningiomas implied stronger intensities and higher percentages of immunoexpressing tumor cells. Additionally, the average

Table 1 The immunostain scores of cortactin in various WHO grades of meningiomas and astrocytomas.

	Number of cases	Average intensity score (means ± standard error)	Average pcercentage score (means ± standard error)	Average immunostain score (means ± standard error)	Correlation#
Normal brain tissue	5	0	0	0	0
WHO grades of meningiomas					
Meningiomas, WHO grade I	41	1.3±0.7	2.5±1.3	3.7±2.2	Positive correlation (P = 0.041*)
Atypical meningiomas, WHO grade II	18	2.0±0.6	2.7±0.9	5.3±2.5	
Anasplastic meningiomas, WHO grade III	6	2.3±0.5	2.8±0.7	6.7±2.3	
WHO grades of astrocytomas					
Pilocytic astrocytoma, WHO grade I	4	0.8±0.5	1.3±1.0	1.3±1.0	No significant correlation (P = 0.461)
Diffuse astrocytoma, WHO grade II	9	1.1±0.8	1.4±1.0	2.1±1.9	
Anasplastic astrocytomas, WHO grade III	9	1.2±0.7	2.1±1.1	2.9±1.8	
Glioblastoma multiformes WHO grade IV	23	2.3±0.9	2.7±11	7.1±3.7	
Gliosarcoma, WHO grade IV	6	1.0±0.8	1.5±0.8	2.0±1.3	

The correlation was analyzed by Spearman's correlation test

* Means statistical significance

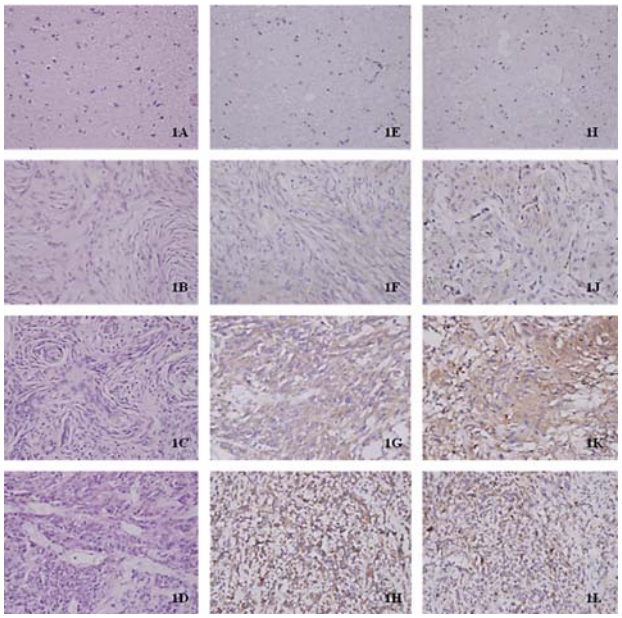

Fig. 1 Hematoxylin and eosin staining of normal brain tissue (1A), meningothelial meningioma (1B), atypical meningioma (1C), anaplastic meningioma (1D); and immunohistochemical analysis of cortactin in normal brain tissue (1E), meningothelial meningioma (1F), atypical meningioma (1G), anaplastic meningioma (1H); and fascin-1 expression in normal brain tissue (1I), meningothelial meningioma (1J), atypical meningioma (1K), anaplastic meningioma (1L). (Original magnification ×400).

immunostain scores of cortactin were 3.7±2.2 in grade I, 5.3±2.5 in grade II and 6.7±2.3 in grade III meningiomas. According to the results of statistical analysis, higher immunostain scores of cortactin significantly correlated with advanced WHO grades of meningiomas (P =0.041, Table 1, Fig. 1). In addition, the intensity, percentage and total immunostain scores of fascin-1 in these included the maningiomas list as follows: 1.3±0.6, 2.2±1.2, 3.2±2.5 in WHO grade I; 2.1±0.9, 2.9±0.9, 6.0±3.8 in WHO grade II, and 2.3±0.5, 2.7±1.2, 6.7±4.3 in WHO grade III tumors. The intensity, percentage and total immunostain scores of fascin-1 showed a significantly positive correlation with various WHO grades of meningiomas (P = 0.047, Table 2, Fig. 2). Our results successfully demonstrated overexpression of cortactin and fascin-1 were statistically associated with more advanced tumor grades of meningiomas.

Immunostain scores of cortactin and fascin-1 in various WHO grades of astroctyoma

According to the criteria of WHO classification of the central nervous system tumors, we divided 51 astrocytic tumors into 5 groups, including 4 cases of pilocytic astrocytoma (WHO grade I), 9 cases of diffuse astrocytoma (WHO grade II), 9 cases of anaplastic astrocytoma (WHO grade III), 23 cases of glioblastoma multiforme (WHO grade IV) and 6 cases of gliosarcoma (WHO grade IV). The average immunostain score of cortactin

Table 2 The immunostain scores of fascin-1 in various WHO grades of meningiomas and astrocytomas.

	Number of cases	Average intensity score (means ± standard error)	Average pcercentage score (means ± standard error)	Average immunostain score (means ± standard error)	Correlation#
Normal brain tissue	5	0	0	0	0
WHO grades of meningiomas					
Meningiomas, WHO grade I	41	1.3±0.6	2.2±1.2	3.2±2.5	Positive correlation (P = 0.047*)
Atypical meningiomas, WHO grade II	18	2.1±0.9	2.9±0.9	6.0±3.8	
Anasplastic meningiomas, WHO grade III	6	2.3±0.5	2.7±1.2	6.7±4.3	
WHO grades of astrocytomas					
Pilocytic astrocytoma, WHO grade I	4	0.8±0.5	1.0±0.8	1.0±0.8	Positive correlation (P = 0.045*)
Diffuse astrocytoma, WHO grade I	9	1.2±0.7	2±1.2	2.9±2.5	
Anasplastic astrocytomas, WHO grade III	9	2.2±0.7	3.3±0.7	7.4±2.7	
Glioblastomas, WHO grade IV	23	2.4±0.9	3.1±0.9	7.8±3.9	
Gliosarcoma, WHO grade IV	6	1.8±0.8	2.3±1.2	4.3±2.7	

The correlation was analyzed by Spearman's Correlation test

* Means statistical significance

in glioblastoma multiforme (7.1±3.7) was significantly higher than pilocytic astrocytoma (1.3±1.0), diffuse astrocytoma (2.1±1.9) and anaplastic astrocytoma (2.9±1.8). However, compared with WHO grade I, II and III astrocytomas, the immunostain scores of cortactin in WHO grade IV astrocytomas revealed no statistical difference (P = 0.461, Table 1, Fig. 2). Additionally, the immunostain scores of fascin-1 in anaplastic astrocytoma (7.4±2.7), glioblastoma multiforme (7.8±3.9) and gliosarcoma (4.3±2.7) were higher than pilocytic astrocytoma (1.0±0.8) and diffuse astrocytoma (2.9±2.5). The statistical analysis showed positive correlation of fascin-1 immunostain scores with the WHO grades of astrocytic tumors (P= 0.045, Table 2, Fig. 2).

DISCUSSION

The WHO grade is one of several factors used to predict prognosis, tumor recurrence, and therapeutic response in PBTs.[4] The current WHO grading systems for diffuse astrocytic tumors are primarily based on histopathologic features and may be complemented by immunohistochemistry.[4] Similarly, according to the criteria of the WHO grading system, meningiomas are also graded by histological differentiation, brain invasion, mitotic activity and the existence of necrosis.[22,23] However, a diagnostic discrepancy indeed exists in meningiomas with heterogenous components and various degrees of nuclear atypism. Otherwise, the challenge for making a precise diagnosis in gliomas requires an accurate assessment of tumor invasion and proliferative activity.[24] The assistance of immunohistochemistry may play an important role in diagnosing PBTs, especially in difficult cases. Unfortunately, most practical immunohistochemical markers are limited to confirming brain tumor differentiation, but not WHO grades. Therefore, some biomarkers need to be developed to assist pathologists in predicting the prognosis and assigning accurate WHO grades in PBTs, especially gliomas and meningiomas.

In human, both cortactin and fascin-1 are important intercellular adhesion molecules.[7,13] The concomitant overexpression of cortactin and fascin-1 has been identified in several advanced carcinomas, including gastric[8], esophagus[25], ovary[26], liver[27], and skin.[28] Roma and Prayson showed fascin overexpression in glioblastoma multiformes was more common than in low grade astrocytomas, but not to a level of statistical significance.[21] Our results demonstrated higher immunostain scores of cortactin and fascin-1 were significantly correlated with more advanced WHO grades of meningiomas. Nevertheless, our statistical results revealed high grade astrocytomas were only associated with overexpression of fascin-1, but not with cortactin. Our study suggested the possible roles of cortactin and fascin-1 in inducing tumor progression

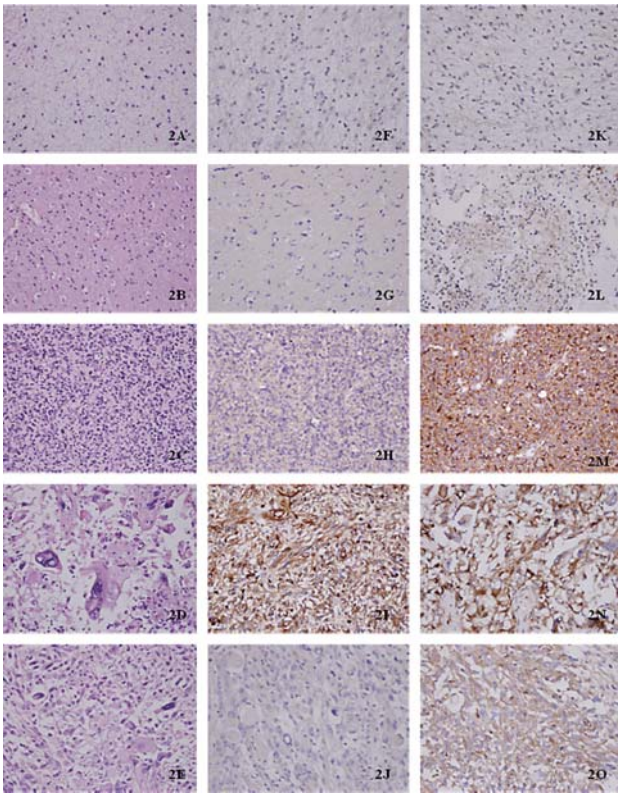

Fig. 2 Hematoxylin and eosin staining of pilocytic astrocytoma (2A), diffuse astrocytoma (2B), anaplastic astrocytoma (2C), glioblastoma multiforme (2D), gliosarcoma (2E); and immunohistochemical analysis of cortactin in pilocytic astrocytoma (2F), diffuse astrocytoma (2G), anaplastic astrocytoma (2H), glioblastoma multiforme (2I), gliosarcoma (2J); and fascin-1 expression in pilocytic astrocytoma (2K), diffuse astrocytoma (2L), anaplastic astrocytoma (2M), glioblastoma multiforme (2N), and gliosarcoma (2O). (Original magnification × 400).

and invasion, the immunohistochemical stains of these biomarkers could help clinicians and pathologists predict the recurrence rate, and prognosis in meningiomas and most astrocytomas.

From our results, the average percentage scores of fascin-1 in anaplastic meningioma were slightly less than atypical meningioma, but did not reach statistical significance. One reason for this is the existence of an experimentally insignificant deviation. The other reason is the definitions of the WHO grading system in meningiomas. The criteria of atypical meningioma mainly depend on either more than 4 mitotic figures per 10 high power fields (HPF) or intraparenchymal brain invasion. Otherwise, the most important criterion of anaplastic meningioma focus is more than 20 mitotic figures per 10 HPF. The differences between atypical and anaplastic meningiomas mainly depend on cellular proliferation ability, but not brain invasion. The interaction between cells and the neighboring matrix has been proven to be related to tumor invasion ability. Therefore, the percentage of fascin-1 expression in atypical meningiomas was higher than in anaplastic meningiomas.

In our study, WHO grade IV astrocytomas included 23 glioblastoma multiformes and 6 cases of gliosarcomas. The immunostain scores of cortactin and fascin-1 in gliosarcoma were lower than glioblastoma multiformes and anaplastic astrocytomas. The detailed mechanism is still unclear. Our hypothesis involves the histological differences between gliosarcomas and the other astrocytomas. Gliosarcoma was defined as a glioblastomas with a partial area of sarcomatous component.[4] The cell adhesion abilities in the sarcomatous differentiated area were weaker than glial cell component.[29] Therefore, the immunohistochemical stains of cortactin and fascin-1 in gliosarcoma were lower than other high grade astrocytomas.

To our knowledge, this is the first study to discuss the relationships between cortactin and fascin-1 with WHO grades of meningiomas and astrocytomas by immunohistochemistry. Although some inevitable experimental deviations occurred, we demonstrated the immunohistochemical stains of some biomarkers are possibly associated with clinicopathological parameters in several human malignancies.[17,30-31] Therefore, these biomarkers might have some benefits in predicting the tumor grades of meningiomas and astrocytomas, excluding the cases of gliosarcoma. However, more evidence will be needed to check if the development of pharmacological agents to suppress the expression of cortactin and fascin-1 might slow tumor progression in patients with meningiomas and astrocytomas.

DISCLOSURE

The authors declare that they have no conflict of interest.

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