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Characterization of pituitary tumor transforming gene in meningiomas

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ABSTRACT

Background: Pituitary tumor transforming gene (PTTG) is an oncogene and has been detected in several tumors of unrelated histological origin. However, its role in meningiomas is unknown so far. We aim to investigate PTTG expression in intracranial meningiomas, and clarify the relationship between PTTG and the histopathological types of tumors.
Materials and methods: Over a 7-year period, 195 meningioma specimens were collected from 195 patients. Seventeen nonneoplastic meningeal tissues were used as controls. We analyze PTTG expression by tissue microarray with immunohistochemistry.
Results: Immunoexpression of PTTG was identified in 172 of 195 meningiomas, accounting for 88.2%. All of immunoexpression of tumors were found to be cytoplasmic, and no nuclear expression was observed. In the control group, there were 3 of 17 specimens (17.6%) with positive PTTG expression. The percentage of high expression WHO subtypes of meningiomas ranged from 0% to 95.7%. We further stratified the tumors into 3 subgroups based on pathological grading (WHO grade I, WHO grade II and III, control), and there was significant intergroup difference in PTTG expression ($p < 0.001$).
Conclusion: This study demonstrated that PTTG was expressed in most of meningioma tissues, and the degree of PTTG immunostaining was variable in the subtypes of tumors. Further investigations into PTTG expression are required to broaden the pathogenesis research of meningiomas.

1. Introduction

Meningiomas are the most common benign intracranial tumors, and originate from the cell lining of the arachnoid membrane [1]. Complete surgical resection of the tumor remains the primary treatment of choice, but the long-term result is not always satisfactory. Even after total removal of tumors (Simpson grade I, II, III resection), recurrence rates of 7.5% at 10 years and 9.3% at 20 years have been reported [2]. In addition, the prognosis of patients after surgery is highly variable, and depends on age, extent of tumor resection, World Health Organization (WHO) histological grade, brain invasion, or adjuvant radiotherapy [3,4]. In comparison with gliomas, the biological factors or genetic changes that drive tumorigenesis of meningiomas is relatively less studied, and an increased understanding of the tumorigenesis may provide an opportunity to improve the therapeutic outcomes.

Pituitary tumor transforming gene (PTTG) is an oncogene of pituitary adenomas and involves in cell proliferation, transformation, angiogenesis, DNA repair, or tumor invasion [5,6]. PTTG is also overexpressed in a variety of endocrine and nonendocrine-related tumors, including thyroid, breast, ovarian, central nervous, pulmonary, or gastrointestinal tumors [7]. However, no research is conducted to address the role of PTTG in meningiomas so far. As a result, in this study, we aim to investigate PTTG expression in intracranial meningiomas by tissue microarray with immunohistochemistry, and clarify the relationship between PTTG and the histopathological types of tumors.

2. Materials and methods

2.1. Specimen collection

This study was carried out at clinical medical college of Yangzhou University in China. Over a 7-year period (January 2005–December 2011), 195 tumor specimens were collected from 195

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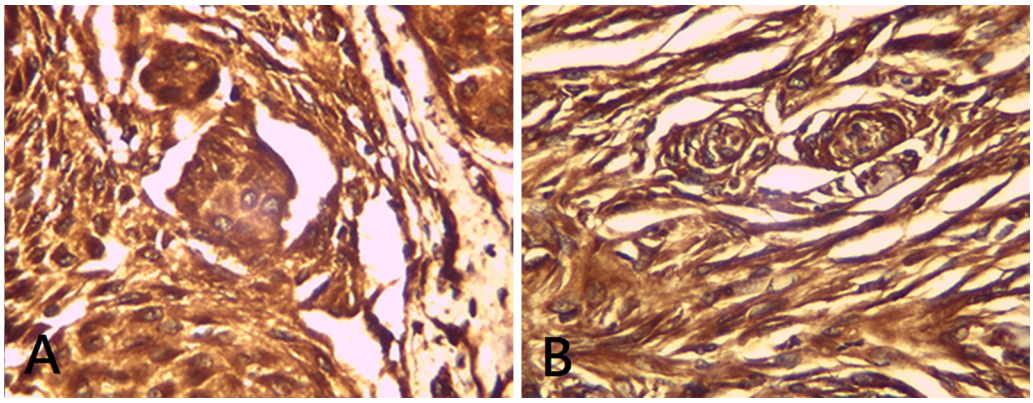

Fig. 1. PTTG expression in meningothelial (A) and transitional (B) meningioma; original magnification 400×.

patients with intracranial meningiomas that were histologically confirmed according to WHO classification. We used 17 meningeal specimens from 17 patients undergoing craniotomy for traumatic brain injury as controls. Written informed consent for tissue procurement was obtained from the participants, and the study protocol was approved by the Institutional Review Board.

2.2. Tissue microarray and immunohistochemistry

After reviewing slides from the primary tumors (formalin-fixed and paraffin-embedded), the two representative areas of each specimen were selected and the core biopsies were punched. These tissue cores were then inserted in a recipient paraffin block in a precisely spaced, array pattern. Sections of 4 μm were then cut from array blocks and transferred to glass slides for immunohistochemical analysis. Briefly, these tissue microarray sections were dewaxed and dehydrated. Then the slides were treated with 10% normal goat serum to block the non-specific sites and incubated overnight at 4 °C with PTTG antibodies (1:50 diluted; Abcam, Cambridge, MA, USA). The Envision system was used to visualize the immunostaining.

2.3. Analysis of PTTG expression

PTTG expression was evaluated using a semi-quantitative scoring method. The sections were examined under a light microscope at an original magnification of 400×. The number of positively-stained cells and the immunostaining intensity were recorded for each specimen. The percentage of positively-stained cells was scored as 0 (0%), 1 (1–10%), 2 (11–50%), and 3 (>50%). The immunostaining intensity was scored as 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). The index of PTTG expression in each case was calculated by the formula: the percentage category score × the intensity category score. The degree of PTTG expression based on the index was presented as follows: −(0, 1), +(2, 3), ++(4, 6), and +++(9).

2.4. Statistical analysis

The categorical variables were compared using the chi-square test or Fisher's exact test. The continuous variables were assessed using the Student's *t*-test or Mann–Whitney *U*-test. A *p* value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

The patient cohort included 54 male and 141 female subjects. The mean age at the time of diagnosis was 54 years (range, 16–79 years). The locations of intracranial meningiomas were as follows: 78 tumors in cerebral convexity, 53 in parasagittal regions, 38 in skull base, and 14 in tentorium, 9 in lateral ventricles, and 3 in posterior fossa. Pathological examinations showed 48 tumors with meningothelial type, 39 with fibrous type, 69 with transitional type, 11 with psammomatous type, 8 with angiomatous type, 5 with atypical type, 1 with chordoid type, and 14 with anaplastic type. Therefore, the number (%) of meningiomas with WHO grade I, II, and III, was 175 (89.7%), 6 (3.1%), and 14 (7.2%), respectively.

3.2. Features of PTTG expression

Immunoexpression of PTTG was identified in 172 of 195 meningiomas, accounting for 88.2%. All of immunoexpression were found to be cytoplasmic, and no nuclear expression was observed. The demonstration specimens were presented in Fig. 1 and Fig. 2. In the control group, there were 3 of 17 specimens (17.6%) with positive PTTG expression. A nuclear pattern of staining was evident in these 3 normal meningeal specimens.

3.3. PTTG expression in subtypes of meningiomas

The degree of PTTG expression in all meningioma subtypes was shown in Table.1. Based on the degree of PTTG expression, the tumors were defined as low expression (− or +) or high expression (++ or +++) meningiomas. The percentage of high expression subtypes of meningiomas ranged from 0% to 95.7%. The highest one was transitional menigioma followed by menigothelial, angiomatous, fibrous, anaplastic, psammomatous, atypical, and cordoid meningioma subsequently.

3.4. Comparison of PTTG expression between WHO grades

We stratified the tumors into 3 subgroups based on pathological grading (WHO grade I, WHO grade II and III, control). Table 2 demonstrated the comparison of expression of PTTG between the 3 groups, and there was significant intergroup difference ($p < 0.001$). The results between each group were further compared: WHO grade I vs. control ($p < 0.001$); WHO grade II and III vs. control ($p = 0.001$); WHO grade I vs. WHO grade II and III ($p = 0.018$).

4. Discussion

Meningiomas exhibit a wide range of subtypes according to the WHO classification, and the 5-year overall survival is 92% for grade I meningiomas, 78% for grade II meningiomas, and 47% grade III meningiomas [3,8,9]. Thus the molecular characterization of these diverse meningiomas is mandatory to discover candidate markers for tumor behavior evaluation. Moreover, gene expression profiling