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Research paper

Genetic alterations in meningiomas of different textures

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ABSTRACT

Meningiomas are complex brain tumors and 20% of meningiomas are clinically aggressive and recur. Aside from descriptors such as "soft" or "hard", the precise molecular mechanisms underlying these two subtypes have been unclear. In our study, we applied Affymetrix GeneChip Human Transcriptome Array 2.0 against 3 "soft" texture meningioma patients and 3 "hard" textures meningiomas as well as 3 normal controls. The array data showed that 949 coding genes and 568 non-coding RNAs in soft texture meningioma groups and 796 coding genes and 479 non-coding RNAs in hard textures were differentially expressed compared with control group. We further discovered 283 overlapped up-regulated genes and 279 overlapped down-regulated genes in soft and stiff groups. Osteomodulin and Alpha-2 Type I Collagen changed most in soft and hard texture meningiomas respectively. Gene ontology analysis against the differentially changed genes revealed that extracellular matrix assembly and disassembly dysfunction might lead to the differences between soft and hard textures. Meanwhile, pathway analysis demonstrated that extracellular matrix was the nature cause of the difference between the two subtypes. Our data firstly provide the molecular difference between soft and hard textures which are propitious to dissecting the pathological mechanism of meningiomas and targeted therapy.

1. Introduction

Meningiomas are one of the most common central nervous system tumors accounting for around 20% of all central nervous system tumors. These tumors are very complex since they occur under various pathogenic factors and display high histological heterogeneity. Fortunately, meningiomas are often benign and curable by surgery. The World Health Organization (WHO) classifies meningiomas into three histological grades: grade I (benign), grade II (atypical), and grade III (anaplasic) in accordance with the clinical prognosis (Louis et al., 2007). Although considered as benign, atypical and anaplasic meningiomass are aggressive and often recur (Perry et al., 1999). During operation, some meningiomas are very soft and could be removed using suction and micro scissors and the patient's neurological function improved rapidly after surgery while others are hard and the prognosis are poor (Sitthinamsuwan et al., 2012; Little et al., 2005; Kim et al., 2008). The texture of meningioma has been increasingly recognized as one of the most important factors affecting operation difficulty. A variety of neuroimaging methods have been proposed to distinguish the different textures (Shiroishi et al., 2016), as well as meningioma consistency grading system (Zada et al., 2013). However, all of them failed to be accepted universally because there are conflicting results and lack of objectivity. It is very important to gain further pathological and biological knowledge of meningiomas since a comprehensive understanding will aid us in personalized treatment as well as operations. However, no study has ever discussed the differences between soft and hard textured meningiomas, especially at transcriptome level.

Genetic surveys revealed that chromosomal abnormalities including losses of 1p, 6q, 9p, 10p, 10q, 14q and 18q, and gains of 1q, 9q, 12q, 15q, 17q and 20q were closely associated with the pathogenesis of meningiomas (Perry et al., 2004). Besides, studies further found that lost or mutation of genes like neurofibromin 2 (NF2), p16INK4a/CDKN2A, p14ARF/CDKN2A and CDKN2B are relevant to development and progression of meningiomas (Fontaine et al., 1991; Liu et al., 2003; Bostrom et al., 2001). Recently, Aruga et al. (Aruga et al., 2010) discovered that Zic family genes including ZIC1, ZIC2, and ZIC5 were highly expressed in meningiomas, indicating that these Zic proteins might be novel molecular biomarkers for meningiomas. Meanwhile, Saydam et al. (Saydam et al., 2010) found that minichromosome maintenance (MCM) family gene expression were significantly increased in meningioma samples compared to arachnoidal tissues, also suggesting the roles of MCMs in serving as biomarkers for meningiomas. Recent gene

Abbreviation: NF2, neurofibromin 2; ZIC, Zinc finger protein; MCM, minichromosome maintenance; EGFL6, EGF-like domain multiple 6; LMO3, LIM domain only 3; IGF1R, Insulin like growth factor 1 receptor; GO, Gene ontology; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes; OMD, Osteomodulin; SFRP2, Secreted frizzled-related protein 2; DSP, Dorsal switch protein; OGN, Osteoglycin; COL3A1, Collagen Type III Alpha 1; COL1A2, Collagen Type I Alpha 2; COL1A1, Collagen Type I Alpha 1; SPT, Serine palmitoyltransferase; KIF5C, Kinesin heavy chain isoform 5C; SCG3, Secretogranin III; CNTN1, Contactin-1; GRIK2, Glutamate receptor, ionotropic kainate 2.

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expression profiling in meningiomas have demonstrated that activation of PI3K/Akt and integrin-mediated signaling pathways were involved in the pathogenesis of benign and anaplastic meningiomas respectively and more importantly, EGF-like domain multiple 6 (EGFL6) was increased in benign meningiomas (Wang et al., 2012). Gene expression profiles of metabolic aggressiveness and tumor recurrence in benign meningiomas had been carried out and found LIM domain only 3 (LMO3) and Insulin like growth factor 1 receptor (IGF1R) as biosignatures for the early detection of clinically aggressive meningiomas (Serna et al., 2013).

Our work for the first time compared the gene expression variation between soft and hard textures via applying Human Transcriptome Array. We performed micro-array with 3 soft texture patients and 3 hard texture patients as well as 3 normal controls. We found that 949 coding genes and 568 non-coding RNAs in soft texture groups and 796 coding genes and 479 non-coding RNAs in stiff group were differentially expressed compared with normal control. Further analysis revealed that the differentially expressed genes focus on cell matrix adhesion pathway and extracellular matrix receptor interaction pathway indicating that these pathways might be the cause of the difference between soft and hard textured meningiomas.

2. Materials and methods

2.1. Patients and tissue samples

Our study was approved by the Ethics Committee of the RenJi Hospital, School of Medicine, Shanghai Jiao-Tong University. Written consent was obtained from patients or guardians on behalf of the minor enrolled in the study. 6 patients with histologically confirmed meningiomas at RenJi Hospital, Shanghai Jiao-Tong University were recruited for this study. Their diagnoses were independently re-reviewed by two pathologists, classified by WHO criteria. The inclusion/selection criteria for the 6 cases were: 1) singe intracranial meningioma without radiotherapy or chemotherapy before; 2) no other tumor disease history; 3) the tumor was completely resected and the postoperative pathology proved to be WHO grade I benign meningioma. The subtypes of the 3 cases of soft meningioma were fibrous meningioma, transitional meningioma, and fibrous meningioma (as Fig. 1A shown from top to bottom). The subtypes of the 3 cases of hard meningioma were psammomatous meningioma, mixed meningioma, and psammomatous meningioma (as Fig. 1B shown from top to bottom). All the patients underwent surgery with total resection of tumor. The follow-up period was 6 months to 3 years. No significant neurological dysfunction was found after surgery.

2.2. Two class differention

RVM *t*-test was applied to filter the differentially expressed genes for the control and experiment group because the RVM *t*-test can raise degrees of freedom effectively in the cases of small samples. After the significant analysis and FDR analysis, we selected the differentially expressed genes according to the P-value threshold. P value < 0.05 was considered as significant difference.

2.3. Cluster

The Hierarchical Clustering tab allows you to perform hierarchical clustering on your data. This is a powerful and useful method for analyzing all sorts of large genomic datasets. Many published applications of this analysis are given in the references section at the end. Cluster currently performs four types of binary, agglomerative, hierarchical clustering. The basic idea is to assemble a set of items (genes or arrays) into a tree, where items are joined by very short branches if they are very similar to each other, and by increasingly longer branches as their similarity decreases. The first step in hierarchical clustering is to calculate the distance matrix between the gene expression data. Once this matrix of distances is computed, the clustering begins. Agglomerative hierarchical processing consists of repeated cycles where the two closest remaining items (those with the smallest distance) are joined by a node/branch of a tree, with the length of the branch set to the distance between the joined items. The two joined items are removed from list of items being processed and replaced by a item that represents the new branch. The distances between this new item and all other remaining items are computed, and the process is repeated until only one item remains.

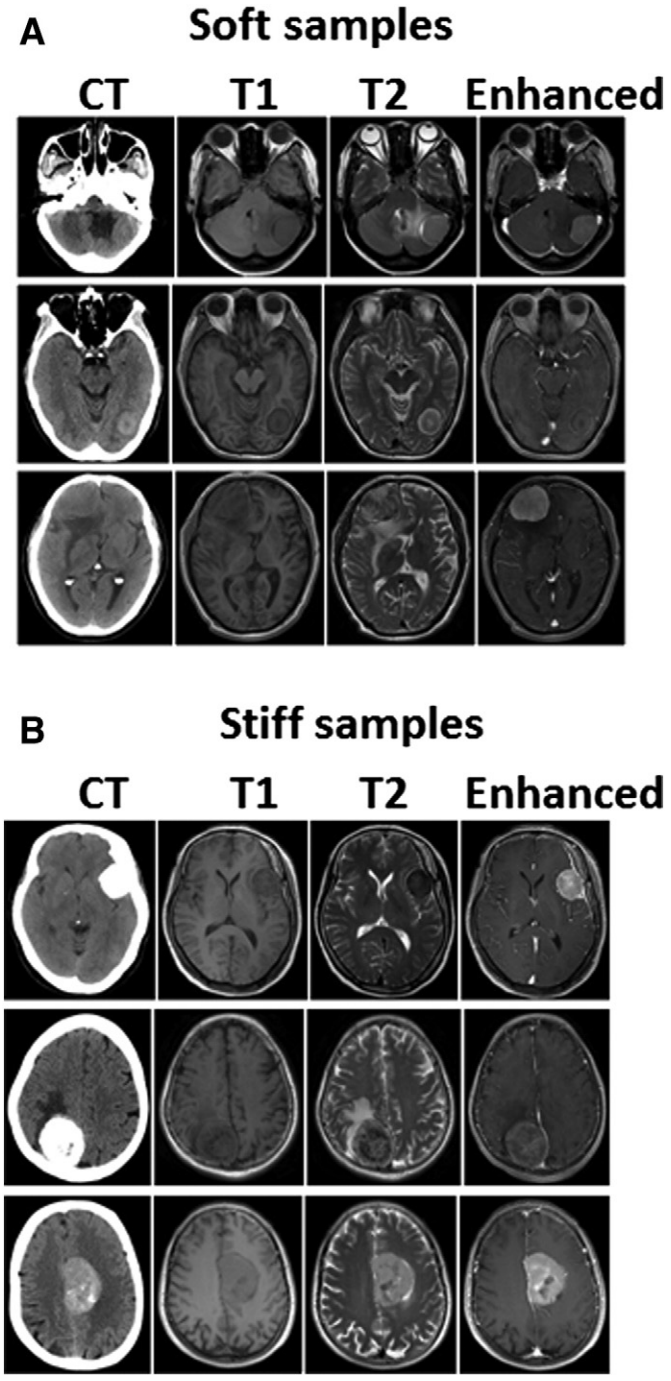

Fig. 1. The computed tomogram (CT) and magnetic resonance imaging (MRI) images representing soft texture (A) and firm texture (B) samples from meningioma patients. From the computed tomogram (CT) images, we can see the hard meningiomas were obviously calcified.