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The effect of galectin-3 genetic variants on the susceptibility and prognosis of gliomas in a Chinese population

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ABSTRACT

The aim of this study is to explore the association between the polymorphisms of galectin-3 gene and clinico-pathological characteristics and prognosis of gliomas. We enrolled 190 histologically diagnosed gliomas and 210 healthy controls in this study. Two genetic variants at galectin-3 single nucleotide polymorphism (SNP) sites (galectin-3 +191 A>C and +292 A>C) were determined. We found that the A/A genotype at galectin-3 gene +292 A>C was significantly more prevalent in gliomas patient than in controls (42.1% vs. 29.0%, $P = 0.021$); the A allele frequency was markedly higher in gliomas subjects than in controls (61.8% vs. 45.0%, $P = 0.008$). There was a markedly higher prevalence of AA carriers in high-grade subgroup than in low-grade subgroup (50.5% vs. 31.8%, $P = 0.012$). The Kaplan–Meier analyses showed that the gliomas patients carrying AA genotype of galectin-3 gene +292 A>C had marked shorter overall survival period than those did not (AA vs. AC+CC, 22.2 ± 3.8 months vs. 38.3 months $\pm$ 7.9; $P = 0.04$). The SNPs at +191 A>C of galectin-3 gene did not show positive association with clinico-pathological characteristics and prognosis of gliomas. The results of this study suggest the SNPs at +292 A>C, not SNPs at +191 A>C, of galectin-3 gene were associated with the tumor grade and prognosis of gliomas.

1. Introduction

Gliomas, the most common type of brain tumors, are derived from glial cells that surround and support neurons in the brain, accounting for more than 50% of all primary brain tumors [9]. Despite advances in diagnosis and treatment, gliomas patients still have a poor prognosis, with a median survival expectancy of only 14 months [21,20,26].

Galectin-3, is an approximately 30 kDa galactoside-binding protein. The biological functions regulated by galectin-3 include mRNA splicing, cell growth, cell cycle and apoptosis resistance, while secreted galectin-3 modulates cellular adhesion and signaling, immune response, angiogenesis and tumorigenesis by binding to cell surface glycoconjugates such as laminin, fibronectin, and collagen IV [5]. Galectin-3 has been implicated with the progression and metastasis of several types of human cancers, including prostate cancer, colorectal cancer, breast cancer, gastric cancer and lung cancer [18,6,8,3,4,14].

The association between galectin-3 protein and gliomas was reported previously. An in vitro study showed that the percentage of galectin-3 positive cells was significantly higher in the tumor parenchyma of glioblastomas than in anaplastic and low-grade astrocytomas [23]. Other studies have also confirmed that astrocytic tumors express high levels of galectin-3 [15,19,25,10].

Two genetic variants at galectin-3 single nucleotide polymorphism (SNP) sites (rs4644 and rs4652) were reported to change the galectin-3 protein level [12]. The SNP rs4644, galectin-3 +191 A>C, renders residue 64 of galectin-3 changing from histidine to proline (Gal-3 64 His to Pro), whereas the SNP rs4652, galectin-3 +292 A>C, changes the threonine at residue 98 to a proline (Gal-3 98 Thr to Pro). Based on the role of galectin-3 in gliomas, we assumed there might be a genetic association between galectin-3 SNPs and gliomas. We thus conducted this case–control study in a Chinese population to study the potential association.

2. Methods

2.1. Patients

The current study included 190 gliomas patients. According to histological diagnosis, the gliomas patients were stratified into

Abbreviations: SNP, single nucleotide polymorphism; OS, overall survival; HRs, hazard ratios; CIs, confidence intervals.

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three subgroups: 85 glioblastomas, 79 astrocytomas (including diffuse astrocytomas, anaplastic astrocytomas or other astrocytomas except for glioblastoma) and 26 other gliomas (including oligodendrogliomas, enpendymomas or mixed gliomas). All tissue specimens were obtained at initial diagnosis by resection or by biopsy before initial resection and were classified morphologically and graded according to the current WHO system (grades: WHO I, WHO II, WHO III and WHO IV) [22]. 210 age and sex matched healthy tumor-free volunteers were recruited from annual checkup visitors as control subjects. All participants were genetically unrelated ethnic Han Chinese people. Each eligible subject was interviewed by two trained personals that were not aware of the case and control with a structured questionnaire to obtain detailed information on demographic factors, family history of cancer, smoking status, and other health characteristics. Smokers were defined as those who had smoked more than one cigarette per day and more than 1 year in their lifetime. The exclusion criteria for healthy subjects included central nervous system-related disease, self-reported history of any cancer and previous radiotherapy and chemotherapy for unknown disease conditions. This study received approval from the institutional review boards at our hospital. All patients gave written informed consent to participate in the present study.

2.2. Determination of vital status

Medical records were reviewed for patient characteristics at diagnosis; treatment characteristics including surgery extent and number; chemotherapy (type, dose and duration), radiation (dose, field, and duration); and date of death or last follow-up.

2.3. Genetic typing of galectin-3 single nucleotide polymorphism

The genomic DNA was prepared from peripheral blood leukocytes. Variants at rs4644 and rs4652 of galectin-3 gene were genotyped using polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) and sequence-specific oligonucleotide probe hybridization as previously described [12].

2.4. Statistical analysis

The Fisher's exact Chi-square test was first used to compare the frequency distribution of age, gender, smoking status between cases and controls, if appropriate. The Kaplan–Meier method was used to estimate overall survival (OS), defined as the time between study registration and a patient's death. The OS periods were compared with log-rank test. We performed univariate and multivariate Cox proportional hazard regression analyses to estimate the effect of galectin-3 polymorphisms on survival in the presence of other known prognostic factors, including age, sex, smoke, extent of tumor resection, chemotherapy, radiation therapy, etc. We calculated hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). Analyses were performed using the software SPSS 16.0 (SPSS Inc., Chicago, IL, USA). All P values were two-sided, and a P value <0.05 was considered significant.

3. Results

3.1. The characteristics of patients and control

The characteristics of case patients and control subjects are summarized in Table 1. There were no significant differences in the mean age at diagnosis, sex and family history between the cases and the controls. Gliomas subjects had a higher percentage of smokers than controls ($P = 0.034$).

Table 1
The characteristics of gliomas patients and control subjects.

Variable	Patients	Controls	P
Gender (male, %)	45.7	45.1	NS
Age (years)	44.6 ± 4.6	44.9 ± 3.9	NS
Smoker (%)	36.7	28.4	0.034
BMI (kg/m^2)	23.6 ± 4.5	23.9 ± 4.2	NS
Family history of cancer (%)	17.8	16.9	NS

Table 2 shows the clinico-pathological characteristics of gliomas patients. There were no significant differences in the histology type, WHO grade and treatment between female and male subjects.

3.2. Glectin-3 SNPs and risk of gliomas

The genotype frequencies of all the four SNPs were in Hardy–Weinberg equilibrium (all $P > 0.05$). The genotype distribution and allele frequency at galectin-3 +191 A>C were similar between the patients and controls (Table 3). However, the genotype distribution at galectin-3 +292 A>C showed significant difference between patient and control groups. The A/A genotype of galectin-3 +292 A>C was significantly more prevalent in patient than in controls (42.1% vs. 29.0%, $P = 0.02$). Subsequently, the A allele frequency was markedly higher in gliomas subjects than in controls (61.8% vs. 45.0%, $P = 0.01$). By multivariable analyses, a significantly higher risk for gliomas was observed in A/A genotype carriers of galectin-3 +292 A>C (odds ratio = 2.11, 95% confidence interval: 1.14–3.11, $P = 0.01$, compared with C/C) after adjustment for age, sex, smoke status, histology, stage and therapy status. The A/C genotype did not determine the risk for gliomas (OR = 1.23, 95% CI: 0.99–1.78, $P = 0.071$, compared with C/C).

3.3. Gliomas histological grades according to genotypes

We further analyzed the histological grade according to the genotypes at +191 A>C and +292 A>C of glectin-3 gene. We combined the grades I and II as low-grade subgroup and grades III and IV as high-grade subgroup. For glectin-3 +292 A>C polymorphisms, we found there was a markedly higher prevalence of AA carriers in high-grade subgroup than in low-grade subgroup (50.5% vs. 31.8%, $P = 0.012$). For the glectin-3 +191 A>C polymorphisms, the genotype distributions were similar between the high-grade and low-grade subgroups ($P = 0.72$) (Table 4).

The genotype distribution and allele frequency in the different tumor histology types according to the genotypes at +191 A>C and +292 A>C were analyzed as well. We did not observe significant difference in the genotype distribution and allele frequency among gliomas subjects from glioblastoma, astrocytomas and other gliomas subgroups (data not shown).

Table 2
The clinico-pathological characteristics of gliomas patients.

Variables	Male	Female	P
Histology type			
Astrocytomas	41	40	NS
Glioblastoma	43	36	
Other gliomas	19	11	
WHO grade			
WHO I	21	13	NS
WHO II	33	29	
WHO III	29	32	
WHO IV	20	13	
Treatment			
Surgery + chemotherapy	46	42	NS
Surgery + radiotherapy	57	45	