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Original Article

Tumor necrosis factor-α (TNF-α) and its receptor gene polymorphisms association with the susceptibility to papillary thyroid cancer in Chinese Han population

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Abstract: Background: The interaction of tumor necrosis factor-α (TNF-α) with its receptors: TNF receptors 1 and 2 (TNFR1 and TNFR2) is critical for the promotion of tumor growth, invasion and metastasis. To better understand the roles of single nucleotide polymorphisms (SNPs) of the TNF-α, TNFR1 and TNFR2 genes in the development of papillary thyroid cancer (PTC). Methods and materials: Here, we recruited 250 PTC cases，and 520 matched healthy controls. Genotyping of TNF-α, TNFR1 and TNFR2 polymorphism was determined by polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP) analysis. Deviation of Hardy–Weinberg equilibrium was tested by using the χ^2 test for goodness of fit. Results: A total of 250 PTC patients and 520 healthy controls were enrolled in our study. In the present study, we evaluated the associations between the functional polymorphisms of TNF-α, TNFR1 and TNFR2 (rs1800629 and rs361525 of TNF-α sequences; rs767455, rs4149577 and rs1800693 of TNFR1 sequences; rs1061622 and rs1061624 of TNFR2) and risk of PTC. With respect to PTC susceptibility, our data suggest that the TNFR1 rs4149577 CT and TNF-α rs1800629 AA are risk factors of PTC risk. However, the results of allele distribution of TNF-α rs361525, TNFR1 with rs767455 and rs1800693, and TNFR2 SNP (rs1061622 and rs1061624) in cases and controls showed that no single allele was associated with the risk of PTC. Conclusion: In conclusion, we found that the variant genotypes of rs4149577and rs1800629 may contribute to an increased risk of PTC. Moreover, no allele was associated with the incidence of PTC in Chinese Han population patients.

Keywords: Papillary thyroid cancer, polymorphism, case-control study, tumour-necrosis factor-α

Introduction

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, representing 75-85% of all thyroid cancer cases [1-3]. It occurs more frequently in women and presents in the 20-55 year ages group. It is also the predominant cancer type in children with thyroid cancer, and in patients with thyroid cancer who have had previous radiation to the head and neck. It is often well-differentiated, slow-growing, and localized, although it can metastasize [4]. Recently, progress has been made through epidemiological studies investigating environmental risk factors for PTC. PTC may be related to gastro esophageal reflux (GER), white race, male gender, tobacco smoking, consumption of salt and salt-preserved foods, and alcohol abuse [5-8].

Tumor necrosis factor (TNF), a pluripotent pro-inflammatory cytokine, plays a pivotal role in inflammation, proliferation, and apoptosis [9]. TNF-α is an inflammatory cytokine mainly produced by activated macrophages and monocytes. Many studies have demonstrated that TNF-α has an important role in the development of different kind of cancer. For example, TNF-α induces a cascade of other inflammatory cytokines and chemokine's, and has been considered as one of the key mediators of inflammation [10-12]. When expressed locally by immune cells, TNF-α has a therapeutic role in destroying tumor blood vessels and inducing the apoptosis and necrosis of tumor cells [13-16]. However, when chronically produced and inflammation persists in the tumor microenvironment, TNF-α can act as a tumor promoter by promoting DNA damage, enhancing pro-antigenic functions,

increasing the expression of matrix metalloproteinase (MMP) and endothelial adhesion molecules and inducing a milieu of growth-promoting hormone [17, 18].

Since its discovery, TNF has been the center of study for its roles in normal physiology, acute inflammation, chronic inflammation, autoimmune disease and cancer-related inflammation. The biological effects of TNF-α are primarily transduced by two distinct receptors referred to as TNF receptors 1 and 2 (TNFR1 and TNFR2), which are encoded by the genes TNFR1 and TNFR2, respectively, both of which are involved in increasing expression of other cytokines and immune-regulatory molecules through the activation of nuclear factor dB [19, 20]. Numerous studies have shown that the abnormal expression of these three genes is involved in the pathogenesis and treatment outcomes of various malignant tumors, including PTC. Moreover, in PTC cell lines, blocking TNFR1 or TNFR2 with specific antibodies impairs tumor survival signaling and the biological function of TNF-α [21-23]. These results indicate that TNF1 and TNFR2 also play important roles in tumor cell proliferation, invasion and metastasis [24].

Through extensive examinations of expression and function, some genetic variations have been shown to explain inter-individual variation. To date, the polymorphisms in the promoter region of tumor necrosis factor-α (TNF-α) gene are related to different kinds of cancer, including PTC [25]. Two functional polymorphisms (rs1800629 and rs361525) in TNF-α genes have been studied more than the other polymorphisms [26-28]. However, no accordant conclusion was got in different ethnicity and data sources. Besides, the polymorphisms in TNFR1 and TNFR2 gene might be potential biomarkers of PTC and no previous studies were conducted. A gene-disease association study was performed to investigate the relationship between TNF-α, TNFR1 and TNFR2 polymorphisms and the genetic susceptibility to PTC, and provide information about the molecular mechanism of PTC susceptibility to Chinese Han population.

Materials and methods

Ethics statement

The Medical Ethics Committee of the First People's Hospital of Jingmen City approved this study. Written informed consents conforming to the tenets of the Declaration of Helsinki were obtained from each participant prior to the study.

Study population

In this case-control study, the investigate population consisted of 250 PTC cases and 520 healthy controls in Department of Endocrinology, the First People's Hospital of Jingmen City from February 2012 to December 2016. All subjects were ethnic Chinese Han. Enrollment criteria including histologically identified diagnosis, no previous surgical or medical treatment of gastric disease, no history of familial PTC, and no other kinds of cancers. The control population consisted of 520 cancer-free healthy subjects recruited from the Department of Clinic Service. Each eligible subject was interviewed to gather demographic data (such as age, sex and ethnicity) and environmental exposure history, including smoking, alcohol consumption, meat and vegetable intake status. All the control subjects were frequency matched to PTC cases on age and gender. The healthy controls were frequency-matched to the patients by age and were randomly selected from the routine physical examination program in the same district. All the healthy subjects had no documented history of cancer or autoimmune diseases.

DNA extraction

In both the case and control groups, 1.5 ml of whole blood was extracted from each participant and stored at -80°C in our clinical laboratory as described previously. DNA from each whole blood sample was extracted with the QIAamp DNA mini Kit (Qiagen, Hilden, Germany), as directed following the manufacturer's instructions. The concentration of DNA and the purity of each sample were measured by an ultraviolet spectrophotometer (GE Healthcare, USA). DNA samples were routinely stored at -80°C until for further research.

Genotyping

Genotyping of TNF-α, TNFR1 and TNFR2 polymorphism was determined by polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP) analysis. The primers are as the following: rs1800629 (forward 5'-AGGCAATAGGTTTTGAGGGCCAT-3' and reverse 5'-TGCACCTTCTGTCTCGGTTTCTT-3'); rs36-

Table 1. Clinical pathologic features of patients with PTC and healthy controls

Characteristic	Cases (n=250)	Percentage (%)	Control (n=520)	Percentage (%)	*P* value
Age (years, year ± SD)	53.9 ± 10.2		52.5 ± 10.3		0.127
< 60	120	51.82	270	48.67	0.571
≥ 60	130	48.18	280	51.33	
Gender					
Male	194	79.67	402	52.27	0.241
Female	56	21.33	118	47.73	
Smoking status					
Never	77	27.92	222	29.27	0.021
Ever	173	72.08	298	70.73	
Alcohol consumption					
Never	112	41.52	239	31.53	0.054
Ever	138	58.48	281	68.47	
Vegetable intake					
< 3 times/w	96	34.83	202	40.60	0.129
≥ 3 times/w	154	65.17	318	59.40	
Meat intake					
< 3 times/w	122	46.67	241	46.80	0.896
≥ 3 times/w	128	53.33	270	53.20	
Family history					
Yes	64	22.50	33	4.51	0.015
No	186	77.50	481	95.49	
TNM stage					
I	20	7.32			
II	25	9.18			
III	170	68.51			
IV	35	13.92			

1525 (forward 5'-AGAAGACCCCCCTCGGAACC-3' and reverse 5'-AGAGGAGGGcGGGGAAAG-AA-3'); rs767455 (forward: 5'-AGTGGCTGAGG-TTAGGAC-3' and reverse 5'-CTATGCCCGAGT-CTCAAC-3'); rs4149577 (forward 5'-GCAAGT-TAAAGCCTGAATGAAG-3' and reverse 5'-ATG-ACCATTTCCCTGACCC-3'); rs1800693 (forward 5'-ACTGTGTTTCATTCTTCTGC-3' and reverse 5'-TAAACCAATGAAGAGGAGG-3'); rs1061622 (forward 5'-GCACACATCGTCACTCTC-3' and reverse 5'-AAGGAGTGAATGAATGAGAC-3') and rs106-1624 (forward: 5'-CTGTGTCGTAGCCAAGGTG-3' and reverse 5'-GGCAGGTCACAGAGAGTCAG-3') which were designed based on the related gene were used for PCR. PCR amplification was carried out in a 20 μL reaction volume containing 2.0 μL of 1 × PCR buffer, 0.4 μL of each primer 10 pmol), 2.0 μL of each dNTP (2.0 mmol/L), 9.3 μL of sterilized water, 0.6 μL of $MgCl_2$, 0.3 μL of Taqenzyme (2.5 U/μL), and 5 μL of template DNA. The PCR reaction conditions consisted of an initial denaturation at 95°C for 15 min, followed by 35 cycles of 94°C for 30 s, 53°C for 1 min and 65°C for 1 min, and a final extension cycle at 72°C for 7 min. The PCR products were separated by 3% agarose gel electrophoresis.

Assay of serum TNF-α levels

The serum level of TNF-α was determined by ELISA Quantikine Human carbonic anhydrase II immunoassay kit (Biosource, USA). The lower limit of detection ranged from 4 to 6 pg/mL. Assay was carried out according to the manufacturers' instructions.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (SD), or frequencies (number of cases) and percentages as required depending on their distribution. The Hardy-Weinberg equilibrium (HWE) was assessed for each variation to identify the deviation. The differences of the genotypes and alleles of TNF-α, TNFR1 and TNFR2 between patients and normal controls were evaluated by using chi-square test. The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Unpaired Student's t test or Mann-Whitney tests were used for two-group comparisons. Linkage disequilibrium (LD) analysis and haplotype reconstruction was performed using Haploview 4.2 (http://www.broad.mit.edu/mpg/haploview). Logistic regression analysis was performed in order to determine the

Table 2. Genotype distribution of TNF-a, TNFR1 and TNFR2 gene polymorphisms in gastric carcinoma patients and healthy controls

SNP	Genotype	Cases	Control	*P* value	OR (95% CI)
TNF-α rs1800629	GG	157	311	—	Reference
	AG	30	95	0.222	1.25 (0.87-1.80)
	AA	63	114	0.015	3.49 (0.33-6.72)
	Dominant			0.613	0.79 (0.36-7.21)
	Recessive			0.582	0.76 (0.53-1.02)
rs361525	GG	216	443	—	Reference
	AG	23	55	0.311	2.86 (0.71-3.43)
	AA	11	12	0.051	1.93 (0.09 -2.37)
	Dominant			0.398	1.86 (0.52-2.43)
	Recessive			0.953	1.84 (0.09-3.55)
TNFR1 rs767455	TT	169	383	—	Reference
	CT	66	116	0.086	1.29 (0.91-1.83)
	CC	5	13	0.872	0.87 (0.31-2.48)
	Dominant			0.129	1.25 (0.89-1.76)
	Recessive			0.326	1.07 (0.84-1.35)
rs4149577	CC	109	303	—	Reference
	CT	77	120	0.071	1.51 (1.07-2.12)
	TT	64	97	0.032	3.55 (2.18-5.67)
	Dominant			0.058	1.39 (1.00-1.93)
	Recessive			0.042	2.12 (0.88-2.43)
rs1800693	AA	160	380	—	Reference
	AG	74	119	0.712	1.43 (1.01-2.02)
	GG	16	21	0.532	1.28 (0.46-3.51)
	Dominant			0.045	1.41 (1.01-1.98)
	Recessive			0.523	1.16 (0.43-3.18)
TNFR2 rs1061622	TT	150	310	—	Reference
	GT	80	177	0.091	0.88 (0.61-1.19)
	GG	20	33	0.236	0.81 (0.41-1.88)
	Dominant			0.341	1.21 (0.62 -1.18)
	Recessive			0.562	1.02 (0.43-1.97)
rs1061624	AA	80	173	—	Reference
	AG	128	271	0.719	0.88 (0.70-1.38)
	GG	42	76	0.298	1.32 (0.62-1.68)
	Dominant			0.318	0.99 (0.72-1.37)
	Recessive			0.427	1.23 (0.66-1.63)

OR and 95% CI. Unpaired Student's t test or Mann-Whitney tests were used for two-group comparisons. If a positive association was found in the initial analysis, Bonferroni correction was performed. Three genotype models were presented: the general model (common allele homozygotes coded as 1, heterozygotes as 2, and recessive allele homozygotes as 3); the dominant model (common allele homozygotes coded as 1 and heterozygotes plus minor allele homozygotes as 2); and the recessive model (common allele homozygotes plus heterozygotes as 1 and minor allele homozygotes as 2). Logistic regression was performed to adjust for age and gender. Statistical analysis of data was performed using the SPSS software package 18.0 (SPSS Inc. USA). *P*-value less than 0.05 was considered statistically significant.

Results

In the current study, a total of 250 patients with PTC and 520 healthy controls were enrolled in our study. All of the subjects were ethnic Han Chinese. Demographic and other selected characteristics of cases and controls were presented in **Table 1**. Cases and controls did not show statistically significant differences with regard to sex, age, smoking status, meat and vegetable intake status. Besides, the TNM stages of all the PTC cases are reported as well. In general, 20 cases are in stage I, 25 cases in stage II, 170 in stage III and 35 cases in stage IV.

Genotype frequencies of TNF-α polymorphism rs1800629 and rs361525 in the subjects are presented in **Table 2**. The genotype distributions were in Hardy-Weinberg equilibrium in each group studied. As shown in **Table 2**, compared with the AG and AA genotype of rs1800629, the frequencies of AA are significantly changed. However, compared with the GG genotype of rs361525, the frequencies of AG and AA are not significantly changed. In neither dominant nor recessive, there are significant associations were detected for the genotype rs361525.

Table 3. Allele distribution of TNF-a, TNFR1 and TNFR2 single nucleotide polymorphism in PTC patients and healthy controls

SNP	Allele	Cases	Controls	*P* value	OR (95% CI)
rs1800629	G	344	727	Reference	Reference
	A	156	323	0.023	4.72 (0.49-11.07)
rs361525	G	455	941	Reference	Reference
	A	45	99	0.127	0.65 (0.41-1.04)
rs767455	T	404	882	Reference	Reference
	C	96	158	0.384	1.20 (0.89-1.63)
rs4149577	C	295	866	Reference	Reference
	T	205	174	0.008	5.21 (0.91-13.62)
rs1800693	A	398	883	Reference	Reference
	G	102	157	0.042	1.33 (1.01-1.79)
rs1061622	T	388	804	Reference	Reference
	G	102	236	0.293	0.88 (0.67-1.16)
rs1061624	G	289	615	Reference	Reference
	A	211	425	0.584	1.00 (0.80-1.25)

Genotype frequencies of TNFR1 (rs767455, rs4149577 and rs1800693) and TNFR2 (rs1061622 and rs1061624) polymorphism in the subjects are presented in **Table 2**. As shown in **Table 2**, compared with the TT genotype of rs767455, the frequencies of AG and AA are not significantly associated with the incidence of GC. Besides, in neither dominant nor recessive, there are significant associations were detected. However, for the rs4149577 polymorphism, CT genotype is associated with the incidence of PTC (CT vs CC, OR=1.51, 95% CI=1.07-2.12). However, no association was detected for the association of TT genotype of rs4149577 (TT vs CC, OR=3.55, 95% CI=2.18-5.67). For the rs1800693 polymorphism, the genomic analysis did not reveal differences genotypic frequencies with PTC patients and healthy controls.

Besides, the genotype frequencies of TNFR2, including rs1061622 and rs1061624, are reported in **Table 2**. As shown in **Table 2**, compared with the TT genotype of rs1061622, the frequencies of GT and GG are not significantly changed. The advanced analyses showed that neither dominant model nor recessive model could show a significant association. Compared with the AA genotype of rs1061624, the frequencies of AG and GG are not significantly changed. The advanced analyses showed that neither dominant model nor recessive model could show a significant association.

The allele distributions of TNF-α single nucleotide polymorphisms (rs1800629 and rs361525) are reported in **Table 3**. As for rs1800629, A allele was associated with the risk of PTC compared with the G allele (*P*=0.023, OR=4.72, 95% CI=0.49 to 12.07). While for the rs361525 location, A llele was not associated with the risk of GC (OR=0.65; 95% CI=0.41 to 1.04).

For the TNFR1 location, three different single nucleotide polymorphisms (rs767455, rs4149577 and rs1800693) were reported. As for rs767455, C allele is not associated with the risk of GC. Compared with C allele of rs4149577, T allele is associated with PTC risk (P=0.008, OR=5.21, 95% CI=0.91-13.62). Advanced analyses showed that G allele in rs1800693 showed a no significant risk of PTC. For the TNFR2 gene, neither G allele in rs1061622 nor A allele in rs1061624 were associated with PTC risk (in **Table 3**). Furthermore, results revealed at among PTC patients (**Figure 1**), the rs1800629 AA genotypes exhibited significantly higher TNF-α serum levels than that of AG+GG genotype.

Discussion

In the present study, we evaluated the associations between the functional polymorphisms in TNF-α, TNFR1 and TNFR2 (rs1800629 and rs361525 in TNF-α sequences; rs767455, rs4149577 and rs1800693 in TNFR1 sequences and rs1061622 and rs1061624 in TNFR2) and risk of PTC. With respect to PTC susceptibility, our data suggest that the TNF-α rs1800629 and TNFR1 rs4149577 are risk factors of PTC risk. The TNF gene polymorphism and the risk of digestive system cancers have been long discussed and a pretty of previous studies have been reported.

The TNF-α gene on chromosome 6p21.3 encoding. TNF and epidermal growth factor (EGF) are well-known stimuli of cyclooxygenase (COX)-2 expression, and TNF stimulates transactivation of EGF receptor (EGFR) signaling to promote

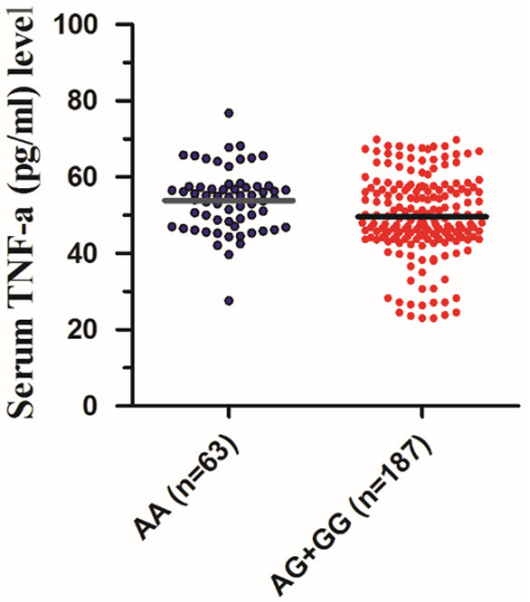

Figure 1. Comparison of Serum levels of TNF-α in PTC group under the genotypes of the rs1800629 polymorphisms. AA genotype of rs1800629 in patients (n=63), AG and GG genotypes of rs1800629 in patients with PTC (n=187).

survival in colon epithelial cells. We hypothesized that COX-2 induction and cell survival signaling downstream of TNF are mediated by EGFR transactivation [25, 29-32]. The TNF-α 308 promoter polymorphism is a allelic G to A polymorphism, and the TNF-α. A allele is associated with increased levels of TNF in plasma. Although studies have reported TNF can modify the risk of PTC, the exact role of TNF as a gastric carcinogen is still controversial. In the present study, we investigated the association between the TNF polymorphism and susceptibility to PTC in Chinese Han population. In our study, there are association between TNF-α polymorphisms and PTC risk. Some case-control studies have been conducted to elucidate the correlation between TNF-α polymorphisms and the risk of PTC [33-35]. The results showed that TNF-α polymorphisms are significantly associated with the risk of PTC [25].

Genetic polymorphisms of TNF-alpha and TNF receptor superfamily member, TNFR1 and TNFR2 have been examined in terms of susceptibility to various cancers. In a previous study, genetic polymorphisms of TNFR2 gene were evaluated Japanese esophageal squamous cell carcinoma (ESCC) patients treated with the definitive 5-FU/CDDP-based chemoradiotherapy and their predictive values of prognosis or severe acute toxicities were assessed [36-38]. Genetic polymorphism of TNFR2 A1466G was found to be predictive response in Japanese ESCC patients with a definitive 5-FU/CDDP-based chemoradiotherapy. Further clinical investigation with a large number of patients or experiments in vitro should be performed to assess the predictive value of TNFR2 A1466G genotype after chemoradiotherapy [25, 39, 40]. A study was conducted to investigate the roles of 2 polymorphisms of the TNFR1 and TNFR2 (a coding polymorphism that results in an amino acid substitution-R92Q), as genetic modifiers of multiple sclerosis (MS), and to evaluate their potential functional implications in the disease [41-45]. These findings suggest that rs4149577 polymorphisms have functional consequences in the TNF-R1 [25]. In a case-only analysis in 335 Caucasian esophageal adenocarcinoma patients that were genotyped for 242 SNPs in 43 apoptotic genes and the results showed that TNFR1 rs4149579 had significant interaction with gastro esophageal reflux disease [23, 25, 46-48]. The results showed that TNF-α expressed by BM-derived cells (BMDCs) stimulates the TNFR1 on BMDCs by an autocuing or paracrine manner, which is important for gastric tumor promotion [41-43, 49-51]. Moreover, the microarray analysis and colony formation assay indicated that NADPH oxidase organizer 1 (Noxo1) and Gna14 are induced in tumor epithelial cells in a TNF-α-dependent manner, and have an important role in tumorigenicity and tumor-initiating cell property of cancer cells [26-28, 52, 53]. Accordingly, it is possible that the activation of TNF-α/TNFR1 signaling in the tumor microenvironment promotes gastric tumor development through induction of Noxo1 and Gna14, which contribute to maintaining the tumor cells in an undifferentiated state. The present results indicate that targeting the TNF-α/TNFR1 pathway may be an effective preventive or therapeutic strategy for cancers [25].

Conclusions

In summary, we found that the variant genotypes of rs4149577and rs1800629 may contribute to an increased risk of PTC. Moreover, no allele was associated with the incidence of PTC in Chinese Han population patients. Association studies with diverse populations

and further functional analysis of the variants are needed to verify our findings. Advanced studies on this point would provide better understanding of PTC pathophysiology and offer potential therapeutics.

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Disclosure of conflict of interest

None.

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