Investigation of Interleukin-17 Gene Polymorphisms and Serum Levels in Patients with Basal Cell Carcinoma of the Skin

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ABSTRACT

Background: Interleukin 17 (IL-17) is a pro-inflammatory cytokine that plays an important role in cancer pathogenesis. **Objective:** To investigate the association of two IL-17 gene polymorphisms (rs2275913 and rs763780), as well as IL-17 serum levels with susceptibility to Basal Cell Carcinoma (BCC) of skin. **Methods:** Two hundred subjects with BCC and 200 healthy controls were recruited. DNA was extracted from peripheral blood leukocytes and genotypes were determined using PCR-RFLP methods. Serum levels were assessed by ELISA. **Results:** At position rs2275913 in IL-17A, the frequencies of GG, AG and AA genotypes were 99 (49.5%), 76 (38%) and 25 (12.5%) in patients and 97 (48.5%), 84 (42%) and 19 (9.5%) in the control group. The distribution of AA, GA and GG genotypes at position rs763780 in IL-17F were 166 (83%), 34 (17%) and 0 (0%) in patients and 158 (79%), 40 (20%) and 2 (1%) in the control group. Haplotype analysis by Arlequin software package revealed that GA haplotype was the most frequent haplotype in both groups. No significant differences were found in alleles, genotypes, and haplotypes frequencies between study groups at both positions ($P>0.05$). While no difference in IL-17 serum levels was observed between individuals with different genotypes, statistical analysis showed higher IL-17A serum levels, but not IL-17F, in patients compared to controls (0.65 ± 0.11 and 0.03 ± 0.02 pg/ml), respectively, ($P<0.001$). **Conclusion:** Our findings do not support the association of rs763780 and rs2275913 gene polymorphisms in IL-17gene with susceptibility of Iranians with BCC. Increased IL-17A serum levels may still play a role in pathogenesis of BCC..

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INTRODUCTION

Interleukin 17 (IL-17) is one of the most important pro-inflammatory cytokines secreted by T Helper-type 17(Th17) cells. This cytokine is a homo-dimmer molecule with two chains of 15 kDa, which are linked by disulfide bonds (1). Considering recent developments in the human genome sequencing and proteomics, five additional members of IL-17 family have been identified and cloned including IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. IL-17A has the highest similarity with IL-17F (2). The receptors identified for IL-17 family members are IL-17R, IL-17RH1, IL-17RL (receptor like), IL-17RD and IL-17RE. IL-17A and IL-17F are secreted by activated T cells whereas IL-17B, IL-17C, IL-17D and IL-17E are expressed in various types of tissues (2). The role of IL-17 cytokine and Th17 cells in cancer remain controversial making IL-17 an interesting target for further investigations. While some observations support the anti-tumor activity of IL-17 and Th17 cells, there are plenty of studies suggesting the roles of this molecule and cells in cancer progression and growth (3, 4). IL-17A and Il-17 F polymorphisms were reported to be associated with the risk of gastric cancer as well as non-gastrointestinal cancers in Asian populations (5, 6). Serum levels of IL-17 may also have a diagnostic and prognostic value in patients with thyroid cancer and small cell lung cancer (7, 8). Based on the cumulated data indicating the gene-disease association of skin cancers, as well as the role of immune system in the progression and/or restriction of BCC, it might be suggested that genetic polymorphisms, which regulate the processes of tumorgenesis and antitumor immunity, affect the susceptibility of individuals to BCC. Here, we investigated the association of two IL-17 gene polymorphisms; IL-17A -197G/A (rs2275913) and IL-17F 7488A/G (rs763780) , as well as IL-17 serum level with susceptibility to BCC, and associations of these with BCC clinicopathological factors including the number of lesions, the size of lesion and the existence of sun exposed lesions.

MATERIALS AND METHODS

This case-control study was carried out on 400 subjects assigned to two groups of BCC patients with average age of 60.94 ± 13.94 years (116 males and 84 females) (N=200) and healthy people with average age of 60.93 ± 13.98 years (116 males and 84 females) (N=200). Patients were recruited from Shahid Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences. After obtaining the informed consent from volunteers, 6 ml of venous blood was collected, of which 4 ml was added to a tube containing anticoagulant agent EDTA (Applichem, Germany), and the rest was used to isolate serum samples. Patients' pathological characteristics were collected from patients' files. Based on the records, all patients were pathologically confirmed to have basal cell carcinoma type of skin cancer. Control subjects included healthy volunteers matched with the patients according to age and sex. Exclusion criteria for healthy controls were the history of cancer or autoimmunity in their first-degree relatives, as well as history of inflammatory or infectious disease in two months prior to sample collection. Genomic DNA was extracted from peripheral blood leukocytes according to salting out method previously described with little changes (9). Genotyping was performed using polymerase Chain

Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) reactions as previously described with slight changes (10). IL-17 A -197 G/A amplification was performed in a 25 µL total reaction volume containing 100 ng of genomic DNA, 1 pM of each primer, 2 U of Taq DNA polymerase, 0.75 mM of dNTP, 2.5 µL of 10x PCR buffer, 0.5 mM $MgCl_2$, and double-distilled water. *Xag*I was used as the restriction enzyme and the products were run on 3% agarose gels. The enzyme fails to digest the 102-bp DNA containing A allele, while in the presence of G allele, it cuts the DNA to two fragments including 68 bp and 34 bp. The IL-F 7488A/G amplification was done with specific primers and under same conditions with IL-17 A -197 G/A. In the presence of A allele, *Nla*III enzyme digests the DNA to two fragments (80 bp and 63 bp), while it is unable to digest this portion in the presence of G allele.

IL-17 gene-specific primers, annealing temperatures, restriction enzymes and the lengths of RFLP-digested fragments are illustrated in Table 1. Based on the distribution of genotypes at positions rs2275913 G/A and rs763780 A/G, we selected, among study participants, 80 patients and 53 controls to be assessed for IL-17A serum level, as well as 81 patients and 53 controls to be sassed for IL-17F serum level (details in result section). The comparison was then made between patients with different genotypes, as well as between patients and controls. Serum samples were collected and stored in −20°C before analysis. IL-17A and IL-17F were measured, in patients and controls with selected genotypes, using commercially available ELISA kit according to the manufacturer's instructions (eBioscienceBMS2017 1030 Vienna, Austria). The OD value at 450 nm was measured. The concentrations of IL-17A and IL-17F were calculated according to the standard curve. The sensitivity of the tests was 0.5pg/ml and 3.3 pg/ml, respectively.

Table 1. IL-17 gene-specific primers and reaction conditions for genotyping IL-17 polymorphisms using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP).

Locus		Primer Sequence	Annealing Temperature	RE*	Length of Digested Fragments	Ref.
Interleukin-17A -197G/A (rs2275913)	Sense	5'-AAC AAG TAA GAA TGA AAA GAG GAC ATG GT-3'	65 ºC	*Xag*I	AA: 102 bp AG: 102، 68 and 34 bp GG: 68 and 34 bp	(10)
	Anti-sense	5'-CCC CCA ATG AGG TCA TAG AAG AAT C-3'				
Interleukin-17F 7488A/G (rs763780)	Sense	5'-ACC AAG GCT GCT CTG TTT CT-3'	65 ºC	*Nla*III	GG:143 bp GA: 143، 80 and 63 bp AA: 63 and 80 bp	(10)
	Anti-sense	5'-GGT AAG GAG TGG CAT TTC TA-3'				

*RE: Restriction enzyme

Statistical analysis. SPSS software package (version 11.5; SPSS Inc, Chicago, IL, USA) was used for data collection and statistical analysis. Test for Hardy–Weinberg equilibrium (HWE), as well as haplotype analysis were performed by using Arlequin software package (11). The distribution of alleles and genotypes between two groups was analyzed using chi-square test. P value less than 0.05 was considered significant. To analyze the data from IL-17 serum levels between groups independent sample t-test and ANOVA test were conducted.

RESULTS

Two hundred patients with BCC and 200 healthy controls were enrolled in the study. Clinicopathological features of the patients were derived from patients' records and pathology reports. Patients' data included sex, age, number of lesions, size of lesion, and occupational exposure to sunlight. The cancer type in all individuals was basal cell carcinoma (BCC). A total of 140 patients had only one lesion (70%). In 9 out of 200 patients (4.5%) the number of lesions was more than 5. The size of the biggest lesion was considered as the tumor size in this study. Out of 193 patients for which the tumor size was collected, 109 (56.5%) had tumor sizes ≤1cm and 84 cases (43.5%) had tumor sizes >1cm. The Clinicopathological features of the patients with BCC are summarized in Table 2.

Table 2. Clinicopathological characteristics of the patients with basal cell carcinoma (BCC) of the skin.

Characteristic	Statistics	
Age (year)	Minimum: 17.00	
	Mean ± SD*: 60.94 ± 13.94	
	Maximum: 91.00	
Gender	Male: 116 (58%)	
	Female: 84 (42%)	
Number of lesions	1 lesion: 140 (70%)	4 lesions: 4 (2%)
	2 lesions: 29 (14.5%)	5 lesions: 5 (2.5%)
	3 lesions: 13 (6.5%)	> 5 lesions: 9 (4.5%)
Presence of sun exposed lesion	Yes: 186 (93.5%)	
	No: 13 (6.5%)	
Maximum size of lesion	≤1cm: 109 (56.5%)	
	>1cm: 84 (43.5%0)	
Occupational exposure to sunlight	Yes: 131 (66.2%)	
	No: 67 (33.8%)	
Occupational exposure to mutagens	Yes: 8 (4.3%)	
	No: 178 (95.7%)	

*SD: Standard deviation

IL-17 genotypes and alleles at positions rs2275913 G/A and rs763780 A/G. The frequencies of genotypes and alleles at rs2275913 G/A, and rs763780 A/G loci in both patients and controls are illustrated in Table 3. Genotype frequencies in both patients and controls were in accordance with the Hardy-Weinberg equilibrium ($p > 0.05$).
As indicated, the frequencies of GG, AG and AA genotypes at position rs2275913 inIL-

17A, were respectively 99/200 (49.5%), 76/200 (38%) and 25/200 (12.5%) in patients and 97/200 (48.5%), 84/200 (42%) and 19/200 (9.5%) in the control group. The frequency of A allele at this locus was 126/400 (31.5%) and 122/400 (30.5%) in patients and controls, respectively. No significant differences were found in the frequencies of genotypes and alleles between BCC patients and the control group at this position (P=0.28, and P=0.82, respectively).

At position rs763780 in IL-17F gene the frequencies of AA, GA and GG genotypes were respectively 166/200 (83%), 34/200 (17%) and 0/200 (0%) in patients, and 158/200 (79%), 40/200 (20%) and 2/200 (1%) in the control group. Although GG genotype occurred only in control group (with a frequency of 2/200 (1%), no significant differences were found in the frequencies of genotypes between BCC patients and the control group at this position (P=0.26). The frequency of G allele in BCC patients (34/400, 8.5%) was lower than that of the control group (44/400, 11%); however, the difference was not statistically significant (P=0.28).

Table 3. Frequencies of genotypes and alleles at positions rs2275913 G/A and rs763780 A/G as well as IL-17 serum level in patients with basal cell carcinoma (BCC) of the skin and healthy controls.

Locus, alleles and genotypes			Group		P value	Odds Ratio (OR)	95% Confidence interval (CI) for OR
			Patients	Controls			
Interleukin-17A -197G/A (rs2275913)	Alleles	G	274 (68.5%)	278 (69.5%)	0.82	0.95	0.70-1.30
		A	126 (31.5%)	122 (30.5%)			
	Genotypes	GG	99 (49.5%)	97 (48.5%)	0.92	1.04	0.69-1.57
		GA	76 (38%)	84 (42%)	0.47	0.85	0.56-1.29
		AA	25 (12.5%)	19 (9.5%)	0.42	1.36	0.69-2.68
Interleukin-17A serum level (pg/ml)			0.65 ± 0.11	0.03 ± 0.02	<0.001	-	-
Interleukin-17F 7488A/G (rs763780)	Alleles	A	366 (91.5%)	356 (89%)	0.28	1.33	0.81- 2.19
		G	34 (8.5%)	44 (11%)			
	Genotypes	AA	166 (83%)	158 (79%)	0.37	1.3	0.76- 2.21
		AG	34 (17%)	40 (20%)	0.52	0.82	0.48-1.40
		GG	0 (0%)	2 (1%)	NA*	NA*	NA*
Interleukin-17F serum level (pg/ml)			0.69 ± 0.4	0.29 ± 0.28	0.46	-	-

*Not applicable

Analysis indicated no significant association between investigated polymorphisms and clinicpathological characteristics of the patients including number of lesions, size of lesion, and existence of sun exposed lesion (p>0.05). The haplotypes emerged from two studied IL-17 polymorphisms (rs2275913 and rs763780) was then calculated and compared between patients and controls. Results are illustrated in Table 4. As indicated,

GA haplotype (rs2275913 G, rs763780 A) was the most frequent haplotype in both groups. No significant differences in the frequencies of haplotypes were found between cases and controls (Table4; p>0.05).

IL-17 serum level. Based on the distribution of genotypes at position rs2275913 G/A in patients, we selected 39 patients with GG genotype, 25 GA genotypes and 16 AA genotypes to be included in IL-17A serum study. The figures for control were respectively 27, 21, and 5. In the cases of rs763780 A/G polymorphism in IL-17F, 62 patients with AA genotype and 19 patients with AG genotypes were included in the IL-17F serum study. The figures for controls were 45 and 8. Totally, 80 patients and 53 controls were assessed for IL-17A serum level, and 81 patients and 53 controls were included in IL-17F serum study. As shown in Table 3, the mean serum levels of IL-17A in patients with BCC and the control group were determined to be 0.65 ± 0.11 and 0.03 ± 0.02 pg/ml, respectively (Mean ± SEM). While no differences in IL-17A serum levels were observed between individuals with different genotypes (data not shown), statistical analysis showed that the mean serum levels of IL-17A in patients with BCC were significantly higher than control groups (P<0.001, Table3). The mean serum levels of IL-17F in patients with BCC and the control groups were respectively 0.69 ± 0.4 and 0.29 ± 0.28 pg/ml, indicating no significant differences between these groups (P=0.46). IL-17 serum levels were not associated with clinicopathological characteristics of the patients (P>0.05; data not shown).

Table 4. Frequencies of IL-17 haplotypes in patients with basal cell carcinoma (BCC) of the skin and healthy controls.

Haplotype (IL-17A -197G/A; IL-17F 7488A/G)	Patients (2n=400, %)	Controls (2n=400, %)	P value	Odds ratio (OR)	95% Confidence interval (CI) for OR
G A	242 (60.5%)	237 (59.25%)	0.77	1.05	0.79-1.41
A A	124 (31%)	119 (29.75%)	0.76	1.06	0.78-1.45
G G	32 (8%)	42 (10.5%)	0.27	0.74	0.45-1.23
A G	2 (0.5%)	2 (0.5%)	NA*	NA*	NA*

* Not applicable

DISCUSSION

IL-17 is a key cytokine in skin cancer molecular pathology and may be considered as a novel prognostic marker in nonmelanoma skin cancers such as BCC (12). Furthermore, elevated levels of IFN-γ, IL-17, IL-23 and IL-22 cytokines were found in BCC lesions that is probably associated with severity of the inflammatory infiltrate (13). Recently, it has been reported that IL-17 in a TRAF4-ERK5 -dependent pathway contributes to keratinocyte proliferation and tumor formation (14). In addition to skin cancers, IL-17 contributes to pathogenesis of psoriasis, and IL-17-blocking agents may potentially serve as the promising therapeutic approach for the treatment of advanced basal cell carcinoma, psoriasis, and metastatic melanoma (15,16).

This study was conducted to investigate 2 single nucleotide polymorphisms in IL-17 gene; IL-17A -197G/A (rs2275913) and IL-17F 7488A/G (rs763780) in patients with BCC and their association with the patients' clinicopathological characteristics. While

no differences in IL-17A serum levels were observed between individuals with different genotypes, the mean serum levels of IL-17A in patients with BCC were significantly higher than control group. Studies indicated that IL-17 might contribute to the progression of some malignancies, such as prostate cancer, skin cancer, gastric carcinomas and lung cancer (17-20). Doroudchi *et al.* reported that the IL-17 serum level is significantly higher in patients with glioma than healthy individuals (28). In another study by Malekzadeh *et al.* 58% of the patients with ovarian papillary serous cystadenocarcinoma had increased levels of IL-17A in their sera, but the cytokine was not detectable in sera of the healthy individuals (26). These findings collectively with our data suggest that although investigated IL-17A polymorphism has no role in IL-17 production and BCC occurrence, IL-17A production in patients are affected by other factors including (but not limited to) other genetic variations. These findings need more investigations.

Analysis of genetic data revealed no significant differences in genotype distribution between patients and controls. -197G/A (rs2275913) polymorphism in IL-17A gene is located in IL-17 gene promoter region. To the best of our knowledge, no study, to date, investigated the association of this genetic variation with BCC. Consistent with our findings, Wu *et al.* reported no association between IL-17A -197G/A polymorphism with gastric cancer susceptibility in Chinese population (10). Wróbel *et al.* indicated no association between this polymorphism and Acute Myeloid Leukemia (AML) (21). Contrary to these findings, Shibata et al. indicated -197AA genotype and -197A to be associated with gastric cancer susceptibility and progression in a population from Japan (22). Investigation of IL-17A -197G/A polymorphism in cervical cancer in a population of Chinese women indicated that the frequencies of A allele and AA genotype were significantly higher in patients than controls. This study also revealed that A allele at this position is associated with higher disease stages (23). Espinoza *et al.* indicated that A allele at -197 position in IL-17 gene (rs2275913) has a higher affinity for NFAT transcription factor and consequently higher IL-17 production in a reporter-gene study (24). The discrepancies may come from the differences in genetic background of individuals, differences in molecular pathology of the investigated diseases and differences in the methods used for cytokine level assessment.

IL-17F 7488A/G (rs763780) polymorphism is located in exon 3 of the gene. Substitution of adenine to guanine at this position led to codon change, and subsequently, amino acid change from histidine to arginine (His161Arg) in protein (25). The results of the current study indicated that the 7488 mutant genotype GG occurred in 2 out of 200 (1%) subjects in control group, whereas this genotype was not observed in patients with BCC. The frequency of mutant G allele was higher in control group than patients with BCC; however, the difference was not statistically significant. Contrary to these findings, Wróbel *et al.* indicated that IL-17F 7488 mutant G allele is associated with risk of Acute Myeloid Leukemia (AML). In the afore-mentioned study, IL-17F 7488G allele was detected in 32.3% of the patients with AML but only in 8.8% of the controls (RR = 4.76) (21). Wu *et al.* reported IL-17F 7488GA and GG genotypes to be significantly increased in patients with gastric cancer. Furthermore, they showed that the association between IL-17F 7488GA genotype and gastric cancer vary with tumor sites and histological types of cancer (10). In the current study, we observed no significant association between IL-17 haplotypes and genetic susceptibility to BCC. However, a previous study in Chinese population indicated that GGGAC and AGGAC haplotypes (emerged from rs1974226, rs2275913, rs3819024, rs4711998 and

rs8193036) were associated with a reduced risk of gastric cancer (adjusted OR = 0.64, 95% CI = 0.46–0.89 and adjusted OR = 0.38, 95% CI = 0.17–0.81, respectively) (26). Another study revealed that haplotype G rs2275913G rs3819025A rs3748067 may predict good prognosis, whereas haplotypes T rs763780 C rs7771511 G rs12203582 G rs9382084 T rs1266828 may be associated with a poor prognosis for breast cancer patients in Chinese population (27). Although the inconsistency observed in different studies dealing with IL-17 genetic variations, may come from different sources, as previously mentioned, these data collectively suggest that a widespread haplotype analysis with adequate sample sizes is required to shed light on different aspects of IL-17 gene polymorphisms in malignancies.

Altogether, the findings of this study, as a preliminary investigation dealing with IL-17 gene and BCC, do not verify any association between IL-17 gene at position rs763780 and rs2275913 with susceptibility to BCC in a population from Iran. However, elevated IL-17A serum levels in patients (not affected by IL-17A -197G/A polymorphism) could be suggestive of a role for this cytokine in BCC. As a limitation of the present study, we were not able to do cytokine assessment for all individuals in the study. Accordingly, haplotype analysis of IL-17 gene (covering all IL-17 SNPS), along with cytokine analysis among the whole population in the study is suggested.

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