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Research Article

IL-10 (-819C/T) SINGLE NUCLEOTIDE POLYMORPHISMS AND RISK FACTORS FOR ORAL SQUAMOUS CELL CARCINOMA (OSCC) IN INDIAN POPULATION

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Background: Interleukin-10 (IL-10) is a pleiotropic cytokine, has both tumor development and tumor suppression properties. The mutation may influence expression of IL-10 gene, resulting in abnormal cell proliferation and development of cancer. Therefore we aim to evaluate the association of IL-10 (-819C/T) gene polymorphism with the risk of OSCC patients in India population.

Methods: A total of 241 OSCC patients and 241 controls were genotyped by polymerase chain reaction-restriction fragment length polymorphism technique for IL-10 (-819C/T).The genotype and allele frequencies of IL-10 (-819C/T) were analyzed by chi-square test and odds ratio (OR) relative risk.

Results: The genotype frequencies of IL-10 (-819C/T) gene polymorphism were significantly increase the risk of OSCC patients (CC vs CT-OR: 0.61; CI: 0.38-0.96; p: 0.044; and CC vs TT-OR: 0.19; CI: 0.090-0.40; p: <0.001).Moreover, the t allele was also associated with increased risk of OSCC (OR: 0.64; CI: 0.50-0.83; p: <0.001). IL-10 (-819C/T) gene polymorphism was not associated with progression of OSCC and environmental risk factor.

Conclusions: The genotype and allele frequencies of IL-10 (-819C/T) gene polymorphism were significantly associated with increased risk of OSCC.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a most common and predominant malignancy of the head and neck region (Attar *et al*., 2010). Worldwide, OSCC is an eighth most frequent cancer with an yearly incidence of more than 42,60,000 cases and ~ 128,000 deaths (WHO, 2013; Mallath *et al*., 2014). In India, the incidence of OSCC is about 1 million with 600,000-700,000 deaths reported per annum, predominant in males (Mallath *et al*. 2014; Srivastava *et al*. 2010). OSCC has multistep progression which is influenced by numerous environmental risk factors, such as tobacco smoking, chewing, and alteration in genes, such as tumor suppressor genes and oncogenes, cytokines (Liu *et al*. 2012; Nagaraj *et al*. 2006). Various studies reported that the common polymorphisms in inflammation, angiogenesis, and thrombosis-related genes are associated with increased risk for OSCC (Dikshit *et al*. 2012). Interleukin-10 (IL-10) is a pleiotropic cytokine, has both tumor promoting and tumor-inhibiting properties (Tanikawa *et al*., 2012; Holan *et al*., 2014; Qi *et al*., 2014; Yu *et al*., 2014; Li *et al*., 2016).

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However, a number of other findings suggest that the biological properties of IL-10 are more complex than this and IL-10 may have immunostimulatory or immunosuppressive properties, depending upon the assay used, cell types involved and other concomitant immune events (Eskdale *et al*., 1997; Turner *et al*., 1997), therefore the actions of IL-10 on tumor development may be more complex. In particular, animal models suggest that IL-10 can induce NK cell activation and so facilitate anti-tumor responses, leading to tumor cell destruction (Park *et al*., 2011).

Hsu *et al*. (2015) reported that the IL-10 polymorphism might have an important role in increasing oral related cancer risk. There are numerous polymorphisms in the IL-10 gene. The IL-10 (-819C/T) is a common single nucleotide polymorphism (SNP) in the promoter region (Li *et al*., 2016). Many studies have reported the association between the IL-10 (-819C/T) gene polymorphism and development of OSCC (Crawley *et al*., 1999; Turner *et al*., 1997). In this study, we aim to evaluate the correlation between the IL-10 (-819C/T) promoter region polymorphism and susceptibility to OSCC in a North Indian population.

MATERIALS AND METHODS

This case-control study were included 241 newly diagnosed, previously treated/untreated and histological/pathological confirmed OSCC patients, who registered in the department of Surgical Oncology, King George Medical University UP, Lucknow. The control group comprised 241 healthy volunteers who either visited with patients or general health checkup teaching/non-teaching staff and self-willing persons. The no evidence of any abnormal growth, suggestive of cancer in the individual and other serious diseases were included as a controls. Informed written consent was obtained from all subjects. For this study the ethical clearance was obtained following the guidelines set down by the institute's ethical committee. Demographical and other clinical information such as age, sex, height, weight, tobacco chewing, smoking, disease status (tumor stage) and history of comorbid conditions (heart disease, stroke, diabetes, emphysema) were taken from patients' medical records.

Blood sample collection and DNA extraction

Blood samples were collected in EDTA vacutainer. The genomic DNA was extracted from blood samples by using the salting out method (Miller *et al*. 1988). The DNA was stored at -80 ^{0}C, until further genomic analysis.

Genotyping of IL-10 (-C819T) gene polymorphism

The PCR of IL-10 (-819 C/T), the final volume of PCR reaction mixture, was 25 µl containing 40 ng genomic DNA, 10 picomole each of forward and reverse primers (F-5'-TAC AGT AGG GTG AGG AAA CC3' and R 5'- GGT AGT GCT CAC CAT GAC CC3') at concentration of 1X, 1X PCR master mixture. Amplification was carried out for 94°C for 5 minutes followed by 35 cycle of 1 minutes at 94°C for denaturation, 1 minutes at 59°C for annealing, 1 minutes at 72°C for extension, with a final extension at 72°C for 7 minutes. Digestion with 3 units *MaeIII* at 37°C for overnight yielded a C allele (125, 84) bp and T allele (209) bp products. The obtained fragments' sizes were analyzed on a 2% agarose gel. After restriction enzyme digestion, the predicted sizes of the fragments are shown in Fig. 1.

Statistical Analysis

All the demographic and clinical data concerning age, sex, weight, height and use of tobacco (smoking or chewing) were compared by chi-square test. Genotype and allele frequencies of IL-10 (-C819T) were analysed by chi-square test among OSCC cases and controls. Odds ratios (ORs) with95% confidence interval (CI) were calculated to estimate the strength of associationof IL-10 (-C819T) gene polymorphism to the risk of OSCC. A p-value <0.05 was considered significant.

RESULTS

Demographic profile such as mean age, gender, weight, height were comparable in between OSCC cases and healthy controls are shown in Table 1. The smoking (p = 0.03) and tobacco chewing (p = 0.026) were significantly different among OSCC patients and controls. Total 63.9% OSCC patients had stage I + II tumor, whereas 36.1% patients had stage III + IV tumor (Table 1). The genotype and allele frequencies of the IL-10 (-819C/T) gene polymorphism among the OSCC patients and controls are shown in Table 2.

Table 1 Demographic distribution of the OSCC cases and controls

	OSCC cases n=241 (%)	Controls n=241 (%)	p-value
Age	46.37±11.10	44.83±8.55	0.087
Sex			
Male	169 (70.12%)	184 (76.35%)	
Female	72 (29.88%)	57 (23.65%)	0.15
Weight (kg)	56.67±8.2	57.97±7.52	0.072
Height (cm)	162.29±6.22	163.11±5.47	0.126
Smoking			
Yes	75 (31.12%)	53 (21.99%)	0.03*
No	166 (68.88%)	188 (78.01%)	
Chewing Status			
Yes	146 (60.58%)	112 (46.47%)	0.026*
No	95 (39.42%)	129 (53.53%)	
Tumor Stage			
I	19 (7.88%)		
II	135 (56.02%)		
II	82 (34.02%)		
IV	5 (2.07%)		

OR-Odds ratio, CI-Confidence interval, *Significant

Table 2 Distribution of genotype and allele frequencies of IL-10 (-819C/T) in OSCC cases and control group

	OSCC cases n=241 (%)	Control n=241 (%)	OR (95% CI)	p-value
Genotype Frequencies				
CC	37 (15.35%)	62 (25.73%)	1.00	Ref.
CT	163 (67.63%)	166 (68.88%)	0.61 (0.38-0.96)	0.044*
TT	41 (17.01%)	13 (5.39%)	0.19 (0.090-0.40)	<0.001*
Allele Frequencies				
C	237 (49.17%)	290 (60.17%)	1.00	Ref.
T	245 (50.83%)	192 (39.83%)	0.64 (0.50-0.83)	<0.001*

OR-Odds ratio, CI-Confidence interval, Ref.-Reference, *Significant

The frequencies of the CC, CT and TT genotypes of IL-10 (-819C/T) were 15.35%, 67.63%, 17.01% in the study cases, and were 25.73%, 68.88%, 5.39% in controls respectively, whereas the allele frequencies of the C and T were 49.17%, 50.83% in the study cases and 60.17%, 39.83% in controls, respectively. Thehomozygous CC and heterozygous CT genotype were significantly associated with increased risk of OSCC (OR: 0.61; CI: 0.38-0.96; p: 0.044) as compared to controls. The homozygous CC and homozygous TT genotype were also significantly difference (OR: 0.19; CI: 0.090-0.40; p: <0.001) in between groups. The C, T allele frequencies of the IL-10 (-819C/T) were also significantly deference in between OSCC patients and control groups (OR: 0.64; CI: 0.50-0.83; p: <0.001) (Table 2).

We categorized the patients into two groups' low-risk OSCC and high-risk OSCC groups. Low OSCC group comprised of stage I + II and high-risk group comprised of patients with stage III + IV. Low-risk OSCC was taken as a reference. The frequencies of CC, CT and TT genotypes and frequency of C and T allele of the IL-10 (-819C/T) gene polymorphism were not significantly difference in between low risk and high-risk tumor status as shown in Table 3.

Table 3 Distribution of genotype and allele frequencies of IL-10 (-819C/T) in among tumor stage in OSCC cases

	Low risk (I+II) n=154 (%)	High risk (III + IV) n=87 (%)	OR (95% CI)	p- Value
Genotype Frequencies				
CC	26 (16.88%)	11 (12.64%)	1.00	Ref.
CT	101 (65.58%)	62 (71.26%)	1.45 (0.67-3.14)	0.448
TT	27 (17.53%)	14 (16.09%)	1.23 (0.47-1.19)	0.862
Allele Frequencies				
C	153 (49.68%)	84 (48.28%)	1.00	Ref.
T	155 (50.32%)	90 (51.72%)	1.06 (0.73-1.53)	0.84

OR-Odds ratio, CI-Confidence interval, Ref.-Reference

This study we also study the possible association of environmental risk factors with IL-10 (-819C/T) gene polymorphisms on OSCC susceptibility. The genotype CC, CT and TT and allele C and T frequencies of the IL-10 (-819C/T) were not significantly associated ($p>0.05$) among subjects not exposed and exposed to environmental risk factors (smoking and tobacco chewing) (Tables 4).

Table 4 Distribution of genotype and allele frequencies of IL-10 (-819C/T) gene polymorphism in oral cancer patients and control group according to environmental risk factor

	Yes	No	OR (95% CI)	p- Value
Tobacco Smoking	n=75	n=166		
Genotype Frequencies				
CC	12 (166.0%)	25 (15.06%)	1.00	Ref.
CT	49 (65.33%)	114 (68.67%)	1.12 (0.52-1.24)	0.932
TT	14 (18.67%)	27 (16.27%)	0.93 (0.36-2.40)	0.873
Allele Frequencies				
C	73 (48.67%)	164 (49.40%)	1.00	Ref.
T	77 (51.33%)	168 (50.60%)	0.97 (0.66-1.43)	0.96
Tobacco Chewing	n=146	n=95		
Genotype Frequencies				
CC	25 (17.12%)	12 (12.63%)	1.00	Ref.
CT	93 (63.70%)	70 (73.68%)	1.57 (0.74-1.34)	0.323
TT	28 (19.18%)	13 (13.68%)	0.97 (0.37-2.51)	0.945
Allele Frequencies				
C	143 (48.97%)	94 (49.47%)	1.00	Ref.
T	149 (51.03%)	96 (50.53%)	0.98 (0.68-141)	0.99

OR-Odds ratio, CI-Confidence interval, Ref.-Reference

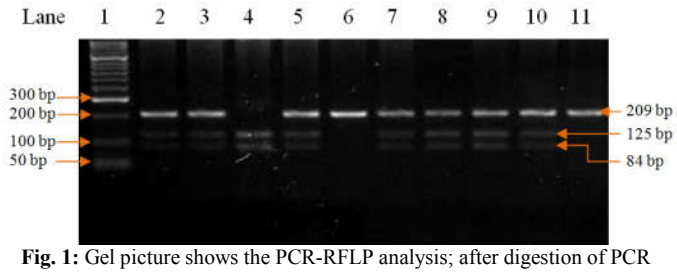

Fig. 1: Gel picture shows the PCR-RFLP analysis; after digestion of PCR product with *MaeIIIrestriction* enzymes; Lane 1: 100 bp DNA ladder; Lane 2, 3, 5, 7, 8, 9, 10: Heterozygous CT genotype; Lane 4: Homozygous CC genotype; Lane 6, 11: Homozygous TT genotype

DISCUSSION

IL-10 is an inflammatory cytokine with anti-inflammatory properties, located on chromosome 1 at q31-32, with five exons and four introns (Fiorentino *et al*., 1989; Moore *et al*., 1990; Eskdale *et al*., 1997). The three most common single nucleotide polymorphism are presented in the IL-10 promoter region −1082A/G, −819T/C and −592A/C (Turner *et al*., 1997; Saxena *et al*., 2012). These alterations influence expression of IL-10 gene, resulting in abnormal cell proliferation and development of cancer (Eskdale *et al*., 1998; Gibson *et al*., 2001). Various previous study reported that the IL-10 gene polymorphisms were significantly associated with various cancer such as breast cancers, lung cancer, cervical cancer, and digestive cancer (Pooja *et al*., 2012; Hsia *et al*., 2014; Singhal *et al*., 2015; Kuo *et al*., 2014).

In our study the use of tobacco (smoking and chewing) was found to be a potent risk factor for OSCC. Several studies reported that the individuals' exposure to environmental risk factors such as tobacco and alcohol consumption increase risk of OSCC (Gupta *et al*., 2013; Ray *et al*., 2013; Loyha *et al*., 2012; Harvey *et al*., 1986). Smoking and tobacco chewing and are most common risk factors for oral cancer (Yang *et al*., 2005 and 2001). Seyedroudbari *et al*. (1998) reported that the smokeless tobacco up-regulated proinflammatory cytokines. Long-time of tobacco chewing and smoking is well known to contribute to carcinogenesis (Yen *et al*., 2008; Nagaraj *et al*., 2006; Lai and Lee 2006).

In this study, we found that the IL-10 (-819C/T) gene polymorphisms were statistically associated with the risk of OSCC. The findings of our study are supported by Niu *et al*. (2015), who suggested that the genotypes of IL-10 (-819C/T) gene polymorphism was significantly associated with increased risk of OSCC in a meta-analysis. Some other studies also reported that the IL-10 gene polymorphisms were significantly associated with the breast cancer (Kozlowski *et al*., 2003 and Giordani *et al*., 2003), lymphoma (Levy *et al*., 1994), colon cancer (Gastl *et al*., 1993) and ovarian cancer (Pisa *et al*., 1992).

In the present study, we did not find any correlation between IL-10 (-819C/T) gene polymorphisms and progression of OSCC. Similarly, Langsenlehner *et al*., (2005) and Giordani *et al*. (2003), did not find any association between IL-10 gene polymorphism and clinic-pathological status such as tumor size, lymph node, histological grade, metastatic.

In this study we also correlated the cytokine gene polymorphism with oral cancer and controls with environmental risk factors. The genotype and allele frequencies of IL-10 (-819C/T) gene polymorphisms were not associated with risk of OSCC in tobacco smoking and chewing individuals. Previously, Hsu *et al*. (2015) reported that the IL-10 gene polymorphism was not significantly associated with oral cancer patients who used tobacco smoking and chewing.

CONCLUSIONS

Our result showed that the IL-10 (-819C/T) gene polymorphism is significantly associated with increased risk to OSCC. There was no association observed in between IL-10 (-819C/T) gene polymorphism and progression of OSCC. Moreover, IL-10 (-819C/T) gene polymorphism was not significantly associated with oral cancer patients who used tobacco smoking and chewing. However, additional studies, involving larger groups of patients and controls, are required to further validate our findings.

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