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Promoter Polymorphism in the Interleukin-10 Confers an Increased Risk of DLBCL in Chinese

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Abstract

Findings suggest that genetic polymorphisms in cytokine genes are associated with an increased risk of Non-Hodgkin Lymphoma (NHL) in Caucasians. This study was designed to assess whether single nucleotide polymorphisms in IL-10 promoter play a role in predisposing individuals to NHL in Chinese populations. We genotyped four SNPs in the distal and proximal IL-10 promoter (IL-10 -3575T/A, IL-10 -1082A/G,-819T/C and -592A/C) using polymerase chain reaction-restriction fragment length polymorphism analysis. We conducted this study in 512 NHL cases and 500 age- and sex-matched healthy controls. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between individual SNP and haplotypes with non-Hodgkin lymphoma overall and two well-defined subtypes [Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL)]. No significant correlation of IL-10-3575T/A, IL-10-1082A/G,-819T/C and -592A/C polymorphisms to risk of NHL overall. When analyses by subtype, the -1082 AG genotypes and G alleles were associated with a significantly increased risk of DLBCL as compared with the -1082 AA genotype and A alleles (OR=1.64, 95% CI 1.06~2.54, P=0.025 for AG; OR=1.57, 95% CI 1.06-2.31, P=0.023 for G allele). Haplotype analyses revealed three common haplotype (TATA, TACC and AGCC), there was no significant differences in the estimated frequencies of haplotypes between overall NHL or subtypes and controls. Our results suggest that IL-10 promoter -1082 SNP might be a risk factor of DLBCL development in Chinese populations.

Keywords: Interleukin-10; Non-Hodgkin lymphoma; Polymorphisms; Diffuse large B-cell lymphoma; Haplotype

Introduction

Non-Hodgkin Lymphoma (NHL) is a cancer of the lymphoid system. The incidence of NHL has increased during the last twenty years around the world, but etiological factors contributing to this phenomenon remain still largely unknown [1,2]. It has been suggested that immune dysfunction may be the underlying basis of lymphomagenesis [3,4]. Therefore, attempts to clarify the mechanisms involved in immune system deregulation in lymphoma should contribute to a better understanding of the pathogenesis of this malignancy. Interleukin-10 (IL-10) is an important

immunoregulatory cytokine mainly produced by monocytes and macrophages, T cells, as well as healthy and neoplastic B lymphocytes and plays a key role in controlling the balance between cellular and humoral immune responses [5]. IL-10 has strong immunosuppressive effects by way of the inhibition of proinflammatory T helper 1 (Th1) lymphocytes, and, conversely, it stimulates the proliferation and differentiation of B and Th2 cells [6]. Numerous studies have shown that IL-10 may be involved in the pathogenesis of lymphoid disorders. It has been found to act as an autocrine growth factor which up-regulates bcl-2 expression in some B-cell malignancies [7]. Increased serum IL-10 levels were also found to be associated with poor prognosis and shorter survival of the patients with NHL [8-12]. The precise mechanisms engaged in the regulation of IL-10 production remain undetermined, although inherited factors appear to play an important role. The gene encoding IL-10 is located on chromosome 1 (1q31-1q32). A large number of polymorphisms of the IL-10 gene promoter have been described. These include IL-10-1082(A/G), -819(T/C) and -592(A/C) in the proximal region and IL-10-3575(A/T) in the distal region of the promoter, which influence the transcription of IL-10 messenger RNA and the expression of IL-10 *in vitro*[14,15].

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Several studies have evaluated whether polymorphisms in IL-10 promoter are associated with an increased risk of NHL [16-26]. Cunningham et al. [16] observed that the frequency of the low IL-10 producing A allele (at position -1082) was significantly higher in patients with aggressive lymphomas compared to in controls. However, in a larger study group, Lech-Maranda E et al. [17] found that the frequency of IL-10-1082G allele was higher in patients with diffuse large B-cell lymphoma (DLBCL) than in controls. The most influential of the studies identified genotypes AA or TA at position -3575 of IL-10 to be associated with an increased risk of NHL in the largest pooled analysis to date. In this project, we wish to explore whether IL-10 polymorphisms were associated with susceptibility of NHL in a Chinese population.

Methods

Study subjects

The study included 560 cases newly diagnosed non-Hodgkin lymphoma recruited from Shandong Cancer Hospital and Institute and Shandong Provincial Hospital ages 18 to 83 years (mean age ± SD, 51.5 ± 14.0 years) between January 2011 and January 2016. 540 Population controls (age range, 20-80 years, mean age ± SD, 51.9 ± 12.2 years) were accrued from healthy volunteers who visited the general health check-up division at the two hospitals between February 2011 to February 2016. Selection criteria for controls were no evidence of any personal or family history of cancer or other serious illness. Randomly selected controls were matched to the cases by age (± 5 years) and gender. All subjects were unrelated ethnic Han Chinese. Written informed consent was obtained from each participant. The study was approved by the Hospital Review Boards of Shandong Cancer Hospital and Institute and Shandong Provincial Hospital. All study participants provide peripheral blood. After exclusions due to inadequate DNA quantity or to other issues related to sample handling and DNA quality, DNA samples from 512 cases (91.4%) and 500 controls (92.5%) were available for genotyping finally. Details of the study group are described in Table 1.

Histological lymphoma subtypes were classified according to the Revised European- American classification of lymphoid neoplasms. Among the cases were 410 B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) (n=204), Follicular Lymphoms (FL) (n=124), mantle cell lymphoma (MCL) (n=36) and other types of B-cell lymphomas (n=46), and T-cell lymphomas (n=102), including NK/T-cell lymphoma(NK/TCL) (n=48), Peripheral T-cell Lymphoma (PTCL)(n=35), and other types of T-cell lymphomas (n=19). All of the cases were diagnosed using standard procedure including immunophenotypic stains and cytogenetics and other markers.

Genotyping

Genomic DNA from peripheral blood was extracted using Qiagen DNA Isolation Kit (Qiagen GmbH, Hilden, Germany). IL–10 promoter polymorphism was analyzed using PCR amplification and restriction analysis (PCR–RFLP). All of the PCR reactions were done in a GeneAmp PCR System 9600 thermocycler (Applied Biosystems, Foster, CA) in a final volume of 25 μl containing 5 pmol of each primer, 50 ng genomic DNA, 1.5 mM MgCl2, 5 uM dNTPs and 1U of Taq DNA polymerase in the PCR buffer containing 10 mM Tris–HCl and 50 mM KCl. The PCR cycles were as follows: 95°C for 5 min, 35 cycles of denaturing at 95°C for 40s, annealing at the indicated temperature for 1 min, extension at 72°C for 40s, and a single final extension at 72°C for 10 min. The amplified products were digested with corresponding restriction endonucleases (New England Biolabs, Inc., Beverly, MA, USA), the Cleaved fragments were separated by electrophoresis in 10% polyacrylamide gel and stained with sliver nitrate for visualization. The outline of PCR-RFLP analysis used in this study is shown in Table 2. To confirm the genotyping results, PCR-amplified DNA samples were examined by DNA sequencing and the results were 100% concordant. In addition, duplicate samples from 80 study subjects that had been regenotyped and resulted in 99% concordance.

Statistical analysis

The SPSS statistical software package ver. 19.0 was used for the statistical analysis. Demographic data between the study groups were compared by chi-square test and by Student's t-test. Genotype and allele frequencies of IL-10 were compared between groups using the chi-sqare test and Fisher exact test when appropriate, and Odds Ratios (OR) and 95% Confidence Intervals (CIs) were calculated using unconditional logistic regression. Hardy-Weinberg equilibrium was tested for with a goodness of fit chi-square test with 1 degree of freedom to compare the observed genotype frequencies among the subjects with the expected genotype frequencies. In addition to conducting analyses of overall NHL, we calculated subtype-specific ORs for the two most prevalent histologic subtypes of NHL: DLBCL and FL. The linkage disequilibrium of the four loci, and haplotypes were estimated by SHEsis software (http://analysis.bio-x.cn/).

Results

A total of 512 NHL cases and 500 controls were recruited for the present study. All subjects were ethnic Chinese. The distributions of cases and controls were similar with respect to gender (P=0.365) and age (P=0.575). Most cases were B-cell lymphomas, predominantly DLBCL and FL (Table 1). The genotype and allele frequencies of the distal region of IL-10 promoter-3575T/A polymorphisms and the proximal region of IL-10 promoter -1082 A/G, -819 T/C and -592 A/C polymorphisms among the controls and the cases are presented in Table 3. The genotype distributions of four polymorphisms among the controls and the cases were in Hardy–Weinberg equilibrium. Overall, no variant allele frequency is significantly different between the controls and all NHL cases (P=0.196 for IL-10-3575; P=0.112 for IL-10-1082; P=0.194 for IL-10-819; P=0.194 for IL-10-592). However, analyses by NHL subtype showed that the frequency of IL-10-1082G allele was higher in patients with DLBCL cases as compared with healthy control subjects (11.3% *vs.* 7.5%, P=0.023). The -1082 AG genotypes and G alleles were associated with a significantly increased risk of DLBCL as compared with the -1082 AA genotypes and A alleles (OR=1.64, 95% CI 1.06~2.54, P=0.025 for AG; OR=1.57, 95% CI 1.06-2.31, P=0.023 for G allele). For the FL subgroup, no significant differences for the analyzed IL-10 loci were found. Haplotype analyses were performed and the possible three haplotype (TATA, TACC, AGCC) frequencies are shown in Table 3. Strong Linkage Disequilibrium (LD) was observed between two pairs of the analyzed SNPs (for IL-10 -3575 and -1082 D′=0.90, r2=0.54; for IL-10 -1082 and −819 D′=0.89, r2=0.34). Complete LD was observed between IL-10 -819 and -592 (D'=1.0, r2=1.0). There were no significant differences in the estimated frequencies of these haplotypes between overall NHL, DLBCL and FL patients and controls.

Discussion

In the present study, we have analyzed the correlation between

Table 1: Characteristics of genotyped study participants.

Characteristics	Patients, no. (%) (n=512)	Controls, no. (%) (n=500)	P
gender			
males	322(62.9)	300(60.0)	0.365
females	190(37.1)	200(40.0)	
age			
less than 40	94(18.4)	87(17.4)	0.575
40-49	99(19.2)	116(23.2)	
50-59	146(28.6)	145(29.0)	
60-69	115(22.5)	99(19.8)	
70+	58(11.3)	53(10.6)	
histological type			
all B cell	410(80.1)		
diffuse large B-cell lymphoma (DLBCL)	204(39.8)		
follicular lymphoma (FL)	124(24.2)		
mantle cell lymphoma (MCL)	36(7.0)		
other B cell	46(9.0)		
all T cell	102(19.9)		
NK/T-cell lymphoma (NK/TCL)	48(9.4)		
peripheral T-cell lymphoma (PTCL)	35(6.8)		
other T cell	19(3.7)		

4 SNPs in the IL-10 promoter distal and proximal regions (-3575 T/A, -1082 A/G, -819 T/C, and -592 A/C) and risk of non-Hodgkin lymphoma. There were no significant differences in allele frequencies or genotype distributions for any of the IL-10 SNPs between patients with NHL and controls. In subtype analyses, the IL-10 -1082 gene variation significant differences between healthy controls and DLBCL patients can be visualized: genotype (AG) and G-allele based analysis showed P-values of 0.025 and 0.023, respectively, suggesting a risk for DLBCL for carriers of the G-allele as described by Lech-Maranda et al. [17]. However, none of haplotypes was significant different between NHL or subtype groups and controls. We observed frequencies of 0.05 for the IL-10-3575 A allele and 0.07 for the IL-10-1082 G allele, which are similar to those frequencies observed in healthy East Asian populations such as Thai population [27] and Korean [28], but significantly lower than those reported for Caucasian populations from the study of the InterLymph (for IL-10-3575 A allele 0.36 and for IL-10-1082 G allele 0.45, respectively, n= 4018) [19]. The-819 T allele and -592 A alleles were in complete linkage disequilibrium in the present study and the allele ratio for -819 T/ -592 A is 0.69, which is significantly higher than those reported for Caucasians (for IL-10-819 T is about 0.22~0.32 and IL-10-592 A is about 0.22~0.32, respectively) [17-21]. Major haplotype frequency of the TATA among the controls in the present study was 0.67, which was significantly higher than those of study performed in the Caucasians [19,21], suggesting that the frequencies of IL-10 gene haplotypes and alleles might vary among the different ethnic groups.

IL-10 is a multifunctional cytokine and is part of a balanced network of immunoregulatory factors, where it also stimulates proliferation of certain B-cell malignancies or suppresses the immune response against cancer. IL-10 has been implicated in certain infectious diseases, autoimmunity, transplantation tolerance and tumorigenesis. It has been reported that there are a number of polymorphisms in the distal and proximal IL-10 gene promoter, including IL-10-3575, IL-10-1082, IL-10-819, and IL-10-592, which may genetically affect interindividual differences in IL-10 production. *In vitro* stimulation of peripheral blood lymphocytes using concanavalin A has revealed that the IL-10-1082 GG is associated with a 1.3-fold increase in IL-10 protein production compared to the low IL-10-producing AA genotype [29]. As well, the GCC haplotype also exhibits significantly higher transcriptional activity than the ATA haplotype in a luciferase reporter system. In addition, The IL10-3575A allele has been reported to be associated with lower IL-10 production than the T allele [13].

A lot of epidemiological studies have investigated the association between the IL-10 polymorphisms and the risk of different cancer types. However, results with respect to NHL were conflicting. In this study, we demonstrated IL-10 promoter -1082 AG genotype and G allels might be a risk factor of DLBCL development in Chinese population. Similarly, Ye et al. [23] reported that IL-10 rs1800896 (-1082) was associated with an increased risk of overall NHL (ORper-minor-allele =2.64, 95% CI (1.75-3.98), B-cell lymphomas (ORper-minor-allele =2.75, 95% CI 1.79-4.23), and DLBCL (ORper-minor-allele =3.03, 95% 1.85-5.01) in Shanghai Chinese's population. A study published by Lech-Maranda et al. [17] showed that IL-10-1082G (high expression) allele may be a risk factor for DLBCL susceptibility, which support the hypothesis that IL-10 as a B-cell stimulatory cytokine may stimulate lymphomagenesis. However, Kube et al. [20] reported that these four IL-10 SNPs frequencies of lymphoma patients are comparable as in healthy controls in Germans. In contrast to our current study, several studies revealed that patient with aggressive non-Hodgkin's lymphoma or B cell lymphoma are more likely to have low IL-10 producing genotypes such as IL-10-3575A or -1082A allele [16,19,21,22]. These results may be interpreted that lower expression of IL-10, a potent downregulator of TNF-α and other macrophage proinflammatory cytokines, may increase lymphoma risk by less efficiently suppressing proinflammatory cytokine production. In

Table 2: Outline of *IL-10* promoter polymorphism PCR-RFLP analysis.

Polymorphism	Primer sequence	Annealing temperature	restriction enzyme	Allele size
IL-10-3575 T/A	5'-GGTTTTCCTTCATTTGCAGC-3'	60°C	*Tsp509I*	T:121,110bp
	5'-ACACTGTGAGCTTCTTGAGG-3'			A:231bp
IL-10-1082G/A	5′-CTCGCTGCA ACCCAACTGGC-3′	58°C	*Mnl I*	A:139bp
	5′-TCTTACCTATCCCTACTTCC-3′			G:106,33bp
IL-10-819C/T	5′-TCATTCTATGTGCTGGAGATGG-3′	59°C	*Mae III*	C:125,84bp
	5′-TGGGGGAAGTGGGTAAGAGT-3′			T:209bp
IL-10-592C/A	5′-GTGAGCACTACCTGACTAGC-3′	58°C	*Rsa* I	C:412bp
	5′-CCTAGGTCACAGTGACGTGG-3′			A:175,237bp

Table 3: Associations between *IL-10* variants and risk of overall NHL, DLBCL and FL; analyses by genotype and haplotype.

Genotype/haplotype	controls			NHL			DLBCL			FL
	n(%)	n(%)	P	OR(95% CI)	n(%)	P	OR(95% CI)	n(%)	P	OR(95% CI)
IL-10(-3575T/A)										
Genotype										
TT	452(90.4)	450(87.9)		1	177(86.8)		1	111(89.5)		1
TA	45(9.0)	58(11.3)	0.218	1.3(0.6~1.95)	25(12.3)	0.186	1.4(0.8~2.4)	12(9.7)	0.809	1.09(0.56~2.12)
AA	3(0.6)	4(0.8)	0.703	1.34(0.30~6.02)	2(0.9)	0.562	1.70(0.28~10.27)	1(0.8)	0.792	1.38(0.14~13.17)
Alleles										
T	949(94.9)	958(93.6)		1	379(92.9)		1	234(94.4)		1
A	51(5.1)	66(6.4)	0.196	1.28(0.88~1.87)	29(7.1)	0.142	1.424(0.89~2.28)	14(5.6)	0.73	1.11(0.61~2.05)
IL-10(-1082A/G)										
Genotype										
AA	430(86.0)	422(82.4)		1	161(78.9)		1	104(83.9)		1
AG	65(13.0)	83(16.2)	0.142	1.30(0.92~1.85)	40(19.6)	0.025*	1.64(1.06~2.54)	18(14.5)	0.638	1.15(0.65~2.02)
GG	5(1.0)	7(1.4)	0.547	1.44(0.45~4.52)	3(1.5)	0.522	1.60(0.39~6.78)	2(1.6)	0.551	1.65(0.32~8.64)
Alleles										
A	925(92.5)	927(90.5)		1	362(88.7)		1	226(91.1)		1
G	75(7.5)	97(9.5)	0.112	1.29(1.04~1.74)	46(11.3)	0.023*	1.57(1.06~2.31)	22(8.9)	0.471	1.20(0.73~1.97)
IL-10(-819 C/ T)										
Genotype										
TT	244(48.8)	235(45.9)		1	92(45.1)		1	56(45.2)		1
TC	204(40.8)	211(41.2)	0.595	1.07(0.83~1.39)	84(41.2)	0.621	1.09(0.77~1.55)	52(41.9)	0.625	1.11(0.73~1.69)
CC	52(10.4)	66(12.9)	0.182	1.32(0.88~1.985)	28(13.7)	0.178	1.43(0.85~2.39)	16(12.9)	0.36	1.34(0.71~2.52)
Alleles										
T	692(69.2)	681(66.5)		1	268(65.7)		1	164(66.1)		1
C	308(30.8)	343(33.5)	0.194	1.13(0.94~1.36)	140(34.3)	0.199	1.17(0.92~1.50)	84(33.9)	0.351	1.15(0.86~1.55)
IL-10 (-592 C/A)										
Genotype										
AA	244(48.8)	235(45.9)		1	92(45.1)		1	56(45.2)		1
AC	204(40.8)	211(41.2)	0.595	1.07(0.83~1.39)	84(41.2)	0.621	1.09(0.77~1.55)	52(41.9)	0.625	1.11(0.73~1.69)
CC	52(10.4)	66(12.9)	0.182	1.32(0.88~1.985)	28(13.7)	0.178	1.43(0.85~2.39)	16(12.9)	0.36	1.34(0.71~2.52)
Alleles										
A	692(69.2)	681(66.5)		1	268(65.7)		1	164(66.1)		1
C	308(30.8)	343(33.5)	0.194	1.13(0.94~1.36)	140(34.3)	0.199	1.17(0.92~1.50)	84(33.9)	0.351	1.15(0.86~1.55)
Analysis by haplotype (-3575, -1082, -819, -592)										
TATA	673(67.3)	648(63.2)		1	249(61.1)		1	156(62.9)		1
TACC	251(25.1)	270(26.4)	0.284	1.12(0.91~1.37)	107(26.1)	0.302	1.15(0.88~1.51)	69(27.8)	0.294	1.19(0.86~1.63)
AGCC	37(3.7)	41(4.0)	0.547	1.15(0.73~1.82)	16(4.0)	0.613	1.17(0.64~2.14)	10(4.0)	0.676	1.17(0.57~2.40)

addition, interestingly, Lan et al. [18] reported that two haplotypes both AGCC and TATA were associated with an increased risk for DLBCL. Although the results of our study conflict with others, there are several ways in which they can be explained. Firstly, it may be due to the genetic trait differences, IL-10 gene polymorphisms were distinct in specific population, various ethnicity and geographic region. Secondly, the mutant allele frequencies of IL-10-3575(A) and IL-10-1082(G) are very low in Chinese people shown in the present study, the number of subjects with the homozygous mutant genotype was relatively small although the sample size of our study was comparatively large. Thirdly, IL-10 has a duel biological effects and the precise role of IL-10 gene promoter variants in determining IL-10 expression is still a subject awaiting answers. Finally, cancer is a multi-factorial disease and individual exposure to various environmental factors, and genetic susceptibility might have caused the different results.

Our results showed an important role of a IL-10 promoter SNPs (IL-10-1082) in increased risk of developing NHL. Acknowledging the relatively limited sample size in the subgroups for the low allelic frequencies, further studies including larger sample size and other immune function genes would further clarify the genetic risk factors for NHL.

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