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Original Article

Genetic polymorphisms of interleukin-27 is associated with endometrial cancer susceptibility in Chinese Han women

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Abstract: Interleukin-27 (IL-27) is a new member of the IL-12 family which may play an important role in antitumor immunity. The aim of the present study was to investigate the association between genetic polymorphisms of *IL-27* (rs153109, rs17855750) and susceptibility to endometrial cancer (EC) in Chinese Han women. A total of 272 patients and 320 age-matched healthy controls were included in the study. The variants were discriminated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods. The allele G frequencies of rs153109 significantly increased EC susceptibility (P = 0.007, OR = 1.401, 95% CI = 1.100-1.784). G allele carriers had a 1.66-fold EC risk in the dominant model compared with AA genotype patients (P = 0.0023, OR = 1.66, 95% CI = 1.20-2.31). The allele frequencies of rs17855750 showed no difference, but GG genotype of rs17855750 was only observed in EC patients. No significant association was detected between certain clinical features of EC patients and both polymorphisms. The results of this study demonstrate that genetic polymorphisms in IL-27 are involved in the susceptibility to EC.

Keywords: *IL-27*, polymorphism, endometrial cancer, susceptibility, antitumor

Introduction

With 320,000 newly diagnosed cases in 2012, endometrial cancer (EC) is the second most common gynecological cancer worldwide. The mortality of EC is 76,000 or 2.1% of cancer deaths in women [1]. In China, EC is the sixth most common cancer in women, accounting for 73,188 new cases and 17,160 deaths in 2012 [2]. The etiology of EC remains unclear, but it is now widely accepted that genetic factors together with environmental factors influence the risk of developing cancers [3], and inflammation can contribute to cancer progression [4]. Therefore, the polymorphisms of genes encoding inflammation response molecules may affect the development of tumors potentially.

IL-27, an important member of the IL-12 family, is a novel heterodimeric cytokine formed by the Epstein-Barr virus-induced gene 3 protein (EBI3) and p28, a novel IL-12 p35-related polypeptide. IL-27 can activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and mitogen activated protein kinase (MAPK) signaling, by engaging a receptor composed of gp130 and the IL-27Rα, whose co-expression is required for signal transduction [5, 6]. This cytokine has been shown to lead to the differentiation of Th1 cells, suppress Th2 polarization, enhance IFN-γ production when synergizes with IL-12, and also inhibit the generation of Foxp3+ Treg cells [7]. Since Chiyo et al. [8] evaluated the antitumor activity of IL-27 against a murine tumor model of colon carcinoma; subsequent studies have confirmed an antitumor role for IL-27 [9-11]. The human *IL-27* gene is located on chromosome 16p11, containing five exons. As well as many immune diseases, such as asthma [12], inflammatory bowel disease (IBD) [13], polymor-

Table 1. Descriptive characteristics of the study population

Characteristics	Number of cases (%)	Number of controls (%)	*P-value*
Sample size	272	320	
Mean age ± SD (range) (years)	51.79±9.82 (25-81)	50.27±12.73 (19-71)	0.11
BMI Mean ± SD (kg/m^2)	24.23±3.46	23.85±3.52	0.188
Menopausal status			0.869
Premenopausal	131 (48.2)	151 (47.2)	
Postmenopausal	141 (51.8)	169 (52.8)	
Uterine bleeding			
YES	264 (97.1)		
NO[a]	8 (2.9)		
FIGO stage			
I	202 (74.3)		
II	25 (9.2)		
III	30 (11.0)		
IV	13 (4.8)		
Unknown[b]	2 (0.7)		
FIGO grade			
G1	95 (34.9)		
G2	101 (37.1)		
G3	76 (28.0)		
Histology			
Endometrioid adenocarcinoma	232 (85.3)		
Non-endometrioid adenocarcinoma[c]	40 (14.7)		

SD, standard deviation; *BMI,* body mass index; [a]Five for routine physical examination abnormal, three for abdominal pain. [b]No surgery. [c]Serous adenocarcinoma: eleven. Clear cell adenocarcinoma: five. Neuroendocrine carcinoma: two. Mixed: twenty-two (Adenosquamous carcinoma: twelve; other: ten).

phisms of the *IL-27* gene have been reported to be associated with individual susceptibility of cancers, including bladder cancer [14], ovarian cancer [15], breast cancer [16], etc. But little is known about whether the polymorphisms of *IL-27* gene are associated with susceptibility to EC.

In this study, we analyzed the influence of *IL-27* polymorphisms (rs153109, rs17855750) on the prevalence of endometrial cancer in Chinese Han women through a hospital-based study.

Materials and methods

Study population

This study enrolled 272 endometrial cancer patients hospitalized in the West China Second Hospital of Sichuan University between July 2008 and July 2014 with histological confirmation. The clinical stage of EC was defined according to the International Federation of Gynecology and Obstetrics (FIGO, 2014) criteria. The control series comprised of 320 age-matched healthy women referred for routine physical examination. They had no clinical symptoms (such as abnormal vaginal bleeding, abdominal pain) of endometrial cancer, had no any other history of malignancy, and their gynecologic examination, B ultrasound and cervical cytology tests results were normal. Clinical characteristics of the study population are presented in **Table 1**. This study was approved by the hospital ethics committee, and all the participants gave written informed consent.

DNA isolation and genotyping

Two single nucleotide polymorphisms (SNPs), rs153109 (-964 A/G) and rs17855750 (-2905 T/G), were genotyped. Genomic DNA was extracted by a whole-blood DNA isolation kit from Bioteke (Peking, China), and the procedure was performed according to the manufacturer's protocol. Genotyping was performed using polymerase chain reaction-restriction

Table 2. Genotype and allele distribution of two single-nucleotide polymorphisms in patients with EC and controls

Genotype or allele	Genotype	Patients	Controls	Logistic regression	
		N = 272 (%)	N = 337 (%)	OR (95% CI)	*P-value*
rs153109					
Genetic model					
Codominant	AA	103 (37.9%)	161 (50.3%)	1.00	**0.0098**
	AG	132 (48.5%)	124 (38.8%)	**1.66 (1.17-2.36)**	
	GG	37 (13.6%)	35 (10.9%)	1.65 (0.98-2.79)	
Dominant	AA	103 (37.9%)	161 (50.3%)	1.00	**0.0023**
	AG/GG	169 (62.1%)	159 (49.7%)	**1.66 (1.20-2.31)**	
Recessive	AA/AG	235 (86.4%)	285 (89.1%)	1.00	0.32
	GG	37 (13.6%)	35 (10.9%)	1.28 (0.78-2.10)	
Overdominant	AA/GG	140 (51.5%)	196 (61.2%)	1.00	**0.017**
	AG	132 (48.5%)	124 (38.8%)	**1.49 (1.07-2.07)**	
Log-additive	---	---	---	**1.39 (1.09-1.77)**	**0.007**
Allele					
	A	338 (62.1)	446 (69.7)	1.00 (reference)	**0.007**
	G	206 (37.9)	194 (30.3)	**1.401 (1.100-1.784)**	
rs17855750					
Genetic model					
Codominant	TT	236 (86.8%)	267 (83.4%)	1.00	**0.032**
	TG	33 (12.1%)	53 (16.6%)	0.70 (0.44-1.13)	
	GG	3 (1.1%)	0 (0%)	**NA (0.00-NA)**	
Dominant	TT	236 (86.8%)	267 (83.4%)	1.00	0.26
	TG/ GG	36 (13.2%)	53 (16.6%)	0.77 (0.49-1.22)	
Recessive	TT/TG	269 (98.9%)	320 (100%)	1.00	**0.03**
	GG	3 (1.1%)	0 (0%)	**NA (0.00-NA)**	
Overdominant	TT/GG	239 (87.9%)	267 (83.4%)	1.00	0.13
	TG	33 (12.1%)	53 (16.6%)	0.70 (0.44-1.11)	
Log-additive	---	---	---	0.85 (0.55-1.32)	0.47
Allele					
	T	505 (92.8)	587 (91.7)	1.00	0.514
	G	39 (7.2)	53 (8.3)	0.855 (0.556-1.315)	

Boldfaced values indicate a significant difference at the 5% level. *N*: number; *OR*: odds ratio; *CI*: confidence interval.

fragment length polymorphism (PCR-RFLP) methods. Genome region was amplified by PCR, using primer sequences: F: 5'-CTG-ATCCTGACCTCACTCAACGC-3' and R: 5'-CTGAC-TGGGACTGGGACTCAGC-3' for rs153109, F: 5'-ATCTCGCCAGGAAGCTGCGC-3' and R: 5'-CT-GTTAGTGGGGGCCAGAAGGGA-3' for rs178557-50. The PCRs were performed in a total volume of 10 μL, including 20 ng DNA, 20 nmol/L of each primer, 5 μL 2× Power Taq PCR MasterMix. PCR conditions were as follows: initial denaturation step at 95°C for 4 min, 32 cycles of 95°C for 30 s, 60°C annealing temperature for 30 s for rs17855750 while 66°C for 30 s for rs17855750, and 72°C for 30 s. The final extension step was performed at 72°C for 10 min. PCR products of these two polymorphisms were digested with restriction enzyme BstUI at 60°C for 2 h, then the samples were run on 6% polyacrylamide gel and stained with 1.5 g/L of argent nitrate: for rs153109, allele G was represented by 100- and 19-bp bands, allele A was identified by the presence of 119 bp band. For rs17855750, allele G, which had restriction site, produced two bands as 101- and 19-bp, allele T produced only one band as 120 bp. The genotypes were confirmed by an Applied Biosystems 3730DNA Analyzer (Tsing Ke,

Table 3. Association between the genotype distribution of the rs153109 polymorphism of *IL-27* gene and clinical features

Clinical features	Rs153109											
	Genotype			Genetic model								
	AA	AG	GG	Codominant (AA VS. AG VS. GG)		Dominant (AA VS. AG/GG)		Recessive (AA/AG VS. GG)		Overdominant (AA/GG VS. AG)		Log-additive	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
FIGO stage													
I	80	92	30	AG: 1.44 (0.79-2.61)	0.31	1.28 (0.72-2.28)	0.39	0.66 (0.27-1.58)	0.33	1.51 (0.87-2.63)	0.14	1.03 (0.68-1.54)	0.9
II-IV	23	38	7	GG: 0.81 (0.32-2.09)									
FIGO grade													
I	43	41	11	AG: 1.56 (0.91-2.67)	0.21	1.58 (0.95-2.64)	0.077	1.33 (0.63-2.83)	0.45	1.36 (0.82-2.25)	0.23	1.37 (0.94-2.00)	0.097
II-III	60	89	26	GG: 1.69 (0.76-3.79)									
Pathological type													
Endometrioid adenocarcinoma	91	111	30	AG: 1.30 (0.60-2.81)	0.54	1.40 (0.67-2.91)	0.36	1.52 (0.61-3.76)	0.38	1.09 (0.55-2.16)	0.81	1.33 (0.80-2.18)	0.27
Non-endometrioid adenocarcinoma	12	19	7	GG: 1.77 (0.64-4.90)									
Lymph node status													
Negative	95	118	34	AG: 1.21 (0.47-3.07)	0.92	1.17 (0.48-2.87)	0.73	0.94 (0.26-3.33)	0.92	1.19 (0.51-2.81)	0.69	1.07 (0.57-2.00)	0.84
Positive	8	12	3	GG: 1.05 (0.26-4.18)									
Peritumor intravascular cancer emboli													
Negative	91	106	34	AG: 1.72 (0.81-3.63)	0.16	1.46 (0.71-3.03)	0.3	0.48 (0.14-1.66)	0.21	1.89 (0.94-3.78)	0.07	1.04 (0.63-1.71)	0.89
Positive	12	24	3	GG: 0.67 (0.18-2.52)									

Boldfaced values indicate a significant difference at the 5% level. *OR*: odds ratio; *CI*: confidence interval.

Peking, China). About 10% of the samples were randomly selected to perform the repeated assays, and the results were 100% concordant.

Statistical analysis

Hardy-Weinberg equilibrium was assessed using the chi-squared test. Age and BMI were performed with student's t-test. Genotypic association tests in the codominant, dominant, recessive, overdominant, or log-additive genetic models were performed using SNPstats [17]. Allelic association was performed by chi-square test. The association of each genetic polymorphism with EC was examined by the odds ratios (ORs) and the 95% confidence interval (95% CI). Statistical analysis was performed using SPSS (version13.0; SPSS Inc., Chicago, USA). A *P*-value < 0.05 for two-side was considered as statistically significant.

Results

All samples including patients with EC (n = 272) and healthy controls (n = 320) were successfully analyzed for both rs153109 and rs17855750 polymorphisms. Genotype distribution of these two polymorphisms in both controls and patients were consistent with the Hardy-Weinberg equilibrium (*P* > 0.05).

The genotype and allele frequencies of the two SNPs for both patients and controls are shown in **Table 2**. The allele G frequencies of rs153109 significantly increased in the cases (0.379 vs. 0.303, P = 0.007, OR = 1.401, 95% CI = 1.100-1.784). No significant difference was observed in the allele frequencies of rs17855750 between the two study groups. Significantly increased risk of EC was found to be associated with the AG genotype of rs153109 in the codominant model, compared with AA genotype (P = 0.0098, OR = 1.66, 95% CI = 1.17-2.36). G allele carriers also had a 1.66-fold EC risk in the dominant model compared with AA genotype patients (P = 0.0023, OR = 1.66, 95% CI = 1.20-2.31). Moreover, in the overdominant model, the AG genotype increased EC susceptibility than others (P = 0.017, OR = 1.49, 95% CI = 1.07-2.07). Interestingly, GG genotype of rs17855750 was only observed in EC patients, which is significantly different with controls (codominant model: P = 0.032; recessive model: P = 0.03).

To further evaluate whether the two SNPs of *IL-27* were associated with certain clinical features of patients with EC, we performed stratification analyses for genotype distribution in EC patients with different FIGO stages, different FIGO grades, pathological type, lymph node status, and peritumor intravascular cancer emboli. Nevertheless, no significant association was detected, as shown in **Tables 3** and **4**.

Discussion

To our knowledge, this is the first report to attempt an evaluation of the association between the single nucleotide polymorphisms of the *IL-27* and endometrial cancer. In our study, we demonstrated that that G allele and AG genotype of rs153109 polymorphism, as well as GG genotype of rs17855750 polymorphisms in *IL-27* gene are more frequent in patients with EC.

Among the two SNPs in *IL-27* gene, rs153109 is located in the promoter region. As is well known, promoter region might play an important role in regulating the transcription process and protein expression. And rs17855705 located in the missense codon region, alteration from Tallele to G allele will lead to the amino acid change from serineto alanine. Zhou B et al. found that genotype of rs17855750 may be associated with plasma IL-27 levels in bladder cancer, for GG homozygous subjects were under the detection threshold [14]. However, Zhang Z et al. demonstrated that no significant relationship was found between IL-27p28 mRNA expression and genotype of rs153109 and rs17855750 in epithelial ovarian cancer [15].

We noted that the data from previous findings from epidemiological studies were conflicting. Alhough there were some studies found that the SNPs in *IL-27* were not significantly different between those cancer subjects and healthy controls, including in esophageal cancer, colorectal cancer etc. [18, 19], a meta-analysis with 1684 patients and 1837 controls in Chinese population demonstrated that rs153109 polymorphism was significantly associated with cancer risk (GG vs AA: OR = 1.24, 95% CI = 1.00-1.54, P = 0.05), and no associations between rs17855750 and cancer risk was observed [20]. Maybe sex distribution differential should be taken into account for these dif-

Table 4. Association between the genotype distribution of the rs17855750 polymorphism of *IL-27* gene and clinical features

Clinical features	Rs17855750											
	Genotype			Genetic model								
	GG	TG	TT	Codominant (TT VS. TG VS. GG)		Dominant (TT VS. TG/GG)		Recessive (TT/TG VS. GG)		Overdominant (TT/GG VS. TG)		Log-additive	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
FIGO stage													
I	3	27	172	TG: 0.62 (0.24-1.56)	0.24	0.55 (0.22-1.40)	0.19	0.00 (0.00-NA)	0.19	0.63 (0.25-1.59)	0.31	0.54 (0.23-1.29)-1.29)	0.14
II-IV	0	6	62	GG: 0.00 (0.00-NA)									
FIGO grade													
I	2	11	82	TG: 1.08 (0.50-2.33)	0.53	0.95 (0.46-1.98)	0.9	0.27 (0.02-2.99)	0.27	1.10 (0.51-2.37)	0.81	0.87 (0.46-1.65)	0.67
II-III	1	22	152	GG: 0.27 (0.02-3.02)									
Pathological type													
Endometrioid adenocarcinoma	3	29	200	TG: 0.81 (0.27-2.45)	0.59	0.74 (0.24-2.21)	0.57	0.00 (0.00-NA)	0.34	0.82 (0.27-2.49)	0.73	0.70 (0.25-1.96)	0.48
Non-endometrioid adenocarcinoma	0	4	34	GG: 0.00 (0.00-NA)									
Lymph node status													
Negative	3	30	214	TG: 1.07 (0.30-3.82)	0.76	0.97 (0.27-3.46)	0.97	0.00 (0.00-NA)	0.46	1.08 (0.30-3.87)	0.9	0.90 (0.28-2.89)	0.85
Positive	0	3	20	GG: 0.00 (0.00-NA)									
Peritumor intravascular cancer emboli													
Negative	3	28	200	TG: 1.05 (0.38-2.91)	0.62	0.95 (0.34-2.61)	0.92	0.00 (0.00-NA)	0.33	1.07 (0.39-2.95)	0.9	0.87 (0.34-2.22)	0.77
Positive	0	5	34	GG: 0.00 (0.00-NA)									

Boldfaced values indicate a significant difference at the 5% level. *OR*: odds ratio; *CI*: confidence interval.

ference. And studies in different ethnic group are necessary to confirm these relationships.

As it mentioned before, recent studies has revealed that the cytokine IL-27 have potent antitumor activities. On colon carcinoma, the antitumor activity of IL-27 is mediated mainly through CD8+T cells, IFN-γ, and T-bet [21]. On melanomas, IL-27 has an antiproliferative activity through WSX-1/STAT1 signaling [22]. On prostate cancer, IL-27 down-regulates the pro-angiogenesis-related genes and up-regulated the anti-angiogenesis-related genes in vitro, reduced cancer proliferation and vascularization in vivo [23]. Though there is no study discussing the interaction between IL-27 and endometrial cancer pathogenesis, here we offered genetic evidence that *IL-27* gene polymorphisms may contribute to endometrial cancer susceptibility.

Although we detected the association between the SNPs in *IL-27* and EC, there were limitations in our study. Firstly, the sample size, especially the sub-group of different clinical features of EC patients, which was relatively small, might not be large enough to detect the positive effect if it isn't strong enough. Further large-scale studies in diverse ethnic populations are needed to give stronger evidence for this association. Secondly, we were unable to get the information for more environmental factors and lifestyles of the enrolled subjects, which might have an influence on cancer risk. Thirdly, we did not test the expression level of IL-27, which restricted our further research on clarifying the SNPs' effect on the IL-27 expression level.

In conclusion, the present study suggested that the genetic polymorphisms in *IL-27* was associated with endometrial cancer susceptibility in Chinese Han women. Nevertheless, further larger well-designed studies in different population and functional evaluations are necessary to confirm these findings.

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Disclosure of conflict of interest

None.

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