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ORIGINAL ARTICLE

Association of cytokines polymorphisms with chronic peridontitis and rheumatoid arthritis in a Mexican population

Rubén Abraham Domínguez-Pérez[a,b], Juan Pablo Loyola-Rodriguez[a,b], Carlos Abud-Mendoza[c], Angel Gabriel Alpuche-Solis[d], José Luis Ayala-Herrera[a,b] and Rita Elizabeth Martínez-Martínez[a,b]

[a]Doctorado en Ciencias Biomedicas Basicas, Facultad de Medicina, Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mexico; [b]Advanced Education in General Dentistry, Master Degree Program at San Luis Potosi University, San Luis Potosi University, San Luis Potosi, Mexico; [c]Regional Unit of Rheumathology and Osteoporosis at Central Hospital "Dr. Ignacio Morones Prieto", Faculty of Medicine, San Luis Potosi University, San Luis Potosi, Mexico; [d]Potosino Institute of Scientific and Technological Research, San Luis Potosí, Mexico

ABSTRACT

Objective: Historically, it has been shown that rheumatoid arthritis (RA) and periodontitis (PE) share pathophysiological similarities and possibly a genetic background. In order to elucidate the genetic background between both diseases, we evaluated the distributions of five SNPs genotypes and all the possible haplotypes composed in subjects with isolated RA, PE, combined diseases and healthy controls.

Materials and methods: The study population consisted of 280 Mexican subjects. Genomic DNA was isolated from buccal epithelial cells collected by cheek scrapings and analyzed for the determination of the following SNPs: IL-1α + 4845 (rs17561), IL-1α −889 (rs1800587), IL-1β + 3954 (rs1143634), IL-1β −511(rs16944) and TNF-α −308 (rs1800629).

Results: After adjustment for age, sex and smoking status, multiple logistic regression analysis revealed a no significant association in the genotype frequencies of TNF-α −308 and IL-1α + 4845 SNPs. Otherwise a significant association was observed in IL-1β + 3954 and IL-1β −511 ($p < 0.05$) while IL-1α −889 was of borderline statistical significance ($p = 0.054$). Also, we found three negative associated haplotypes with PE: IL-1α + 4845 **G**/IL-1β −511 **A**, IL-1β + 3954 **C**/IL-1β −511 **A** and interestingly IL-1α −889 **C**/IL-1β −511 **A** also with a positive association with RA.

Conclusions: Some genotypes and haplotypes are associated with the diseases. But it seems that the genetic background of the association between RA and PE needs to be explored deeper.

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Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, it occurs in a genetically susceptible host in response to a trigger factor. Viral or bacterial infections have been considered as putative triggers for this disease [1]. RA has a prevalence of approximately 1% and is characterized by substantial morbidity and accelerated mortality [2,3]. In Mexico, RA is more prevalent than previously considered [4].

Periodontitis (PE) is also a chronic inflammatory condition produced by bacterial biofilm and their virulence factors accumulated in the gingival sulcus. It is one of the most common oral diseases with a prevalence of 10–60% in adults, depending on the diagnostic criteria [5,6].

Similarities between RA and PE were recognized since decades, thence a considerable evidence has been accumulated to support the concept of a strong interrelationship between these two conditions [1,7,8]. Clinically, it has been reported that subjects with RA have a high prevalence of PE of about 65% [9,10], even it has been reported an odds ratio upper than 8 for the presence of PE in RA patients compared with controls [11]. Both diseases are characterized by local destruction of hard and soft tissues as a consequence of inflamatory process. Their pathogenesis includes the release of cytokines and matrix metalloproteinases from inflammatory cells [12] as well as osteoclast activator factors and RANK participation [13].

In the past decade, some studies documented that susceptibility to RA and PE could be in part influenced by single-nucleotide polimorphysms (SNPs) on cytokines genes [14–17] such as IL-1α + 4845, IL-1α −889, IL-1β + 3954, IL-1β −511 and TNF-α −308 that represent the most extensively investigated. Some studies have shown that variant alleles seem to be more frequent in diseased individuals than healthy controls [18,19], while other studies has shown contradictory results [20–22]. These findings lead to the hypothesis that cytokine genotypes and/or their combinations known as haplotypes may contribute to the susceptibility to RA and/or PE. All of these observations could be important as risk predictors for both diseases.

The aim of the present study was to identify the possible associaton of five cytokine SNPs genotypes and haplotypes

CONTACT Rita E. Martínez-Martínez ritae_martinez@hotmail.com The Master's Degree in Dental Science with Specialization in Advanced General Dentistry Program at San Luis Potosi University, Mexico. Fuente de la primavera # 119, Fracc. Balcones del Valle, CP 78369, San Luis Potosi, Mexico

with RA and/or PE to explore if both diseases share genetic features. These assessments may provide valuable information for the identification of subjects at high risk for RA and PE in our population.

Materials and methods

Subject population and clinical evaluation

In total, 280Mexican subjects with Mexican parents and grandparents were enrolled in the present cross-sectional analytic study. They were divided into four groups: 80 patients with RA (RA group), 80 patients with PE (PE group), 40 patients with RA and PE (RA + PE group) and 80 healthy subjects (Control group). The subjects were recruited at the Regional Unit of Reumatology and Osteoporosis at the Central Hospital and at the Oral Medicine Clinic of the Master's Degree in Advanced Education General Dentistry Program at San Luis Potosi University, San Luis Potosi, Mexico. They were selected by a non-probabilistic consecutive sampling performed from November 2014 to March 2016. An informed and voluntary written consent from patients according to the ethical principles of Helsinki declaration was obtained previously to oral and systemic health questionnaire and a clinical examination. The protocol study was reviewed and approved by the Ethical Committee of the Master's Degree in Advanced Education General Dentistry Program at San Luis Potosi University.

RA diagnosis was performed by a rheumatologist in accordance with the criteria of the American College of Rheumatology [23]. PE diagnosis was performed by a calibrated examiner. Clinical periodontal parameters were examined in all patients: probing depth (PD) and clinical attachment level (CAL) were assessed using a North Carolina periodontal probe (Hu Friedy, Chicago, IL) graduated in millimeters (0–15 mm). The probe was inserted parallel to the tooth long axis at six sites around each tooth: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual. CAL was measured from the epithelial attachment to the cement-enamel junction. PE diagnosis was determined when the pocket depth was >3 mm, and the attachment loss was ≥ 2 mm in at least 30% of the measured sites [24]. Subjects were excluded if suffered any genetic or chronic inflammatory disease besides RA and PE.

Genotyping

Genomic DNA was isolated from buccal epithelial cells collected by cheek scrapings and using a commercial kit (Wizard genomic DNA purification kit, Promega, Madison, WI). The samples were genotyped by real-time PCR using TaqMan probes (Applied Biosystems, Foster City, CA). Genotyping was performed in 20-μL reaction mix containing 10 μL of TaqMan universal master mix (Applied Biosystems, Foster City, CA) (2×), 1 μL of TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA) (20×), 2 μL (100ng) of DNA template and 7 μL of distilled water. Thermocycling was performed in the StepOne Real-Time PCR System (Applied Biosystems, Foster City, CA) according to the protocol assigned by the manufacturer. Data analysis was performed by using StepOne Software, version 2.2.3 (Applied Biosystems, Foster City, CA) and TaqMan Genotyper Software, version 1.3 (Life Technologies Corporation, Carlsbad, CA).

After conducting a review of the literature, the five most previously associated with RA and PE susceptibility cytokine gene SNPs were selected for this study. Each DNA sample was analyzed for the following SNPs: IL-1α + 4845 (rs17561), IL-1α −889 (rs1800587), IL-1β + 3954 (rs1143634), IL-1β −511(rs16944) and TNF-α −308 (rs1800629).

Statistical analysis

The examiner was calibrated in PE diagnosis by an expert. Inter-examiner consistence was performed by Spearman's correlation test, the examiner was considered calibrated when values were ≥ 0.80. Qualitative data are expressed as frequency and proportion; quantitative data are expressed as mean, SD and range. For the determination of variable distribution, a Kolmogorov–Smirnov test was applied. To detect statistical differences among groups for quantitative variables, a Kruskal–Wallis test was employed. For gender, smoking status and frequency of genotypes, Fisher's exact test was applied. Statistical significance was set at $p < 0.05$ employing SPSS 18.0 (IBM, Chicago, IL). To analyze the association among SNPs and their haplotypes with the diseases, a Hardy–Weinberg equilibrium test was performed by an online Hardy–Weinberg equilibrium calculator (University of Bristol, Bristol, United Kingdom) [25]. Then SNPStats software (Catalan Institute of Oncology and Autonomous University of Barcelona, Barcelona, Spain) was used to analyze codominant, dominant, recessive and overdominant genetic models of inheritance. The association analysis based on unconditional logistic regression was carried out by calculating the odds ratio (OR) and 95% confidence interval (95% CI) after adjusting for age, sex and smoking status for each SNP in each genetic model; the significance level was set at $p < 0.05$. Also, the association between all possible haplotypes composed by the combination of the four SNPs located in the same chromosome (except for TNF-α −308) and RA or/and EP were analyzed. The results from this online calculator were consistent with those obtained by SPSS 18.0 software.

Results

The inter-examiner consistence was 0.90. Clinical parameters are summarized in Tables 1 and 2. The mean age of the study population was around 47 years old, the gender was predominantly female (89%) and a frequency of smoking subjects of 12.5% was observed. As expected, similar levels of PD and CAL were observed in RA group (2.00 ± 0.43 and 1.21 ± 0.49 mm, respectively) compared to control group (2.14 ± 0.38 and 0.95 ± 0.42 mm, respectively; $p > 0.05$), and similar levels between RA + PE group (3.89 ± 0.82 and 2.38 ± 0.31 mm, respectively) compared to PE group (4.66 ± 0.57 mm and 2.35 ± 0.24 mm; $p > 0.05$) were observed.

Regarding the distribution of cytokines gene SNPs, statistical differences between groups were obtained in two SNPs

Table 1. Clinical characteristics of the study subjects.

	$\dot{X}$ ± SD (Range)			
Group	Control ($n = 80$)	PE ($n = 80$)	RA ($n = 80$)	RA + PE ($n = 40$)
Age (years)[a]	48.8 ± 9.86 (26–74)	45.25 ± 12.0 (23–81)	47.21 ± 13.3 (20–79)	48.7 ± 11.5 (29–76)
Frequency (%)				
Gender[b]				
Male	5 (6.25)	11 (13.75)	9 (11.25)	5 (12.5)
Female	75 (93.75)	69 (86.25)	71 (88.75)	35 (87.5)
Smokers[b]	10 (12.5)	13 (16.25)	9 (11.25)	4 (10)

PE: Periodontitis; RA: Rheumatoid arthritis; $\dot{X}$: Mean; SD: Standard deviation.
[a]Kruskal–Wallis test; $p > 0.05$.
[b]Fisher test; $p > 0.05$.

Table 2. Periodontal status of the study groups.

	$\dot{X}$ ± SD (Range)			
Group	Control ($n = 80$)	PE ($n = 80$)	RA ($n = 80$)	RA + PE ($n = 40$)
Probing depth (mm)[a]	2.14 ± 0.38 (3.2–1.1)	4.66 ± 0.57 (5.8–3.4)	2.00 ± 0.43 (3.1–1.1)	3.89 ± 0.82 (5.8–2.3)
Clinical attachment level (mm)[a]	0.95 ± 0.42 (2.0–0.3)	2.35 ± 0.24 (3.2–2.0)	1.21 ± 0.49 (2.2–0.1)	2.38 ± 0.31 (3.3–1.6)

PE: Periodontitis; RA: Rheumatoid arthritis; $\dot{X}$: Mean; SD: Standard deviation.
[a]Kruskal–Wallis test; $p < 0.0001$.

Table 3. Genotype frequency of SNPs.

	Frequency (%)				
	Control ($n = 80$)	PE ($n = 80$)	RA ($n = 80$)	RA + PE ($n = 40$)	p value[f]
TNF-α −308					
Genotype					
GG	68 (85%)	68 (85%)	66 (82.5%)	34 (85%)	
AG	12 (15%)	12 (15%)	14 (17.5%)	6 (15%)	
AA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.9656
IL-1α −889					
Genotype					
TT	5 (6.2%)	7 (8.8%)	5 (6.2%)	0 (0%)	
TC	39 (48.8%)	34 (42.5%)	22 (27.5%)[a]	15 (37.5%)	
CC	36 (45%)	39 (48.8%)	53 (66.2%)	25 (62.5%)	0.0504
IL-1β +3954					
Genotype					
TT	1 (1.2%)	8 (10%)[c]	0 (0%)	4 (10%)	
TC	22 (27.5%)	22 (27.5%)	9 (11.2)[b]	8 (20%)	
CC	57 (71.2%)	50 (62.5%)	71 (88.8%)	28 (70%)	0.0006
IL-1α +4845					
Genotype					
TT	4 (5%)	5 (6.2%)	4 (5%)	2 (5%)	
TG	29 (36.2%)	36 (45%)	21 (26.2%)	11 (27.5%)	
GG	47 (58.8%)	39 (48.8%)	55 (68.8%)	27 (67.5%)	0.2364
IL-1β −511					
Genotype					
GG	11 (13.8%)	46 (57.5%)	11 (13.8%)	16 (40%)[e]	
AG	34 (42.5%)	34 (42.5%)[d]	39 (48.8%)	12 (30%)	
AA	35 (43.8%)	0 (0%)	30 (37.5%)	12 (30%)	<0.0001

[a]RA vs control ($p = 0.032$, OR: 0.41; 95% CI: 0.21–0.81).
[b]RA vs control ($p = 0.015$, OR: 0.32; 95% CI: 0.14–0.76).
[c]PE vs control ($p = 0.026$, OR: 10.28; 95% CI: 1.22–86.64).
[d]PE vs control ($p < 0.0001$, OR: 0.24; 95% CI: 0.10–0.55).
[e]RA + PE vs control ($p = 0.0041$, OR: 4.84; 95% CI: 1.71–13.67).
Multiple logistic regression analysis after adjustment for age, gender and smoking status.
SNP: Single-nucleotide polymorphism, PE: Periodontitis; RA: Rheumatoid arthritis.
[f]Fisher test.

(IL-1β + 3954 and IL-1β −511; $p < 0.05$), and one of them (IL-1α −889) was of borderline statistical significance ($p = 0.054$). It is important to notice that A/A genotype of TNF-α −308 SNP was not present in any of the subjects included in the study (Table 3).

Prior to statistical analysis to find associations, it was confirmed that the genotype frequencies of the five cytokine SNPs in the control group were in Hardy–Weinberg's equilibrium ($p > 0.05$).

Results of multiple logistic regression analysis adjusting age, gender, and smoking status revealed that genotype GG of IL-1β −511 SNP was positively associated with RA + PE ($p = 0.0041$, OR: 4.84 95% CI: 1.71–13.67). Regarding association with PE, results showed that genotype TT of IL-1β

Table 4. Haplotype distributions and comparisons.

Haplotype		% In groups			
IL-1α−889	IL-1β−511	RA + PE $n = 40$	RA $n = 80$	PE $n = 80$	Control $n = 80$
C	A	37.3	50.8[a]	9.6[b]	46
C	G	43.9	29.1	60.3	23.3
T	A	7.69	10.9	11.6	18.9
T	G	11	9.00	18.4	11.6
IL-1α + 4845	IL-1β−511				
G	A	42.8	52.6	16.6[c]	57.0
G	G	38.4	29.2	54.6	19.8
T	G	16.5	8.9	24.1	15.1
T	A	2.1	9.2	4.6	8.00
IL-1β + 3954	IL-1β−511				
C	G	40	36.9	62.2	23.3
C	A	40	57.4	1.4[d]	61.6
T	G	15	1.1	16.5	11.6
T	A	5	4.4	7.2	3.3
IL-1β + 3954	IL-1α + 4845				
C	G	71.9	79.5	56.7	76.1
C	T	8	14.8	19.5	8.8
T	G	9.3	2.3	14.5	0.006
T	T	10	3.3	9.2	14.3
IL-1α−889	IL-1β + 3954				
C	C	70.5	76.2	55.9	61.4
T	C	9.4	18	20.3	23.5
C	T	10.6	3.7	14	7.9
T	T	9.3	1.9	9.7	7
IL-1α−889	IL-1α + 4845				
C	G	75.9	73.9	55.4	58
T	T	13.4	12	14.1	11.8
T	G	5.3	7.9	15.8	18.7
C	T	5.3	6	14.5	11.2

PE: Periodontitis; RA: Rheumatoid arthritis.
[a]RA vs control ($p < 0.0001$, OR: 9.07; 95% CI: 3.83–21.44).
[b]PE vs control ($p < 0.0001$, OR: 0.03; 95% CI: 0.01–0.12).
[c]PE vs control ($p < 0.0001$, OR: 0.11; 95% CI: 0.05–0.26).
[d]PE vs control ($p < 0.0001$, OR: 0.09; 95% CI: 0.04–0.22).

+3954 SNP was positively related ($p = 0.026$, OR: 10.28 95% CI: 1.22–86.64), and genotype AG of IL-1β−511 SNP was negatively associated ($p < 0.015$; OR: 0.32; 95% CI: 0.14–0.76). Considering RA, there was no genotype positively associated, but TC genotype of IL-1α −889 SNP ($p = 0.032$ OR: 0.41; 95% CI: 0.21–0.81) and TC genotype of IL-1β +3954 ($p = 0.015$; OR: 0.32; 95% CI: 0.14–0.76) showed negative association with RA.

Due to four (IL-1α −889, +4845 and IL-1β + 3954, −511) of the five SNPs studied are nearby on chromosome 2, it was decided to study all possible haplotypes composed by two of them (Table 4). A positive association with RA (OR: 9.07; 95% CI: 3.83–21.44) and a negative association with PE (OR: 0.03; 95% CI: 0.01–0.12) were found in the IL-1α −889 **C**/IL-1β −511 **A** haplotype. Also, two negatively associated haplotypes with PE were found: IL-1α + 4845 **G**/IL-1β −511 **A** (OR: 0.11; 95% CI: 0.05–0.26) and IL-1β + 3954 **C**/IL-1β −511 **A** (OR: 0.09; 95% CI: 0.04–0.22) ($p < 0.0001$).

Discussion

In the past two decades, SNPs of cytokine genes have been studied to identify potential markers of susceptibility, severity and clinical outcomes of different diseases, including RA and PE. Actually, sensible and specific molecular tests are available to allelic discrimination of gene SNPs, such as real-time PCR employing TaqMan probes.

For development of PE, bacteria are considered as the main etiological factor; however, for RA, environmental components are well recognized but the trigger factor is still unknown. It is believed that a genetic factor is involved; however, it has not been plenty recognized or identified.

The association of the five SNPs studied in the present study with RA or PE has been reviewed in different populations but in Mexican people it is still unclear. Due to genotype distribution varies with different ethnic and racial groups [26] only Mexican subjects with Mexican parents and grandparents living in San Luis Potosi (a central state in Mexico) were included in the present study.

All subjects were selected from a homogeneous population with similar age, gender and smoking status. Also, we employed a strict criteria to define PE (30% of probed sites affected with a probing depth >3 mm and attachment loss ≥2 mm) [24]. PE and RA + PE groups were similar about periodontal status. Thus, the population of the current study is very suitable for the investigation of the association between RA, PE and genetic factors.

With respect to comparisons of genotypes frequency between groups, a significant difference was found in IL-1β + 3954 and IL-1β −511 SNPs, while IL-1α −889 SNP was of borderline. On the other side, TNF-α −308 and IL-1α + 4845 SNPs genotypes did not show any difference; even after multiple logistic regression analysis, there was no association between genotypes and diseases, in accordance with

previous reports [27,28]. Interestingly, not even one subject with A/A genotype in TNF-α −308 SNP was detected in this study, in accordance with other report in Mexican population [29].

In the present study, genotype G/G of IL-1β −511 SNP was positively associated with RA + PE, but it was not found any previous report to compare our findings. In contrast, genotype A/G was negatively associated with PE; this result was different with a previous report where a positive association was found [30], moreover Amirisetty et al. [31] reported that A/A genotype was present in a significantly higher frequency in PE subjects, but in contrast, in our population there were no subjects with this genotype in this group.

Regarding genotype T/T of IL-1β + 3954 SNP, it was found a positive association with PE in accordance with Brett et al. [32]; this genotype has been reported with a low frequency or absent in some populations. In our case, it was detected in 13 subjects (4.64% of our total population) while SNPedia did not have reports of this genotype in Mexican population [29]. T allele frequency in Asian populations has a very low prevalence in healthy subjects (<6%) [33,34] and a high prevalence in Caucasian (≥39%) [22,35,36] but, in a study in Chilenean population [37] similar to ours, they had comparable frequency to the present report (13%). On the other hand, the T/C genotype of this SNP was found negatively associated with RA, this result is constradictory to the published by Kobayashi et al. [38]; they found in japanese population the over-representation of this genotype and positive association with RA + PE compared with PE and healthy subjects.

Regarding to IL-1α −889 SNP, the T/C genotype was negatively associated with RA; however, this genotype was not associated with PE, this finding concurs with others reports [22,26,39] and especially with another mixed population like ours [37].

Otherwise the haplotype analysis is a promising approach for identification of genetic factors in disease susceptibility. Because only a relatively small amount of tag SNPs are needed to recover genetic variation within a haplotype set. This approach may be very cost-efficient in the search for genetic markers. In the present study, 24 possible haplotypes were studied of which only 3 were associated with a high significance ($p \leq 0.0001$). All were negatively associated with PE, one of them simultaneously was associated positively with RA, but anyone was associated with RA + PE.

In conclusion, the present study in Mexican population exhibited different distributions of IL-1β + 3954, IL-1α −889, IL-1β −511 genotypes depending on the group they belong (RA + PE, RA, PE or Control), although IL-1α +4845 and TNF-α −308 genotypes did not show differences. G/G genotype of IL-1β −511 was positively associated with RA + PE and T/T genotype of IL-1β + 3954 with PE. Some genotypes are negatively associated with PE and RA separately. Three haplotypes are associated with both diseases, but it seems that the genetic background of the association between RA and PE needs to be explored deeper. It is important to carry out more studies with different designs and larger-sized groups to confirm the association between polymorphisms in the occurrence of PE and RA in different populations.

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Disclosure statement

There is no conflict of interest to declare.

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Note on contributors

Rubén Abraham Domínguez-Pérez, Dental Surgeon, Specialty in Endodontics, PhD Student, Doctorado en Ciencias Biomédicas Basicas, Universidad Autonoma de San Luis Potosi.

Juan Pablo Loyola-Rodriguez, Dental Surgeon, Specialty in Pediatric Dentistry and Doctor in Dental Sciences, Professor of Dental School of Universidad Autonoma de San Luis Potosi, The Master's Degree in Dental Science with Specialization in Advanced General Dentistry and National Researcher.

Carlos Abud-Mendoza, Medical Doctor, Specialty in Internal Medicine and Rheumatology, Director of the Regional Unit of Rheumathology and Osteoporosis at Central Hospital "Dr. Ignacio Morones Prieto". National Researcher.

Angel Gabriel Alpuche-Solis, Biologist, Doctor in Sciences. Professor and Researcher, Director of Laboratory of Molecular Biology. Instituto Potosino de Investigacion Cientifica y Tecnologica.

José Luis Ayala-Herrera, Dental Surgeon, Master in Dental Sciences, Universidad Autonoma de San Luis Potosi, PhD Student, Doctorado en Ciencias Biomédicas Basicas, Universidad Autonoma de San Luis Potosi.

Rita Elizabeth Martinez-Martinez, Dental Surgeon, Master in Dental Sciences, Doctor in Basic Biomedical Sciences. Professor of Dental School of Universidad Autonoma de San Luis Potosi, The Master's Degree in Dental Science with Specialization in Advanced General Dentistry and National Researcher.

ORCID

Rubén Abraham Domínguez-Pérez http://orcid.org/0000-0001-8979-8394

Juan Pablo Loyola-Rodriguez http://orcid.org/0000-0003-0892-0082

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