Clin Exp Med (2015) 15:439–446
DOI 10.1007/s10238-014-0315-4

ORIGINAL ARTICLE

Association of interleukin-10 promoter haplotypes with disease susceptibility and IL-10 levels in Mexican patients with systemic lupus erythematosus

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Received: 30 May 2014 / Accepted: 15 September 2014 / Published online: 25 September 2014

Abstract Systemic lupus erythematosus (SLE) is the prototype autoimmune rheumatic disease. The etiology of this disease is incompletely understood; however, environmental factors and genetic predisposition are involved. Cytokine-mediated immunity plays a crucial role in the pathogenesis of SLE. We investigate the association of interleukin-10 (IL-10) promoter polymorphisms and their haplotypes in SLE patients from the western Mexico. One hundred and twenty-five SLE patients fulfilling the 1997 ACR criteria and 260 unrelated healthy subjects (HS), both Mexican mestizos, were genotyped for *IL-10* −1082A>G, −819C>T, and −592C>A polymorphisms. Haplotypes were inferred using the expectation–maximization algorithm, then allele and haplotype distributions were compared between patients and HS, as well as patients with different clinical variables. We identified at −1082, −819, and −592 four predominant haplotypes ACC (43.70 % in patients vs 46.55 % in HS), ATA (21.45 vs 22.97 %), GCC (16.28 vs 14.21 %), and GTA (14.12 vs 14.12 %). The ATC haplotype was more frequent in SLE respect to HS, suggesting a risk effect (3.23 vs 1.05 %; OR 3.55, CI 1.14–11.11; $p = 0.0293$). SLE patient carriers of −592 CC genotype as well as the dominant model of inheritance showed higher sIL-10 respect to AA genotype, suggesting that −592 C allele is associated with increased production of the cytokine ($p < 0.05$). The ACC haplotype had higher IL-10 serum levels and higher values of Mexican version of the Systemic Lupus Erythematosus Disease Activity Index compared with the other haplotype carriers; however, no association was found regarding autoantibodies. Our data suggest that the *IL-10* promoter haplotypes play an important role in the risk of developing SLE and influence the production of IL-10 in Mexican population. Nevertheless, further studies are required to analyze the expression of mRNA as well as to investigate the interacting epigenetic factors that could help to define the true contribution of this marker in SLE pathogenesis.

Keywords *IL-10* polymorphisms · *IL-10* haplotypes · Systemic lupus erythematosus · Genetic risk factors

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Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease, in which immune regulation is disrupted, and it is characterized by the production of autoantibodies leading to intense inflammation and multiple organ damage. Although the etiopathology of SLE is still not fully clear, genetic susceptibility and environmental factors have been associated with the initiation and promotion of this complex disorder.

It has been suggested that cytokine-mediated immunity plays a crucial role in the pathogenesis of SLE [1, 2]. Interleukin-10 (IL-10) is a multifunctional cytokine that can be produced by almost all leukocytes. It is a potent inhibitor of both antigen-presenting cell and T lymphocyte functions. Moreover, IL-10 is a key mediator in the interferon-γ signaling pathway, thereby inhibits the production of Th1 cytokines and promotes the development of a type 2 cytokines [1, 2]. In addition, IL-10 is defined as a potent stimulator of B lymphocytes and stimulates the production of anti-DNA autoantibodies in SLE patients [3]. The overproduction of IL-10 has been observed in SLE patients and in some of their unaffected relatives [4, 5]. Additionally, SLE activity was correlated with serum IL-10 levels, suggesting that overexpression of IL-10 might play a pathogenic role in severe lupus disease [6, 7].

The *IL-10* gene is located on chromosome 1 at position 1q31–1q32 [8]. Three single nucleotide polymorphisms (SNPs) at −1082A>G, −819C>T, and −592C>A in the promoter region have been associated with the pathogenesis of SLE. However, a number of studies have been examined the potential contributions of these polymorphisms and their haplotypes with susceptibility to SLE, but these findings are not consistent [9–13], possibly because of the ethnic and racial differences [14–16].

In the present case–control study, we investigated whether there is an association between *IL-10* promoter polymorphisms and their haplotypes with susceptibility to SLE in Mexican population.

Materials and methods

Patients

One hundred and twenty-five systemic lupus erythematosus patients, whom fulfilled the 1997 American College of Rheumatology Criteria [17], were recruited from the Rheumatology Department of the Hospital General de Occidente, Zapopan, Jalisco, Mexico. The Mexican version of the Systemic Lupus Erythematosus Disease Activity Index (Mex-SLEDAI) [18] and the Systemic Lupus International Collaborating Clinics index (SLICC) [19] were applied to the SLE patients at the enrollment of the study. Furthermore, the clinical variables and treatment data were taken from clinical records. As a control group, 260 unrelated healthy subjects (HS) were included. SLE patients and HS were from the same ethnical origin region, and we considered as Mexican mestizos only those individuals, who for three generations, including their own, had been born in Mexico having Spanish-derived last name [20]. The institutional Ethics and Research Committees approved the study, and all subjects provided written informed consent.

Laboratory assessments

A complete blood count, including the lymphocyte count, was performed to SLE patients and HS (CELL-DYN 3500R; Abbott Diagnostics, Abbott Park; IL, USA). Double strain DNA (dsDNA), anti-Ro, anti-La, and anti-Sm antibodies were tested in SLE patients using an ELISA test (Binazyme, The Binding Site Ltd.; Birmingham, UK). For dsDNA antibodies, the range of detection was 12.3–1,000 IU/mL, and sensitivity of the assay was 4.6 IU/mL, while for anti-Ro, anti-La, and anti-Sm, the sensitivity of the assay was 4.0 IU/mL. Rheumatoid factor levels (RF) were performed by nephelometry (IMMAGE 4700 Immunochemistry System, Beckman Coulter Inc.).

IL-10 quantification

Soluble interleukin-10 (sIL-10) levels were quantified from sera of SLE patients and HS using a high sensibility ELISA kit (R&D Systems, Minneapolis, MN, USA). The range of detection was 0.78–50 pg/mL, and the sensitivity of the assay was 0.17 pg/mL.

IL-10 polymorphisms genotypification

Genomic DNA was extracted from 3 mL of peripheral blood leukocyte according to Miller's method [21]. Amplification of interleukin-10 promoter region was performed by PCR in a Techne Thermal Cycler (TC-312; Cambridge, UK) using the following primers, one of them containing a single base-pair mismatch (underlined) in order to introduce a restriction site: for *IL-10* −1082A>G polymorphism: 5′-AACACTACTAAGGCTCCTTTGGGA-3′ (Forward) and 5′-CAAGGAAAAGAAGTCAGGATTCCATGGA-3′ (Reverse) [22], for *IL-10* −819C>T polymorphism: 5′-CTACTAAGGCTTCTTTGGG-3′ (Forward) and 5′-AGGTAGTGCTCACCATGACC-3′ (Reverse) [23], and for *IL-10* −519C>A polymorphism: 5′-ATCCAAGACAACACTACTAA-3′ (Forward) and 5′-TAAATATCCTCAAAGTTCC-3′ (Reverse) [11]. The PCR was carried out in a final volume of 25 μL containing 500 ng of DNA, 2.5 μM of each primer, 0.5 U/μL *Taq* DNA polymerase, 1X of supplied 10X buffer enzyme, 2.5 mM $MgCl_2$, and 2.5 mM of each dNTP (Invitrogen™; Carlsbad, CA, USA). The PCR was performed by initial denaturation at 94 °C during 3 min, followed by 35 cycles of amplification at: 94 °C during 30 s for denaturation (95 °C for *IL-10* −592C>A), 60 °C during 30 s for annealing (56 °C for *IL-10* −592C>A), and 72 °C during 30 s for extension. Finally, 72 °C during 1 min for ending extension was applied. In order to identify each polymorphism, 5 μl of PCR product was digested with three units of *EcoNI* (New England Biolabs; Beverly, MA, USA) (*IL-10* −1082A>G), *MsII* (New England Biolabs Beverly; MA,

USA) (*IL-10* −819C>T), and *RsaI* (New England Biolabs; Beverly, MA, USA) (*IL-10* −592C>A) for 3 h at 37 °C. Digested products were observed on a 6 % polyacrylamide gel stained with 2 % $AgNO_3$. For *IL-10* −1082A>G polymorphism, AA homozygote was identified by 102 bp fragment, GG homozygote by 82 and 20 bp, and AG heterozygote by 102, 80 and 20 bp fragments. The genotypes for *IL-10* −819C>T polymorphism were identified by the next fragments: CC homozygote 288 and 60 bp, TT homozygote 348 bp, and CT heterozygote by 348, 288 and 60 bp. Respect to *IL-10* −592C>A polymorphism, fragments of 306, 232, 42, and 8 bp correspond to CC homozygote; 240, 232, 66, 42 and 8 bp identify the AA homozygote, and the CA heterozygote was genotyped by 306, 240, 232, 66, 42 and 8 bp fragments.

Statistical analysis

Statistical analysis was performed using PASW Statistics 18 software (IBM Corporation; Armonk, NY) and GraphPad Prism 5 software (GraphPad Software Inc.; San Diego, CA). Allele and genotype frequencies of *IL-10* polymorphisms were obtained by direct counting. Hardy–Weinberg equilibrium was calculated using chi-square test as well as allele and genotype analysis. Mann–Whitney U test and Kruskal–Wallis analysis of variance were used for non-parametric distribution data. *P* values <0.05 were considered significant. Haplotypes frequencies were inferred using EMHAPFRE software [24]. Pairwise linkage disequilibrium (LD) was expressed as Lewontin's D' corrected coefficient [25]. Comparison data was evaluated by $\chi 2$ test or the Fisher exact test when applicable. LD at three loci was evaluated according to Gavrilets [26]. The *p* corrected (*p*C) values for multiple tests were adjusted by the Bonferroni test [27].

Results

Demographic and clinical characteristics

One hundred and twenty-five SLE patients were included (5 men and 120 women). The average age was 36 years old (range of 16–72) and 7.5 years of disease duration (0–36 years). The SLE patients presented an activity disease score of 2.50 (0.0–11.0) for Mex-SLEDAI and 0.62 (0.0–12.0) score for SLICC damage index. The main clinical manifestations were hematologic, cutaneous, and neurologic (65, 30, and 29 % respectively). The treatment of SLE patients included immunosuppressive drugs (azathioprine, methotrexate, cyclophosphamide, and mycophenolate), chloroquine, and prednisone (Table 1).

Table 1 Demographic and clinical characteristic in SLE patients

	SLE, $n = 125$
Male/female	5/120
Age, years[a]	36 (16–72)
Disease duration, years[a]	7.5 (0–36)
Clinical assessment	
Mex-SLEDAI, score[a]	2.5 (0.0–11.0)
SLICC, score[a]	0.62 (0.0–12.0)
Autoantibodies	
Anti-dsDNA, *n* (%)	61 (48.8)
Rheumatoid factor, *n* (%)	28 (22.4)
Anti-Sm, *n* (%)	23 (18.4)
Anti-Ro, *n* (%)	11 (8.8)
Anti-La, *n* (%)	11 (8.8)
Clinical manifestations	
Hematologic	
Cytopenias, *n* (%)	80 (64)
Hemolytic anemia, *n* (%)	2 (1.6)
Cutaneous, *n* (%)	38 (30.4)
Neurologic, *n* (%)	37 (29.6)
Others	
Antiphospholipid antibody syndrome, *n* (%)	17 (13.6)
Treatment	
Azathioprine, *n* (%)	69 (55.2)
Prednisone, *n* (%)	51 (40.8)
Methotrexate, *n* (%)	47 (37.6)
Antimalarial, *n* (%)	41 (32.8)
Cyclophosphamide, *n* (%)	7 (5.6)
Mycophenolate, *n* (%)	4 (3.2)

Cutaneous clinical manifestations included malar erythema, discoid lupus, oral ulcers, and photosensitivity. Cytopenias included leucopenia and lymphopenia. Neurologic clinical manifestations included neurologic damage, psychosis, and convulsions

Mex-SLEDAI Mexican version of the Systemic Lupus Erythematosus Disease Activity Index, *SLICC* Systemic Lupus International Collaborating Clinics

[a] Data provided in mean (min–max)

IL-10 −1082A>G, −819C>T, and −592C>A polymorphisms

Analysis of *IL-10* −1082A>G, −819C>T, and −592C>A polymorphisms were performed in SLE patients and HS. Observed and expected frequencies were in Hardy–Weinberg equilibrium ($p>0.05$). The AA genotype was more frequent in SLE patients and HS for *IL-10* −1082A>G polymorphism (50 and 51 %, respectively). Respect to *IL-10* −819C>T polymorphisms, the heterozygote genotype (CT) was more frequent in both SLE and HS (49 and 48 %, respectively). Finally, for *IL-10* −592C>A polymorphism, the heterozygote genotype (CA) was also more frequent in

Table 2 Allele and genotype frequencies of *IL-10* polymorphisms in SLE patients and healthy subjects

	SLE, *n*=125 *n* (%)	HS, *n*=260 *n* (%)	*p*
IL-10 −1082A>G			
Allele			
A	174 (70)	369 (71)	
G	76 (30)	151 (29)	0.6980
Genotype			
AA	62 (50)	133 (51)	
AG	50 (40)	103 (40)	0.9772
GG	13 (10)	24 (9)	
Dominant model			
AA	62 (50)	133 (51)	
AG + GG	63 (50)	127 (49)	0.7752
Recessive model			
AA + AG	112 (90)	236 (91)	
GG	13 (10)	24 (9)	0.7154
IL-10 −819C>T			
Allele			
C	153 (61)	316 (61)	
T	97 (39)	204 (39)	0.9086
Genotype			
CC	46 (37)	96 (37)	
CT	61 (49)	124 (48)	0.9910
TT	18 (14)	40 (15)	
Dominant model			
CC	46 (37)	96 (37)	
CT + TT	79 (63)	164 (63)	0.9813
Recessive model			
CC + CT	107 (86)	220 (85)	
TT	18 (14)	40 (15)	0.8003
IL-10 −592C>A			
Allele			
C	158 (63)	325 (63)	
A	92 (37)	195 (37)	0.8507
Genotype			
CC	49 (39)	100 (39)	
CA	60 (48)	125 (48)	0.9975
AA	16 (13)	35 (13)	
Dominant model			
CC	49 (39)	100 (39)	
CA + AA	76 (61)	160 (61)	0.8892
Recessive model			
CC + CA	109 (87)	225 (87)	
AA	16 (13)	35 (13)	0.8577

Statistical analysis was performed using chi-square test

SLE Systemic lupus erythematosus, *HS* healthy subject

SLE patients and HS (48 %). The more frequent allele was the wild in both SLE patients and HS in the three *IL-10* polymorphisms analyzed. No statistical significant differences were observed between SLE patients and HS, even when *IL-10* polymorphisms were analyzed by dominant or recessive models of inheritance (Table 2).

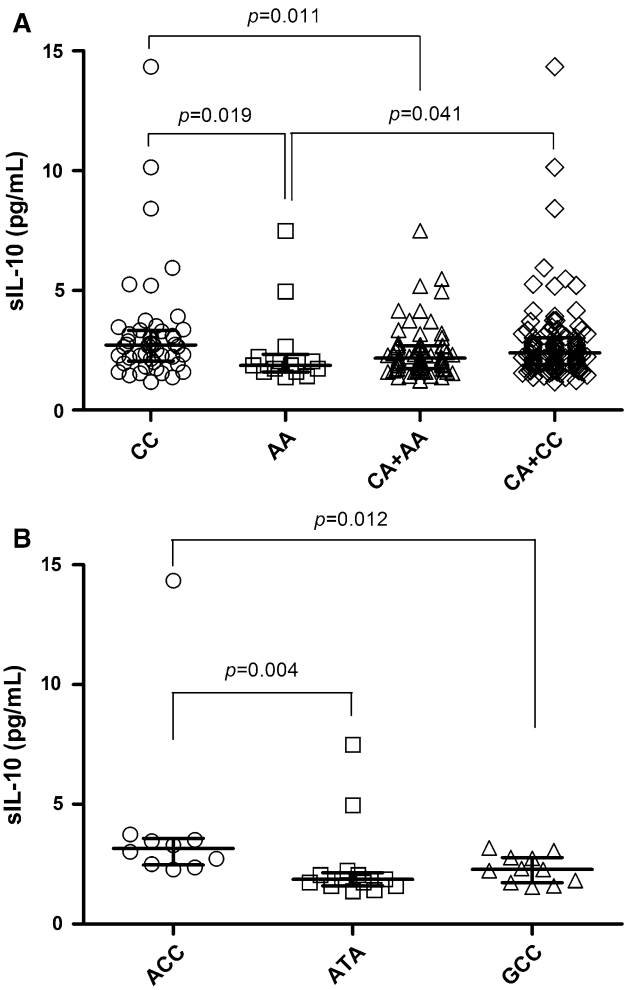

Fig. 1 Soluble IL-10 levels in systemic lupus erythematosus patients. **a** Soluble IL-10 levels according to genotypes, dominant, and recessive model of the *IL-10* −592C>A polymorphism in SLE patients. **b** Soluble IL-10 levels in relation to homozygote haplotypes presents in SLE patients. *SLE* systemic lupus erythematosus, *HS* healthy subjects. Statistical analysis was performed using Mann–Whitney U test. Median with interquartile range is represented by *horizontal lines* and *error bars*, respectively

IL-10 −1082A>G, −819C>T, and −592C>A haplotypes

A strong linkage disequilibrium (LD) was observed for *IL-10* −1082A>G, −819C>T, −592C>A haplotypes (100 %, pC=3.673 × 10^{-18}). The most frequent haplotype in SLE and HS was ACC (43.70 vs 46.55 %, respectively). ATA, GCC, and GTA frequencies in SLE were 21.45, 16.28, and 14.12 % while in HS 22.97, 14.21, 14.14 %, respectively. ATC haplotype was more frequent in SLE respect to HS (3.23 vs 1.05 %; OR 3.55, CI 1.14–11.11; $p = 0.0293$).

Table 3 Clinical characteristics in systemic lupus erythematosus patients according to *IL-10* haplotypes

	Haplotype				
	All, 2*n*=78[&]	ATA, *n*=30	GCC, *n*=22	ACC, *n*=22	*p**
Male/female	4/74	0/30	2/20	2/20	–
Age, years	33 (23–45)	39 (22–48)	31 (24–36)	35 (24–58)	–
Clinical assessment					
Mex-SLEDAI, score	2.0 (0.25–3.0)	1.0 (0.0–2.0)	1.5 (1.0–3.0)	3.0 (2.0–4.5)	**0.03**[a]
SLICC, score	0.0 (0.0–0.75)	0.0 (0.50)	0.0 (0.0–1.5)	0.0 (0.0–0.0)	>0.05
Laboratory data					
sIL-10, pg/mL	2.27 (1.75–3.05)	1.86 (1.59–2.14)	2.27 (1.73–2.77)	3.15 (2.47–3.57)	**<0.05**[b]
Autoantibodies					
Rheumatoid factor, IU/mL	12 (6–15)	12 (6–15)	6 (2.5–13)	11[d] (9–11)	>0.05
Anti-dsDNA, IU/mL	1.23 (0.63–2.99)	1.23 (0.66–4.55)	1.97 (0.95–2.72)	0.45[d] (0.37–0.45)	>0.05
Anti-Ro, IU/mL	4.18 (0.72–41.44)	4.14 (1.16–24.43)	5.71 (0.52–41.44)	0.40[d] (0.28–0.40)	>0.05
Anti-La, IU/mL	1.18 (0.67–2.7)	1.18 (0.71–2.26)	2.38 (0.72–6.82)	0.62[d] (0.31–0.62)	>0.05
Anti-Sm, IU/mL	0.69 (0.19–8.93)	3.05 (0.49–14.64)	0.69 (0.28–16.52)	0.08[d] (0.02–0.08)	**0.02**[c]

Significance ($p < 0.05$) is presented in bold

[&] Haplotypes were inferred from homozygous patients to *IL-10* −1082/−819/−592

* Comparisons were done between ATA versus GCC; ATA versus ACC; GCC versus ACC. [a] ATA versus ACC; [b] ACC versus ATA $p = 0.04$, ACC versus GCC $p = 0.01$; [c] ATA versus ACC. *Mex-SLEDAI* Mexican version of the Systemic Lupus Erythematosus Disease Activity Index, *SLICC* Systemic Lupus International Collaborating Clinics, *sIL-10* soluble IL-10. Statistical analysis was performed using Mann–Whitney U test. Data provided in median (p25–p75). [d] Data provided in median (p25–p50)

IL-10 serum levels

The soluble IL-10 levels showed differences in SLE patients, according to genotypes, dominant, and recessive model of the *IL-10* –592C>A polymorphism. SLE patient carriers of CC genotype showed higher sIL-10 levels than AA carriers and also than recessive model (2.71 vs 1.86 pg/mL, $p = 0.019$; 2.71 vs 2.1 pg/mL, $p = 0.011$, respectively; Fig. 1a) as well as the dominant model showed higher sIL-10 respect to AA genotype (2.39 vs 1.86 pg/mL, $p = 0.041$; Fig. 1a). Analyzing sIL-10 levels in relation to haplotype present in SLE patients, ACC carriers showed higher levels respect to GCC, and ATA carriers (3.15 vs 2.27 pg/mL, $p = 0.012$; 3.15 vs 1.86 pg/mL, $p = 0.04$, respectively; Fig. 1b, Table 3).

IL-10 −1082A>G, −819C>T, −592C>A haplotypes and clinical associations

Systemic lupus erythematosus patients were classified according to *IL-10* haplotypes (Table 3). ACC carriers showed higher activity disease (Mex-SLEDAI index) respect to ATA carriers (3.0 vs 1.0, $p = 0.03$). In addition, ACC carriers presented high levels of sIL-10 ($p = 0.04$ vs ATA haplotype; 3.15 vs 1.86 pg/mL, respectively). However, patients with ATA haplotype showed high levels of anti-Sm antibodies ($p = 0.02$ vs ACC carriers; 3.05 vs 0.08 IU/mL, respectively). Whereas, ATC haplotype carriers showed an increase of rheumatoid factor levels ($p = 0.02$ vs ATA haplotype; 74 vs 12 IU/mL, respectively).

Discussion

IL-10 is a potent stimulator of B cells and a strong inhibitor of antigen-presenting cells and T cells. The aberrant expression of IL-10 contributes to development of autoimmune diseases. Previously, several studies have suggested an association of genetic polymorphisms within the *IL-10* promoter with the constitutive cytokine secretion capacity [28, 29].

In the present work, we evaluated whether polymorphisms of *IL-10* promoter −1082A>G, −819C>T and −592C>A are involved in susceptibility to SLE in Mexicans. Several case–control studies addressed this question showed diverging results [9–13]. Recent meta-analysis indicates that these differences are due largely to the racial and ethnic origin. Regarding *IL-10* −1082A>G polymorphism, the meta-analysis reveals an association between SLE and the *IL-10* −1082G allele in Europeans, but not in Asians [14–16].

In a large group of unrelated Mexican SLE patients, no association with the IL-10.G microsatellites was detected, and an analysis of multicase families from Mexico, Sweden, and Iceland yielded no evidence for linkage between the *IL-10* gene and SLE [30]. However, to our knowledge there are no studies assessing the association for SNPs at

positions −1082, −819, and −592 with SLE in Mexican population. A previous study analyzed the distribution of these SNPs in healthy unrelated Mexican mestizo individuals and shown genotypic and allelic frequencies are similar to those reported in our study [31]. We found no differences when comparing genotypic and allelic frequencies of the selected polymorphisms in 125 SLE patients and 260 unrelated HS, even evaluating genetic models, suggesting that these loci individually analyzed, do not confer susceptibility to SLE in our population.

Furthermore, the haplotype analysis showed strong linkage disequilibrium among the three *IL-10* gene polymorphisms, similar to other populations studied [11–13, 32]. In our population besides the three most frequent haplotypes GCC, ACC, and ATA, we found that the haplotype GTA is present in 14 % in both studied groups. The distribution of these frequencies is similar to those reported in previous studies of Mexican, even of Italian population, which is explained by our ethnic origin. Ancestry studies in Mexican mestizos from Western, underscored the predominance of the European male contribution (∼60–64 %), followed by Amerindian (∼25–21 %), and Africans (∼15 %) [33]. In general, the stratification by ethnicity indicate that GCC haplotype shows a significant association with SLE in Europeans whereas ATA haplotype with SLE in Asians [16]. However, in this study we found no differences in SLE haplotype frequencies when compared with healthy subjects, except for increased frequency of ATC haplotype in SLE, suggesting that it is a risk haplotype for developing SLE in Mexican population (OR 3.55, CI 1.14–11.11; p=0.0293). This haplotype includes the −592 C allele associated with disease activity and lupus nephritis in Chinese patients [34].

In addition, we evaluated IL-10 serum levels according to the genotypes and found that carriers of CC genotype as well as the dominant model of inheritance showed higher sIL-10 respect to AA genotype, suggesting that the −592 C allele is associated with increased production of the cytokine; however, no differences with clinical variables or autoantibodies were observed. Furthermore, when performing the analysis regarding haplotypes, we found that ACC haplotype had higher IL-10 serum levels and higher values of Mex-SLEDAI index compared with the other haplotype carriers, but no association was found regarding autoantibodies. Carriers of GCC and ATA haplotypes are considered as high and low producers of IL-10, respectively [13, 16]. However, these findings are inconsistent, possibly due to the complexity of the in vivo condition that could regulate *IL-10* gene expression.

The role of IL-10 in the pathogenesis of SLE is unknown, but theoretically, IL-10 could stimulate peripheral blood mononuclear cells of SLE patients to produce autoantibodies, and thus be important in the excessive autoantibody production that characterized to SLE [3]. However, other cytokines have been related with SLE activity and the production of autoantibodies, such as cytokine BAFF which also acts in synergy with IL-17, and both are involved in the pathogenesis of SLE [35, 36]. Concerning environmental factors, it has been suggested that infectious agents and even diet play roles in SLE pathogenesis. It has been hypothesized that Epstein–Barr virus and cytomegalovirus may be involved in SLE. In a previous study published by our group, we found an association between high levels of IgG anti-CMV with production of lupus-related autoantibodies to RNA or DNA-protein complex [37].

On the other hand, the immune dysregulation is an important aspect in SLE: T cell dysfunction is pathophysiologically relevant, and evidence suggests that T cells play an important role. T cells are key modulators of B cell activation and class switching necessary for the production of IgG autoantibodies seen in SLE. Several studies suggest that T cells fail to execute their regulatory functions. The CD4+ CD25+ and CD8+ CD28− T regulatory lymphocytes are important in SLE pathogenesis, since both cells are decreased in SLE patients [38, 39]. Specially, CD8+ T suppressor lymphocytes mediate its function through the secretion of IL-10, which affects naïve CD8 T cells activation [40]. It could be interesting to know if the *IL-10* promoter polymorphisms are associated with CD8+ T suppressor lymphocytes, since low IL-10 producer haplotypes may affect their generation or functions. Recently, the expression level of *IL-10, CD70* (expressed on activated T cells), and *OAS2* (and interferon-inducible gene) genes have shown increased in SLE patients with disease activity, and it has been proposed that can differentiate SLE from healthy individuals and patients with other autoimmune diseases [41, 42].

In summary, our data suggest that the *IL-10* promoter haplotypes play an important role in the risk of developing SLE and influence the production of IL-10 in Mexican population. However, further studies are required to analyze the expression levels of specific pathogenesis-linked genes, as well as the interacting epigenetic factors that could help to define the true contribution of these markers in SLE pathogenesis.

Acknowledgments This work was supported by Grant No. 115567 to CAPS of the National Council of Science and Technology (CONACyT, México-Universidad de Guadalajara).

Conflict of interest The authors declare no conflict of interest.

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