Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2010, Article ID 838390, 11 pages
doi:10.1155/2010/838390

Review Article

IL-10 and TNFα Genotypes in SLE

Patricia López,[1,2] Carmen Gutiérrez,[1,3] and Ana Suárez[1]

[1] *Department of Functional Biology, Immunology Area, University of Oviedo, 33006 Oviedo, Asturias, Spain*
[2] *Department of Microbiology and Biochemistry of Dairy Products, Instituto de Productos Lácteos de Asturias (CSIC), 33300 Villaviciosa, Asturias, Spain*
[3] *Department of Immunology, Hospital Universitario Central de Asturias, 33006 Oviedo, Asturias, Spain*

Correspondence should be addressed to Ana Suárez, anasua@uniovi.es

Received 15 January 2010; Accepted 20 April 2010

Academic Editor: Timothy B. Niewold

The production of two regulators of the inflammatory response, interleukin 10 (IL-10) and tumor necrosis factor α (TNFα), has been found to be deeply deregulated in SLE patients, suggesting that these cytokines may be involved in the pathogenesis of the disease. Genetic polymorphisms at the promoter regions of IL-10 and TNFα genes have been associated with different constitutive and induced cytokine production. Given that individual steady-state levels of these molecules may deviate an initial immune response towards different forms of lymphocyte activation, functional genetic variants in their promoters could influence the development of SLE. The present review summarizes the information previously reported about the involvement of IL-10 and TNFα genetic variants on SLE appearance, clinical phenotype, and outcome. We show that, in spite of the heterogeneity of the populations studied, the existing knowledge points towards a relevant role of IL-10 and TNFα genotypes in SLE.

1. Introduction

In spite of its unknown etiology, it is accepted that genetics and environmental factors contribute to systemic lupus erythematosus (SLE) susceptibility and outcome. The levels of various cytokines have been found elevated in SLE patients; so they have been considered essential elements in the etiopathology of the disease. Given that the production of these molecules is controlled at genetic level, functional polymorphisms in their promoters could influence the development and severity of the disease. In particular, the production of interleukin 10 (IL-10) and tumor necrosis factor α (TNFα), two mutually regulated cytokines that play complex and predominantly opposite roles in systemic inflammatory responses, has been found to be deregulated in SLE patients (Figure 1). Besides its stimulated production, various cell types are constitutively capable of producing detectable amounts of these cytokines, mainly cells of myeloid origin and less abundantly T and B lymphocytes. It has been reported that individual steady-state levels of these molecules may deviate an initial immune response towards different forms of T cell activation, influencing the likelihood to transform a limited autoimmune response into an autoimmune disease.

Several evidences suggest that IL-10 could be a strong candidate gene influencing SLE susceptibility. IL-10 is an important immunoregulatory cytokine that inhibits T cell function by suppressing the expression of proinflammatory cytokines such as TNFα, IL-1, IL-6, IL-8, and IL-12 [1, 2]. It also inhibits antigen presenting cells by downregulating major histocompatibility complex class II (MHC-II) and B7 expression [3]. In addition to these inhibitory actions, IL-10 promotes B-cell-mediated functions, enhancing survival, proliferation, differentiation, and antibody production [4]. Hence, increased production of IL-10 could thus explain B cell hyperactivity and autoantibody production, two main features of the immune dysregulation in SLE. In fact, elevated levels of this molecule have been currently reported in SLE patients, frequently associated with indicators of disease activity [5, 6]. Moreover, it has been demonstrated that IL-10 plays an important role in murine lupus. Ishida et al. [7] reported that continuous administration of anti IL-10 antibodies in the

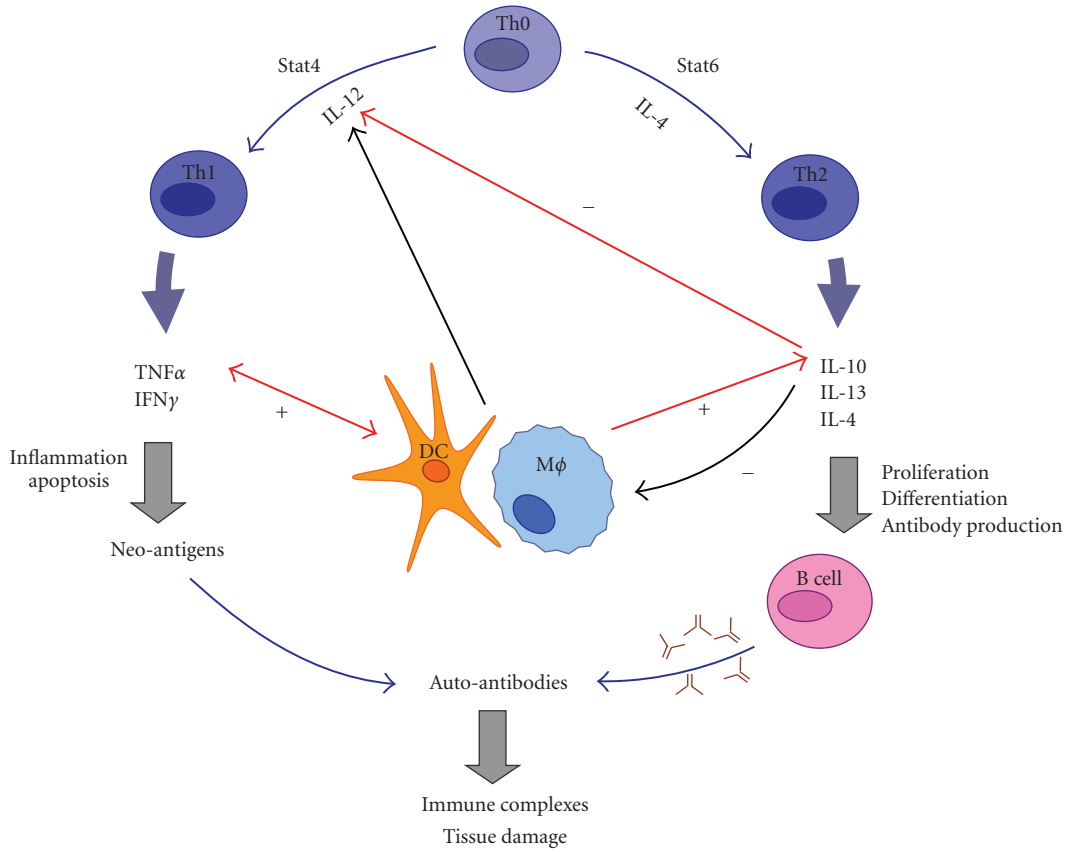

Figure 1: Interplay between IL-10 and TNFα in SLE. This figure represents a simplified model of the complex relationship between IL-10 and TNFα in lupus disease. Both cytokines are produced by multiple cells types of the innate and adaptative immune system, in particular dendritic cells (DCs), monocytes/macrophages, and specific effector T cells. Th1 cells produce the proinflammatory cytokine TNFα which activates DCs and other antigen presenting cells (APCs), and induces the production of IL-10. In addition, TNFα promotes inflammation and apoptosis, generating neoantigens that could result in autoantibody production. On the other hand, IL-10, a Th2 cytokine, antagonize Th1 differentiation and inhibits APCs and T cells. Conversely, IL-10 is a potent stimulator of B cell proliferation, differentiation and antibody production. Thus, B cell activation in presence of neo-antigens may led to autoantibody secretion and immune complexes formation, thus resulting in tissue damage affecting diverse organs. STAT; signal transducer and activator of transcription.

murine lupus model *New Zealand black/white (NZB/W) F1* delayed the onset of autoimmunity and improved the survival rate from 10 to 80%. Interestingly, Llorente et al. [8] demonstrated that constitutive IL-10 production by monocytes and B cells in healthy members of multicase families with SLE was significantly higher than that of healthy unrelated controls, but was similar to that of SLE patients, thus suggesting that a genetically controlled high innate IL-10 production may predispose to SLE development.

In the same way, TNFα is a well-known cytokine for its role in the regulation of inflammation and apoptosis, two processes involved in the pathogenesis of SLE. This molecule stimulates the production of inflammatory cytokines, enhances neutrophil activation and expression of adhesion molecules and acts as a costimulator for T-cell activation and antibody production. Accordingly, *in vivo* and *in vitro* studies demonstrated that high levels of TNFα lead to exacerbation of the inflammatory response. These effects, together with its potent immunomodulator activities [9–11], could support the involvement of TNFα in the pathogenesis of SLE [12]. However, initial studies in murine models of SLE showed contradictory results, probably because different strains of lupus prone mice have different phenotypic features. Thus, whereas the (NZB/W) F1 strain produces relatively low level of TNFα and treatment with recombinant TNFα caused a significant delay in the onset of nephritis and an improved survival rate [13], MRL-lpr/lpr and BXSB strains constitutively produce relatively high amounts of TNFα, being its effect deleterious in the outcome of the disease [14].

Nevertheless, a number of studies showed higher serum levels of TNFα in SLE patients compared with controls, which were frequently linked to SLE activity [15] or to specific immunological or clinical features, such as elevated autoantibody production [10, 11, 16]. All these data lead to suspect that TNFα has an important role in SLE susceptibility or outcome [17, 18].

Table 1: Main functional IL-10 and TNFα SNPs involved in SLE.

	IL-10	TNFα
Functional polymorphism	−1082 A/G	−308G/A
rs number	1800896	1800629
High producer allele	−1082G*	−308A*
Population frequency of high producer allele(1)		
North/Centre European and North American [32, 40, 44, 46]	0.43–0.52	0.11–0.17
South European [30, 36, 39, 45]	0.29–0.40	0.12–0.14
South American [31, 37, 38, 42]	0.29–0.35	0.08–0.03
Asian [29, 34, 35, 41, 43]	0.04–0.06	0.10–0.14

(1)Ranges of allele frequency in healthy population.

2. Functional IL-10 and TNFα Genetic Polymorphisms

Human IL-10, encoded by a gene located at chromosome 1, is secreted by a variety of cell types in response to several activation stimuli. This cytokine could be also constitutively produced at low levels by immune cells, mainly monocytes, macrophages and dendritic cells. In fact, in contrast to many other cytokines, the synthesis of IL-10 is regulated by the transcription factors Sp1 and Sp3, which are constitutively expressed by different cell types [19]. The striking interindividual differences detected in IL-10 levels at both *in vivo* constitutive and *in vitro* following cellular stimulation [20], suggest that its production is genetically controlled. A number of genetic polymorphisms at the promoter region of the IL-10 gene have been reported, some of them associated with different constitutive and induced cytokine production. Among them, the most widely studied include two areas of multiple (CA)n repeats, the microsatellites IL10.R (−4 Kb) and IL10.G (−1.1 Kb) [21, 22] with probable association with IL-10 production, and three single nucleotide polymorphisms (SNPs) located at −1082 (G/A), −819 (C/T) and −592 (C/A) positions upstream of the transcription start site [23]. A complete linkage disequilibrium exists between the alleles present at −819 and −592 positions; so these polymorphisms occurred in tandem and only three haplotypes have been found in Caucasian populations (GCC, ACC and ATA). These SNPs have been associated with variability in IL-10 production [24–26] and carriers of the GCC/GCC genotype are considered as genetically high producers, being −1082G the most relevant allele [24, 27, 28] (Table 1) [29–46].

The gene encoding TNFα is located at the MHC class III region, placed on chromosome 6p21. Similarly to IL-10, an important genetic diversity at the TNFα promoter has been detected. *In vitro* studies indicated that TNFα production varied among different alleles of the five microsatellite markers described (a, b, c, d and e). In addition, several SNPs have been identified [47–49], being −308 G/A and −238 G/A the most extensively examined. The polymorphic variant −238A is associated with DR3 and DR7 in extended haplotypes [50, 51], but no consistent data about their functionality were reported. Polymorphism present at position −308, identified by Wilson et al. [49], has been associated with different levels of cytokine production. The less common TNF2 allele (−308A) has been related to higher TNFα transcription rate than the TNF1 allele (−308G) after *in vitro* activation of lymphocytes with different stimuli [52, 53]. *In vivo* studies on mRNA constitutive levels confirmed this association [54] (Table 1). TNF2 is part of the extended haplotype HLA-A1-B8-DR3-DQ2 [55], associated with high TNFα production [56, 57] and with predisposition to several autoimmune diseases. Nevertheless, carriage of TNF2 allele—in the presence or absence of other loci—leads to an increase in TNFα production that could modify cytokine homeostasis in favor of the development of pathogenic situations.

3. IL-10 Genetic Polymorphisms and SLE Susceptibility

The IL-10 gene is situated in a major SLE susceptibility locus (1q31-32) [58]. However, in spite of the considerable number of genetic studies performed, no definitive result about its involvement in SLE susceptibility was achieved. Some works showed significant associations between IL-10 microsatellites or SNPs with SLE susceptibility or with the development of certain clinical or immunological features, while other studies indicated that these polymorphisms did not appear to have any relevance in the disease (Table 2) [27–31, 34, 45, 59–71]. With respect to microsatellite variants, different alleles of IL10.G have been reported to be associated with SLE incidence in various populations. Thus, frequency of IL10.G9 allele (21 CA repeats) was significantly decreased in European [30, 66, 71] and Mexican-American [70] SLE patients, whereas the long alleles IL10.G10, G11 and G13 (with a CA repeat number greater than 21) were significantly increased in Mexican-American [70], Italian [30, 66] and British [71] patients respectively. On the contrary, an increase in IL10.G4 (short allele) was reported in Chinese patients [29] whereas no significant differences in IL10.G alleles were detected in other cohorts [65, 68, 72, 73]. In addition, a meta-analysis study showed only association of the IL10.G11 allele with SLE susceptibility in the populations analyzed (OR = 1.279; 95% CI: 1.027–1.593; $P = .028$) [62]. It has been reported that LPS-stimulated cells from individuals carriers of the IL10.G allele with 26 CA repeats presented higher IL-10 production than those from carriers of short alleles [25], suggesting that long alleles might be responsible for a high IL-10 production. Thus, accordingly to these data, high IL-10 producer genotypes (with more than 21 CA repeats) could be associated with SLE susceptibility, while presence of short alleles could confer a protective effect [60, 66].

Conflicting results were also obtained after examining the possible association between SLE susceptibility and SNPs at −1082, −819 and −592 positions of IL-10 gene in the different populations in which they were investigated. The frequency of high IL-10 producers (carriers of −1082G allele or GCC haplotype) was found to be increased in several works with Asian [62, 74] or European [59, 75] patients,

Table 2: Summary of association studies of IL-10 promoter polymorphisms with SLE.

Reference	Population	SLE/controls	Polymorphisms	Associations
Rosado et al. (2008) [59]	Spanish	116/51	IL10G, IL10R −1082/ − 819/ − 592	No association of microsatellites Increased GCC in SLE
Guarnizo-Zuccardi et al. (2007) [31]	Colombian	120/102	−1082/ − 819/ − 592	No association
Chen et al. (2006) [60]	Taiwanese	237/304	IL10G	Increased G9 and decreased G8 in SLE. G13 associated with anticardiolipin IgM antibodies and G8 with neurologic affectation.
Sung et al. (2006) [61]	Korean	350/330	−592	No association with susceptibility −592C associated with SLE activity
Nath et al. (2005) [62]	Meta-analysis	2391/3483	IL10G/IL10R −1082/ − 819/ − 592	Increased G11 in whole population Increased −1082G in Asian populations
Khoa et al. (2005) [63]	Vietnamese	64/57	−1082	Increased −1082G in SLE
Chong et al. (2004) [29]	Chinese	550/689 554/708	IL10G, IL10R −1082/ − 819/ − 592	Increased G4 in SLE Increased −592CC in SLE
Schotte et al. (2004) [65]	German	210/158	IL10G, IL10R	No association with susceptibility R2-G14 associated with anti-Sm antibodies
Suarez et al. (2004) [45]	Spanish	248/343	−1082, −819, −592	No association with susceptibility. Association of −1082G with discoid lesions
Dijstelbloem et al. (2002) [64]	Caucasian	180/163	−1082	No association
D'Alfonso et al. (2002) [66]	Italian	217/173	−1082/ − 851/ − 592 IL10G	Association of IL10G "long alleles" with SLE
D'Alfonso et al. (2000) [30]	Italian	159/164	IL10G, IL10R	Increased G11 and decreased G9 in SLE
van der Linden et al. (2000) [67]	Mixed	44/125	−1082/ − 851/ − 592	No association
Alarcon-Riquelme et al. (1999) [68]	Mexican	330/368	IL10G	No association
Rood et al. (1999) [28]	Dutch	92/162	−1082/ − 819/ − 592	Increased ATA in neuropsychiatric SLE
Crawley et al. (1999) [69]	Anglo-saxon	120/274	−1082/ − 819/ − 592	No association
Mok et al. (1998) [34]	Chinese	83/88	−1082/ − 819/ − 592	No association with susceptibility Increased ATA in renal disease
Mehrian et al. (1998) [70]	Mexican-American	158/220	IL10G	Increased G10 and decreased G9 in SLE
Eskdale et al. (1997) [71]	Anglo-Saxon	56/102	IL-10G, IL-10R	Increased G13 and decreased G9 in SLE
Lazarus et al. (1997) [27]	Anglo-Saxon	76/199	−1082/ − 819/ − 592	GCC associated with anti-SSa

although most of the studies performed in Caucasian populations did not show significant associations [27, 31, 34, 45, 64, 67, 69, 76].

4. TNFα Genetic Polymorphisms and SLE Susceptibility

Less controversial data exist with regard to TNFα SNPs, since genotypes associated with high cytokine production have been linked to SLE susceptibility in different populations (Table 3) [31, 38–46, 74, 77–90]. Thus, an increased risk of developing SLE, independent of the HLA-DR genotype, has been reported for carriers of TNF2 allele in Caucasian [31, 44–46, 78, 81, 90], African American [91], Chinese [82, 85], Colombian [31, 38, 92] and Mexican [42] populations, while no relation was found in a few works analyzing mestizo Mexican [83], Caucasian [39, 84], African Americans [81] or Asian [41, 60, 74, 85] cohorts. In fact, the allele-based comparisons of 21 studies [77], after stratification by ethnicity,

Table 3: Summary of association studies of TNFα promoter polymorphisms with SLE.

Reference	Population	SLE/controls	Polymorphisms	Associations
Jiménez-Morales et al. (2009) [42]	Mexican	328/400	−238/ − 308	Increased −308A in SLE. No association with −238.
Lin et al. (2009) [43]	Taiwanese	162/213	−308	No association with susceptibility −308A associated with malar rash, discoid rash, photosensitivity, oral ulcers and serositis.
Hirankarn et al. (2007) [74]	Thai	154/154	−238/ − 308/ − 863	Increased −863A/ − 308G/ − 238G haplotype in SLE
Guarnizo-Zuccardi et al. (2007) [31]	Colombian	120/102	−308	Increased −308A in SLE and association with anti-Sm and anti-SSa antibodies
Lee et al. (2006) [77]	Meta-analysis	3060/4479	−308	Increased −308 AA in European, but not in Asian populations
Schotte et al. (2005) [78]	German Caucasian	205/157	microsatellites −308	Increased TNFd1 and −308A in SLE
Takeuchi et al. (2005) [79]	Japanese	61/111	microsatellites	No association
Tobon et al. (2005) [80]	Colombian	113/65	−308	No association
Parks et al. (2004) [81]	North American	230/276	−238/ − 308	Increased −308A in Caucasians, but not in African Americans
Azizah et al. (2004) [82]	Chinese	70/59	−308	Increased −308A in SLE and associated with central nervous system involvement and with anti-SSb antibodies
Correa et al. (2004) [38]	Colombian	100/430	−308	Increased −308A in SLE
Suarez et al. (2004) [45]	Spanish	248/343	−308	Increased −308A in SLE and association with anti-SSa antibodies
Rood et al. (2000) [44]	Caucasian	99/177	−238/ − 308	Increased −308A in SLE
van der Linden et al. (2001) [46]	Caucasian	91/253	−308	Increased −308A in SLE
Zuñiga et al. (2001) [83]	Mexican mestizo	51/55	−238/ − 308	No association with −308. Increased −238A in SLE
Tsuchiya et al. (2001) [84]	Southern California	91 families	−238/ − 308	No association
Wang et al. (1999) [85]	Han ethnic group (China)	89/70	−308	Increased −308A in SLE and associated with anti-SSa antibodies and lupus nephritis
Tarassi et al. (1998) [86]	Greek	46/62	microsatellites	Increased TNF a11, a2, b3 in SLE (linkage disequilibrium with HLA)
Hajeer et al. (1997) [87]	Caucasian	91/109	microsatellites	Increased TNF a2, b3, d2 in SLE and associated with photosensitivity and Raynaud's phenomenon
Chen et al. (1997) [88]	Chinese	100/107	−308	No association
Rudwaleit et al. (1996) [89]	Anglo-Saxon South African	49 white 49 black	−238/ − 308	Increased −308A in white UK (linkage disequilibrium with DR3)
DAlfonso et al. (1996) [39]	Italian	123/199	microsatellites −238/ − 308	No association
Fong et al. (1996) [41]	Chinese	67/89	−308	No association
Danis et al. (1995) [40]	Anglo-Saxon	40/57	−308	Increased −308A in SLE and associated with DR3
Wilson et al. (1994) [90]	Caucasian	81/168	−308	Increased −308A in SLE and associated with anti-SSa/SSb autoantibodies

detected a significant association of the −308A allele in the European-derived groups, but not in Asian-derived or African-derived populations. Conversely, no association between −238 TNF SNP and SLE was observed in the great majority of the populations analyzed [42, 44, 74, 81, 89, 92]. On the other hand, the influence of TNFα microsatellite variants in SLE incidence has been poorly investigated. Alleles a2, b3 and d2 have been found to be increased in SLE patients from various European populations [86, 87, 93], showing linkage disequilibrium with HLA-DR3 haplotypes associated with SLE risk. On the contrary, no association was found in a study with Japanese patients [79].

5. Influence of IL-10 and TNFα Genotypes on Autoantibody Production

The presence of autoantibodies, mainly directed against nuclear antigens (ANAs), is one of the most characteristic features of SLE. It has been observed that the incidence of ANAs is more frequent among nonaffected family members of SLE patients than in the healthy population, suggesting that presence of autoantibodies may be, at least in part, genetically controlled [94–96]. The effect of IL-10 genotypes did not seem to be especially relevant, although it has been reported an increased prevalence of antibodies against several extractable nuclear *antigens* (anti-ENA) in patients with the allele IL-10.G9 [71], and the presence of anti-Sm antibodies was found significantly overrepresented among patient carriers of G14 and G15 alleles and R2-G15 and R2-G14 haplotypes [65].

On the other hand, an association of the high producer TNFα genotypes (−308 AA or AG) with the presence of autoantibodies has been consistently reported. It has been described an association between carriage of the TNF2 allele and presence of anti-SSa or anti-SSb antibodies [45, 82, 85]. This finding is in accordance with the increased frequency of TNF2 allele reported in patients with cutaneous lupus erythematosus [76, 97], congenital heart block [98] and cutaneous neonatal lupus [99], all of them being pathologies linked to the presence of anti-SSa antibodies. However, it is important to consider that the actions of cytokines may be profoundly conditioned by the presence of other cytokines, and this is particularly true in the case of IL-10 and TNFα, two mutually regulated molecules which have opposite roles in the inflammatory reactions. In fact, the investigations about the effect of combined IL-10 and TNFα genotypes in SLE supported this interaction. Specifically, the highest percentage of antibodies against SSa and SSb was found among carriers of the combined genotype "low IL10 (−1082AA-AG)/high TNFα (−308AA-AG)" [45], the genotype linked to the highest TNFα production [100]. Association of high TNFα genotypes, alone or in combination, and autoantibody appearance has also been described in patients with other autoimmune pathologies such as inflammatory bowel disease or Sjögren's syndrome [101–103]. This effect of TNFα could be mediated by its highly proapoptotic activity since, as it has been reported, sera from SLE patients react with proteins phosphorylated during apoptosis [104], probably by recognising new epitopes generated by phosphorylation or proteolysis [105]. Thus, we can hypothesize that the proapoptotic properties of elevated TNFα levels could not be counterbalanced by the low amounts of IL-10 in patients with the high TNFα/low IL-10 genotype, thus triggering an autoimmune response to antigenically modified autoproteins generated during the apoptotic process.

6. Genetic Polymorphisms and Clinical Outcome

Increased circulating levels of IL-10 and TNFα have been consistently reported in the sera of patients with SLE. However, there were no definitive data on the association of IL-10 or TNFα polymorphisms and specific clinical manifestations, probably due to the heterogeneity of the disease. For instance, renal involvement has been associated with both high (GCC) [27, 106] and low (ATA) [107] IL-10 producer genotypes. High prevalence of neuropsychiatric [28] and cardiovascular disorders [108] has been reported in patients with low genetic production whereas high IL-10 production has been linked to an increased incidence of serositis, hematological disorder [29], SLICC/ACR Damage Index [61] and presence of discoid or mucocutaneous lesions [45, 68]. This last association was supported by the increased frequency of the high producer −1082G allele observed in patients with discoid lupus erythematosus [45, 67] and by the fact that cutaneous manifestations improved in SLE patients under anti IL-10 monoclonal antibody treatment [109].

With respect to TNFα genotype, most works did not find relevant relationships with clinical parameters, although it has been reported an increased frequency of the TNF2 allele in patients with nephritis [85], central nervous system involvement [82] and presence of malar rash, discoid lesions, photosensitivity, oral ulcers or serositis [43]. However, it is worth noting the interesting association detected between TNFα genotype and clinical outcome after antimalarial treatment. Antimalarial drugs (hydroxychloroquine, chloroquine, and quinacrine) have been widely used as disease-modifying antirheumatic agents mainly in the treatment of SLE and rheumatoid arthritis [110]. Nevertheless, their beneficial mechanisms have not been fully defined. Several *in vitro* experiments have demonstrated that antimalarials decreased the production of proinflammatory cytokines induced by LPS or CpG oligonucleotides in monocytes and macrophages [111–114] by a nonlysosomotropic mechanisms [115] and/or by blocking the interaction between TLR9 and CpG in monocyte endosomes [116]. More recently, this valuable antiinflammatory effect has been documented in patients with SLE, in whom antimalarial-treatment has been shown to downregulate serum levels of TNFα [100, 117]. But the most interesting finding was that antimalarial effect seems to be influenced by polymorphisms of the genes encoding TNFα and IL-10. Specifically, the greatest beneficial effect of antimalarial treatment appeared in patients carriers of the combined genotype low IL-10/high TNFα, since they presented better clinical response, lower

amount of circulating TNFα and increased number and function of $CD4^+CD25^{high}$ Treg cells [118] as compared with other genotypes. Of note, antimalarial treated SLE patients which were carriers of the opposite high IL-10/low TNFα genotype, presented higher circulating IFNα levels, thus suggesting an interesting relationship between TNF$\alpha$and IFNα in lupus disease [119].

7. Conclusions and Perspectives

It seems to be clear that carriage of the high producer TNF2 allele is a risk factor for SLE appearance in Caucasian populations. However, in spite of the wide number of studies performed, conclusive data on the involvement of IL-10 genetic variants have not been obtained. Nevertheless, the inverse relationship existing between both cytokines, could determine a role for IL-10 in the phenotype and/or outcome of the disease. SLE patients carriers of the high TNFα genotype probably developed the disease due to the effect of environmental or genetic factors added to their high TNFα production. The elevated levels of this cytokine may be involved in diverse pathological mechanisms and, therefore, a clinical benefit could be expected under a treatment that diminishes TNFα production. In fact, a strong association was found between carriage of this genotype, in combination with low IL-10 producer alleles, and good response to antimalarial therapy, a treatment that downregulated TNFα levels. Thus, we would expect that carriage of the proinflammatory genotype low IL-10/ high TNFα may predispose to develop anti-SSa/SSb antibodies and mild disease presenting a good course under antimalarial therapy. In addition, the conflicting data about the association of IL-10 and TNFα genotypes with clinical features which were observed by the various studies performed supports the heterogeneity of the disease and the involvement of diverse etiopathogenic factors. Thus, treatments and management of the disease might be individualized depending on IL-10 and TNFα genotypes.

References

[1] R. De Waal Malefyt, J. Haanen, and H. Spits et al., "Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression," *Journal of Experimental Medicine*, vol. 174, no. 4, pp. 915–924, 1991.

[2] D. F. Fiorentino, M. W. Bond, and T. R. Mosmann, "Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones," *Journal of Experimental Medicine*, vol. 170, no. 6, pp. 2081–20095, 1989.

[3] L. Ding, P. S. Linsley, L.-Y. Huang, R. N. Germain, and E. M. Shevach, "IL-10 inhibits macrophage costimulatory activity by selectively inhibiting the up-regulation of B7 expression," *Journal of Immunology*, vol. 151, no. 3, pp. 1224–1234, 1993.

[4] F. Rousset, E. Garcia, and T. Defrance et al., "Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 5, pp. 1890–1893, 1992.

[5] F. A. Houssiau, C. Lefebvre, B. M. Vanden, M. Lambert, J.-P. Devogelaer, and J.-C. Renauld, "Serum interleukin 10 titers in systemic lupus erythematosus reflect disease activity," *Lupus*, vol. 4, no. 5, pp. 393–395, 1995.

[6] J. K. Lacki, W. Samborski, and S. H. Mackiewicz, "Interleukin-10 and interleukin-6 in lupus erythematosus and rheumatoid arthritis, correlations with acute phase proteins," *Clinical Rheumatology*, vol. 16, no. 3, pp. 275–278, 1997.

[7] H. Ishida, T. Muchamuel, S. Sakaguchi, S. Andrade, S. Menon, and M. Howard, "Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice," *Journal of Experimental Medicine*, vol. 179, no. 1, pp. 305–310, 1994.

[8] L. Llorente, Y. Richaud-Patin, and J. Couderc et al., "Dysregulation of interleukin-10 production in relatives of patients with systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 40, no. 8, pp. 1429–1435, 1997.

[9] T. Hehlgans and K. Pfeffer, "The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: players, rules and the games," *Immunology*, vol. 115, no. 1, pp. 1–20, 2005.

[10] Y.-S. Kim, H.-M. Ko, and N.-I. Kang et al., "Mast cells play a key role in the development of late airway hyperresponsiveness through TNF-α in a murine model of asthma," *European Journal of Immunology*, vol. 37, no. 4, pp. 1107–1115, 2007.

[11] S. K. Raghav, B. Gupta, C. Agrawal, V. P. Chaturvedi, and H. R. Das, "Expression of TNF-α and related signaling molecules in the peripheral blood mononuclear cells of rheumatoid arthritis patients," *Mediators of Inflammation*, vol. 2006, 2006.

[12] M. Aringer and J. S. Smolen, "Complex cytokine effects in a complex autoimmune disease: tumor necrosis factor in systemic lupus erythematosus," *Arthritis Research and Therapy*, vol. 5, no. 4, pp. 172–177, 2003.

[13] C. O. Jacob and H. O. McDevitt, "Tumour necrosis factor-α in murine autoimmune 'lupus' nephritis," *Nature*, vol. 331, no. 6154, pp. 356–358, 1988.

[14] C. O. Jacob, F. Hwang, G. D. Lewis, and A. M. Stall, "Tumor necrosis factor alpha in murine systemic lupus erythematosus disease models: implications for genetic predisposition and immune regulation," *Cytokine*, vol. 3, no. 6, pp. 551–561, 1991.

[15] A. Studnicka-Benke, G. Steiner, P. Petera, and J. S. Smolen, "Tumour necrosis factor alpha and its soluble receptors parallel clinical disease and autoimmune activity in systemic lupus erythematosus," *British Journal of Rheumatology*, vol. 35, no. 11, pp. 1067–1074, 1996.

[16] S. Sharma, A. Sharma, S. Kumar, S. K. Sharma, and B. Ghosh, "Association of TNF haplotypes with asthma, serum IgE levels, and correlation with serum TNF-α levels," *American Journal of Respiratory Cell and Molecular Biology*, vol. 35, no. 4, pp. 488–495, 2006.

[17] N. Shakoor, M. Michalska, C. A. Harris, and J. A. Block, "Drug-induced systemic lupus erythematosus associated with etanercept therapy," *Lancet*, vol. 359, no. 9306, pp. 579–580, 2002.

[18] S. Vermeire, M. Noman, A. G. Van, F. Baert, S. K. Van, and N. Esters, "Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study," *Gastroenterology*, vol. 125, pp. 32–39, 2003.

[19] K. W. Moore, R. De Waal Malefyt, R. L. Coffman, and A. O'Garra, "Interleukin-10 and the interleukin-10 receptor," *Annual Review of Immunology*, vol. 19, pp. 683–765, 2001.

[20] R. G. J. Westendorp, J. A. M. Langermans, T. W. J. Huizinga, C. L. Verweij, and A. Sturk, "Genetic influence on cytokine production in meningococcal disease," *Lancet*, vol. 349, no. 9069, pp. 1912–1913, 1997.

[21] J. Eskdale, D. Kube, and G. Gallagher, "A second polymorphic dinucleotide repeat in the 5' flanking region of the human IL10 gene," *Immunogenetics*, vol. 45, no. 1, pp. 82–83, 1996.

[22] D. Kube, C. Platzer, and A. Von Knethen et al., "Isolation of the human interleukin 10 promoter. Characterization of the promoter activity in Burkitt's lymphoma cell lines," *Cytokine*, vol. 7, no. 1, pp. 1–7, 1995.

[23] C. Platzer, E. Fritsch, T. Elsner, M. H. Lehmann, H. D. Volk, and S. Prosch, "Cyclic adenosine monophosphate-responsive elements are involved in the transcriptional activation of the human IL-10 gene in monocytic cells," *European Journal of Immunology*, vol. 29, pp. 3098–3104, 1999.

[24] C. J. Edwards-Smith, J. R. Jonsson, D. M. Purdie, A. Bansal, C. Shorthouse, and E. E. Powell, "Interleukin-10 promoter polymorphism predicts initial response of chronic hepatitis C to interferon alfa," *Hepatology*, vol. 30, no. 2, pp. 526–530, 1999.

[25] J. Eskdale, G. Gallagher, C. L. Verweij, V. Keijsers, R. G. J. Westendorp, and T. W. J. Huizinga, "Interleukin 10 secretion in relation to human IL-10 locus haplotypes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 16, pp. 9465–9470, 1998.

[26] D. M. Turner, D. M. Williams, D. Sankaran, M. Lazarus, P. J. Sinnott, and I. V. Hutchinson, "An investigation of polymorphism in the interleukin-10 gene promoter," *European Journal of Immunogenetics*, vol. 24, no. 1, pp. 1–8, 1997.

[27] M. Lazarus, A. H. Hajeer, and D. Turner et al., "Genetic variation in the interleukin 10 gene promoter and systemic lupus erythematosus," *Journal of Rheumatology*, vol. 24, no. 12, pp. 2314–2317, 1997.

[28] M. J. Rood, V. Keijsers, and M. W. Van Der Linden et al., "Neuropsychiatric systemic lupus erythematosus is associated with imbalance in interleukin 10 promoter haplotypes," *Annals of the Rheumatic Diseases*, vol. 58, no. 2, pp. 85–89, 1999.

[29] W. P. Chong, W. K. Ip, W. H.-S. Wong, C. S. Lau, T. M. Chan, and Y. L. Lau, "Association of interleukin-10 promoter polymorphisms with systemic lupus erythematosus," *Genes and Immunity*, vol. 5, no. 6, pp. 484–492, 2004.

[30] S. D'Alfonso, M. Rampi, D. Bocchio, G. Colombo, R. Scorza-Smeraldi, and P. Momigliano-Richiardi, "Systemic lupus erythematosus candidate genes in the Italian population: evidence for a significant association with interleukin-10," *Arthritis and Rheumatism*, vol. 43, no. 1, pp. 120–128, 2000.

[31] P. Guarnizo-Zuccardi, Y. Lopez, M. Giraldo, et al., "Cytokine gene polymorphisms in Colombian patients with systemic lupus erythematosus," *Tissue Antigens*, vol. 70, no. 5, pp. 376–382, 2007.

[32] J. Hulkkonen, M. Pertovaara, J. Antonen, N. Lahdenpohja, A. Pasternack, and M. Hurme, "Genetic association between interleukin-10 promoter region polymorphisms and primary Sjögren's syndrome," *Arthritis and Rheumatism*, vol. 44, no. 1, pp. 176–179, 2001.

[33] K. Koss, G. C. Fanning, K. I. Welsh, and D. P. Jewell, "Interleukin-10 gene promoter polymorphism in English and Polish healthy controls. Polymerase chain reaction haplotyping using 3′ mismatches in forward and reverse primers," *Genes and Immunity*, vol. 1, no. 5, pp. 321–324, 2000.

[34] C. C. Mok, J. S. Lanchbury, D. W. Chan, and C. S. Lau, "Interleukin-10 promoter polymorphisms in Southern Chinese patients with systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 41, no. 6, pp. 1090–1095, 1998.

[35] H. W. Tso, W. K. Ip, W. P. Chong, C. M. Tam, A. K. S. Chiang, and Y. L. Lau, "Association of interferon gamma and interleukin 10 genes with tuberculosis in Hong Kong Chinese," *Genes and Immunity*, vol. 6, no. 4, pp. 358–363, 2005.

[36] E. Urcelay, J. L. Santiago, and H. de la Calle et al., "Interleukin-10 polymorphisms in Spanish type 1 diabetes patients," *Genes and Immunity*, vol. 5, no. 4, pp. 306–309, 2004.

[37] G. M. Xavier, A. R. D. Sá, A. L. S. Guimarães, T. A. D. Silva, and R. S. Gomez, "Investigation of functional gene polymorphisms interleukin-1β, interleukin-6, interleukin-10 and tumor necrosis factor in individuals with oral lichen planus," *Journal of Oral Pathology and Medicine*, vol. 36, no. 8, pp. 476–481, 2007.

[38] P. A. Correa, L. M. Gómez, and J. M. Anaya, "Polymorphism of TNF-alpha in autoimmunity and tuberculosis," *Biomedica*, vol. 24, pp. 43–51, 2004.

[39] S. D'Alfonso, G. Colombo, B. S. Della, R. Scorza, and P. Momigliano-Richiardi, "Association between polymorphisms in the TNF region and systemic lupus erythematosus in the Italian population," *Tissue Antigens*, vol. 47, no. 6, pp. 551–555, 1996.

[40] V. A. Danis, M. Millington, V. Hyland, R. Lawford, Q. Huang, and D. Grennan, "Increased frequency of the uncommon allele of a tumour necrosis factor alpha gene polymorphism in rheumatoid arthritis and systemic lupus erythematosus," *Disease Markers*, vol. 12, no. 2, pp. 127–133, 1995.

[41] K. Y. Fong, H. S. Howe, S. K. Tin, M. L. Boey, and P. H. Feng, "Polymorphism of the regulatory region of tumour necrosis factor alpha gene in patients with systemic lupus erythematosus," *Annals of the Academy of Medicine Singapore*, vol. 25, no. 1, pp. 90–93, 1996.

[42] S. Jiménez-Morales, R. Velázquez-Cruz, and J. Ramírez-Bello et al., "Tumor necrosis factor-α is a common genetic risk factor for asthma, juvenile rheumatoid arthritis, and systemic lupus erythematosus in a Mexican pediatric population," *Human Immunology*, vol. 70, no. 4, pp. 251–256, 2009.

[43] Y.-J. Lin, R.-H. Chen, and L. Wan et al., "Association of TNF-α gene polymorphisms with systemic lupus erythematosus in Taiwanese patients," *Lupus*, vol. 18, no. 11, pp. 974–979, 2009.

[44] M. J. Rood, M. V. Van Krugten, and E. Zanelli et al., "TNF-308A and HLA-DR3 alleles contribute independently to susceptibility to systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 43, no. 1, pp. 129–134, 2000.

[45] A. Suárez, P. López, L. Mozo, and C. Gutiérrez, "Differential effect of IL10 and TNFα genotypes on determining susceptibility to discoid and systemic lupus erythematosus," *Annals of the Rheumatic Diseases*, vol. 64, no. 11, pp. 1605–1610, 2005.

[46] M. W. Van Der Linden, A. R. Van Der Slik, and E. Zanelli et al., "Six microsatellite markers on the short arm of chromosome 6 in relation to HLA-DR3 and TNF-308A in systemic lupus erythematosus," *Genes and Immunity*, vol. 2, no. 7, pp. 373–380, 2001.

[47] T. Higuchi, N. Seki, and S. Kamizono et al., "Polymorphism of the 5'-flanking region of the human tumor necrosis factor (TNF)-α gene in Japanese," *Tissue Antigens*, vol. 51, no. 6, pp. 605–612, 1998.

[48] A. M. Uglialoro, D. Turbay, and P. A. Pesavento et al., "Identification of three new single nucleotide polymorphisms in the human tumor necrosis factor-α gene promoter," *Tissue Antigens*, vol. 52, no. 4, pp. 359–367, 1998.

[49] A. G. Wilson, F. S. Di Giovine, A. I. F. Blakemore, and G. W. Duff, "Single base polymorphism in the human Tumour Necrosis Factor alpha (TNFα) gene detectable by NcoI restriction of PCR product," *Human Molecular Genetics*, vol. 1, no. 5, p. 353, 1992.

[50] S. D'Alfonso and P. M. Richiardi, "A polymorphic variation in a putative regulation box of the TNFA promoter region," *Immunogenetics*, vol. 39, no. 2, pp. 150–154, 1994.

[51] F. Pociot, S. D'Alfonso, S. Compasso, R. Scorza, and P. M. Richiardi, "Functional analysis of a new polymorphism in the human TNF α gene promoter," *Scandinavian Journal of Immunology*, vol. 42, no. 4, pp. 501–504, 1995.

[52] K. M. Kroeger, J. H. Steer, D. A. Joyce, and L. J. Abraham, "Effects of stimulus and cell type on the expression of the -308 tumour necrosis factor promoter polymorphism," *Cytokine*, vol. 12, no. 2, pp. 110–119, 2000.

[53] A. G. Wilson, J. A. Symons, T. L. Mcdowell, H. O. Mcdevitt, and G. W. Duff, "Effects of a polymorphism in the human tumor necrosis factor α promoter on transcriptional activation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 7, pp. 3195–3199, 1997.

[54] A. Suárez, P. Castro, R. Alonso, L. Mozo, and C. Gutiérrez, "Interindividual variations in constitutive interleukin-10 messenger RNA and protein levels and their association with genetic polymorphisms," *Transplantation*, vol. 75, no. 5, pp. 711–717, 2003.

[55] P. Price, C. Witt, and R. Allcock et al., "The genetic basis for the association of the 8.1 ancestral haplotype (A1, B8, DR3) with multiple immunopathological diseases," *Immunological Reviews*, vol. 167, pp. 257–274, 1999.

[56] L. J. Abraham, M. A. H. French, and R. L. Dawkins, "Polymorphic MHC ancestral haplotypes affect the activity of tumour necrosis factor-alpha," *Clinical and Experimental Immunology*, vol. 92, no. 1, pp. 14–18, 1993.

[57] C. O. Jacob, Z. Fronek, G. D. Lewis, M. Koo, J. A. Hansen, and H. O. McDevitt, "Heritable major histocompatibility complex class II-associated differences in production of tumor necrosis factor α: relevance to genetic predisposition to systemic lupus erythematosus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, no. 3, pp. 1233–1237, 1990.

[58] B. Johanneson, G. Lima, J. Von Salomé, D. Alarcón-Segovia, and M. E. Alarcón-Riquelme, "A major susceptibility locus for systemic lupus erythemathosus maps to chromosome 1q31," *American Journal of Human Genetics*, vol. 71, no. 5, pp. 1060–1071, 2002.

[59] S. Rosado, I. Rua-Figueroa, and J. A. Vargas et al., "Interleukin-10 promoter polymorphisms in patients with systemic lupus erythematosus from the Canary Islands," *International Journal of Immunogenetics*, vol. 35, no. 3, pp. 235–242, 2008.

[60] J.-Y. Chen, C.-M. Wang, S.-C. Lu, Y.-H. Chou, and S.-F. Luo, "Association of apoptosis-related microsatellite polymorphisms on chromosome 1q in Taiwanese systemic lupus erythematosus patients," *Clinical and Experimental Immunology*, vol. 143, no. 2, pp. 281–287, 2006.

[61] Y.-K. Sung, B. L. Park, H. D. Shin, L. H. Kim, S.-Y. Kim, and S.-C. Bae, "Interleukin-10 gene polymorphisms are associated with the SLICC/ACR Damage Index in systemic lupus erythematosus," *Rheumatology*, vol. 45, no. 4, pp. 400–404, 2006.

[62] S. K. Nath, J. B. Harley, and Y. H. Lee, "Polymorphisms of complement receptor 1 and interleukin-10 genes and systemic lupus erythematosus: a meta-analysis," *Human Genetics*, vol. 118, no. 2, pp. 225–234, 2005.

[63] P. D. Khoa, T. Sugiyama, and T. Yokochi, "Polymorphism of interleukin-10 promoter and tumor necrosis factor receptor II in Vietnamese patients with systemic lupus erythematosus," *Clinical Rheumatology*, vol. 24, no. 1, pp. 11–13, 2005.

[64] H. M. Dijstelbloem, B. G. Hepkema, C. G. M. Kallenberg, et al., "The R-H polymorphism of Fcγ receptor IIa as a risk factor for systemic lupus erythematosus is independent of single-nucleotide polymorphisms in the interleukin-10 gene promoter," *Arthritis and Rheumatism*, vol. 46, no. 4, pp. 1125–1126, 2002.

[65] H. Schotte, M. Gaubitz, P. Willeke, et al., "Interleukin-10 promoter microsatellite polymorphisms in systemic lupus erythematosus: association with the anti-Sm immune response," *Rheumatology*, vol. 43, no. 11, pp. 1357–1363, 2004.

[66] S. D'Alfonso, M. Giordano, and M. Mellai et al., "Association tests with systemic lupus erythematosus (SLE) of IL10 markers indicate a direct involvement of a CA repeat in the 5′ regulatory region," *Genes and Immunity*, vol. 3, no. 8, pp. 454–463, 2002.

[67] M. W. Van der Linden, R. G. J. Westendorp, A. Sturk, W. Bergman, and T. W. J. Huizinga, "High interleukin-10 production in first-degree relatives of patients with generalized but not cutaneous lupus erythematosus," *Journal of Investigative Medicine*, vol. 48, no. 5, pp. 327–334, 2000.

[68] M. E. Alarcón-Riquelme, A.-K. B. Lindqvist, and I. Jonasson et al., "Genetic analysis of the contribution of IL10 to systemic lupus erythematosus," *Journal of Rheumatology*, vol. 26, no. 10, pp. 2148–2152, 1999.

[69] E. Crawley, P. Woo, and D. A. Isenberg, "Single nucleotide polymorphic haplotypes of the interleukin-10 5' flanking region are not associated with renal disease or serology in Caucasian patients with systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 42, no. 9, pp. 2017–2018, 1999.

[70] R. Mehrian, F. P. Quismorio Jr., and G. Strassmann et al., "Synergistic effect between IL-10 and bcl-2 genotypes in determining susceptibility to systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 41, no. 4, pp. 596–602, 1998.

[71] J. Eskdale, P. Wordsworth, S. Bowman, M. Field, and G. Gallagher, "Association between polymorphisms at the human IL-10 locus and systemic lupus erythematosus," *Tissue Antigens*, vol. 49, no. 6, pp. 635–639, 1997.

[72] C. Johansson, C. Castillejo-López, and B. Johanneson et al., "Association analysis with microsatellite and SNP markers does not support the involvement of BCL-2 in systemic lupus erythematosus in Mexican and Swedish patients and their families," *Genes and Immunity*, vol. 1, no. 6, pp. 380–385, 2000.

[73] T. T. Ou, W. C. Tsai, and C. J. Chen et al., "Genetic analysis of interleukin-10 promoter region in patients with systemic lupus erythematosus in Taiwan," *The Kaohsiung journal of medical sciences*, vol. 14, no. 10, pp. 599–606, 1998.

[74] N. Hirankarn, J. Wongpiyabovorn, and O. Hanvivatvong et al., "The synergistic effect of FC gamma receptor IIa and interleukin-10 genes on the risk to develop systemic lupus erythematosus in Thai population," *Tissue Antigens*, vol. 68, no. 5, pp. 399–406, 2006.

[75] A. Sobkowiak, M. Lianeri, M. Wudarski, J. K. Lacki, and P. P. Jagodzinski, "Genetic variation in the interleukin-10 gene promoter in Polish patients with systemic lupus erythematosus," *Rheumatology International*, vol. 29, no. 8, pp. 921–925, 2009.

[76] T. P. Millard, E. Kondeatis, and A. Cox et al., "A candidate gene analysis of three related photosensitivity disorders: cutaneous lupus erythematosus, polymorphic light eruption and actinic prurigo," *British Journal of Dermatology*, vol. 145, no. 2, pp. 229–236, 2001.

[77] Y. H. Lee, J. B. Harley, and S. K. Nath, "Meta-analysis of TNF-alpha promoter—308 A/G polymorphism and SLE susceptibility," *European Journal of Human Genetics*, vol. 14, no. 3, pp. 364–371, 2006.

[78] H. Schotte, P. Willeke, and N. Tidow et al., "Extended haplotype analysis reveals an association of TNF polymorphisms with susceptibility to systemic lupus erythematosus beyond HLA-DR3," *Scandinavian Journal of Rheumatology*, vol. 34, no. 2, pp. 114–121, 2005.

[79] F. Takeuchi, K. Nakano, and H. Nabeta et al., "Genetic contribution of the tumour necrosis factor (TNF) B + 252*2/2 genotype, but not the TNFa,b microsatellite alleles, to systemic lupus erythematosus in Japanese patients," *International Journal of Immunogenetics*, vol. 32, no. 3, pp. 173–178, 2005.

[80] G. J. Tobón, P. A. Correa, L. M. Gomez, and J.-M. Anaya, "Lack of association between TNF-308 polymorphism and the clinical and immunological characteristics of systemic lupus erythematosus and primary Sjögren's syndrome," *Clinical and Experimental Rheumatology*, vol. 23, no. 3, pp. 339–344, 2005.

[81] C. G. Parks, J. P. Pandey, and M. A. Dooley et al., "Genetic polymorphisms in tumor necrosis factor (TNF)-α and TNF-β in a population-based study of systemic lupus erythematosus: associations and interaction with the interleukin-1α-889 C/T polymorphism," *Human Immunology*, vol. 65, no. 6, pp. 622–631, 2004.

[82] M. R. Azizah, S. H. Kuak, S. S. Ainol, M. N. Rahim, Y. Normaznah, and K. Norella, "Association of the tumor necrosis factor alpha gene polymorphism with susceptibility and clinical-immunological findings of systemic lupus erythematosus," *Asian Pacific Journal of Allergy and Immunology*, vol. 22, no. 2-3, pp. 159–163, 2004.

[83] J. Zúñiga, G. Vargas-Alarcón, G. Hernández-Pacheco, C. Portal-Celhay, J. K. Yamamoto-Furusho, and J. Granados, "Tumor necrosis factor-α promoter polymorphisms in Mexican patients with systemic lupus erythematosus (SLE)," *Genes and Immunity*, vol. 2, no. 7, pp. 363–366, 2001.

[84] N. Tsuchiya, A. Kawasaki, B. P. Tsao, T. Komata, J. M. Grossman, and K. Tokunaga, "Analysis of the association of HLA-DRB1, TNFα promoter and TNFR2 (TNFRSF1B) polymorphisms with SLE using transmission disequilibrium test," *Genes and Immunity*, vol. 2, no. 6, pp. 317–322, 2001.

[85] M. Wang, Y. Dong, and S. Huang, "Study on the association between tumor necrosis factor alpha gene polymorphism and systemic lupus erythematosus," *Zhonghua Nei Ke Za Zhi*, vol. 38, no. 6, pp. 393–396, 1999.

[86] K. Tarassi, D. Carthy, and C. Papasteriades et al., "HLA-TNF haplotype heterogeneity in Greek SLE patients," *Clinical and Experimental Rheumatology*, vol. 16, no. 1, pp. 66–68, 1998.

[87] A. H. Hajeer, J. Worthington, E. J. Davies, M. C. Hillarby, K. Poulton, and W. E. R. Ollier, "TNF microsatellite a2, b3 and d2 alleles are associated with systemic lupus erythematosus," *Tissue Antigens*, vol. 49, no. 3, pp. 222–227, 1997.

[88] C.-J. Chen, J.-H. Yen, and W.-C. Tsai et al., "The TNF2 allele does not contribute towards susceptibility to systemic lupus erythematosus," *Immunology Letters*, vol. 55, no. 1, pp. 1–3, 1997.

[89] M. Rudwaleit, M. Tikly, and M. Khamashta et al., "Interethnic differences in the association of tumor necrosis factor promoter polymorphisms with systemic lupud erythematosus," *Journal of Rheumatology*, vol. 23, no. 10, pp. 1725–1728, 1996.

[90] A. G. Wilson, C. Gordon, and F. S. Di Giovine et al., "A genetic association between systemic lupus erythematosus and tumor necrosis factor alpha," *European Journal of Immunology*, vol. 24, no. 1, pp. 191–195, 1994.

[91] K. E. Sullivan, C. Wooten, B. J. Schmeckpeper, D. Goldman, and M. A. Petri, "A promoter polymorphism of tumor necrosis factor α associated with systemic lupus erythematosus in African-Americans," *Arthritis and Rheumatism*, vol. 40, no. 12, pp. 2207–2211, 1997.

[92] P. A. Correa, L. M. Gomez, J. Cadena, and J.-M. Anaya, "Autoimmunity and tuberculosis. Opposite association with TNF polymorphism," *Journal of Rheumatology*, vol. 32, no. 2, pp. 219–224, 2005.

[93] G. Sturfelt, G. Hellmer, and L. Truedsson, "TNF microsatellites in systemic lupus erythematosus—a high frequency of the TNFabc 2-3-1 haplotype in multicase SLE families," *Lupus*, vol. 5, no. 6, pp. 618–622, 1996.

[94] F. C. Arnett, R. G. Hamilton, J. D. Reveille, W. B. Bias, J. B. Harley, and M. Reichlin, "Genetic studies of Ro (SS-A) and La (SS-B) autoantibodies in families with systemic lupus erythematosus and primary Sjogren's syndrome," *Arthritis and Rheumatism*, vol. 32, no. 4, pp. 413–419, 1989.

[95] S. Miles and D. Isenberg, "A review of serological abnormalities in relatives of SLE patients," *Lupus*, vol. 2, no. 3, pp. 145–150, 1993.

[96] Y. Shoenfeld, H. Slor, and S. Shafrir et al., "Diversity and pattern of inheritance of autoantibodies in families with multiple cases of systemic lupus erythematosus," *Annals of the Rheumatic Diseases*, vol. 51, no. 5, pp. 611–618, 1992.

[97] V. P. Werth, W. Zhang, K. Dortzbach, and K. Sullivan, "Association of a promoter polymorphism of tumor necrosis factor-α with subacute cutaneous lupus erythematosus and distinct photoregulation of transcription," *Journal of Investigative Dermatology*, vol. 115, no. 4, pp. 726–730, 2000.

[98] R. M. Clancy, C. B. Backer, X. Yin, R. P. Kapur, Y. Molad, and J. P. Buyon, "Cytokine polymorphisms and histologic expression in autopsy studies: contribution of TNF-α and TGF-β1 to the pathogenesis of autoimmune-associated congenital heart block," *Journal of Immunology*, vol. 171, no. 6, pp. 3253–3261, 2003.

[99] R. M. Clancy and J. P. Buyon, "More to death than dying: apoptosis in the pathogenesis of SSA/Ro-SSB/La-associated congenital heart block," *Rheumatic Disease Clinics of North America*, vol. 30, no. 3, pp. 589–602, 2004.

[100] P. López, J. Gómez, L. Mozo, C. Gutiérrez, and A. Suárez, "Cytokine polymorphisms influence treatment outcomes in SLE patients treated with antimalarial drugs," *Arthritis Research and Therapy*, vol. 8, no. 2, 2006.

[101] P. Castro-Santos, A. Suarez, L. Mozo, and C. Gutierrez, "Association of IL-10 and TNFα genotypes with ANCA appearance in ulcerative colitis," *Clinical Immunology*, vol. 122, no. 1, pp. 108–114, 2007.

[102] J. E. Gottenberg, M. Busson, P. Loiseau, M. Dourche, J. Cohen-Solal, and V. Lepage, "Association of transforming growth factor beta1 and tumor necrosis factor alpha polymorphisms with anti-SSB/La antibody secretion in patients with primary Sjogren's syndrome," *Arthritis and Rheumatism*, vol. 50, pp. 570–580, 2004.

[103] M. Roussomoustakaki, J. Satsangi, and K. Welsh et al., "Genetic markers may predict disease behavior in patients with ulcerative colitis," *Gastroenterology*, vol. 112, no. 6, pp. 1845–1853, 1997.

[104] P. J. Utz, M. Hottelet, P. H. Schur, and P. Anderson, "Proteins phosphorylated during stress-induced apoptosis are common targets for autoantibody production in patients with systemic lupus erythematosus," *Journal of Experimental Medicine*, vol. 185, no. 5, pp. 843–854, 1997.

[105] A. Rosen and L. Casciola-Rosen, "Autoantigens as substrates for apoptotic proteases: implications for the pathogenesis of systemic autoimmune disease," *Cell Death and Differentiation*, vol. 6, no. 1, pp. 6–12, 1999.

[106] L.-J. Zhu, Z.-H. Liu, C.-H. Zeng, Z.-H. Chen, C. Yu, and L.-S. Li, "Association of interleukin-10 gene -592 A/C polymorphism with the clinical and pathological diversity of lupus nephritis," *Clinical and Experimental Rheumatology*, vol. 23, no. 6, pp. 854–860, 2005.

[107] C. C. Mok, C. S. Lau, T. M. Chan, and R. W. S. Wong, "Clinical characteristics and outcome of southern Chinese males with systemic lupus erythematosus," *Lupus*, vol. 8, no. 3, pp. 188–196, 1999.

[108] G.-Z. Fei, E. Svenungsson, J. Frostegård, and L. Padyukov, "The A-1087IL-10 allele is associated with cardiovascular disease in SLE," *Atherosclerosis*, vol. 177, no. 2, pp. 409–414, 2004.

[109] L. Llorente, Y. Richaud-Patin, C. Garcia-Padilla, E. Claret, J. Jakez-Ocampo, and M. H. Cardiel, "Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 43, pp. 1790–1800, 2000.

[110] R. I. Rynes, "Antimalarial drugs in the treatment of rheumatological diseases," *British Journal of Rheumatology*, vol. 36, no. 7, pp. 799–805, 1997.

[111] I. Karres, J.-P. Kremer, I. Dietl, U. Steckholzer, M. Jochum, and W. Ertel, "Chloroquine inhibits proinflammatory cytokine release into human whole blood," *American Journal of Physiology*, vol. 274, no. 4, pp. R1058–R1064, 1998.

[112] M. Seitz, J. Valbracht, J. Quach, and M. Lotz, "Gold sodium thiomalate and chloroquine inhibit cytokine production in monocytic THP-1 cells through distinct transcriptional and posttranslational mechanisms," *Journal of Clinical Immunology* , vol. 23, pp. 477–484, 2003.

[113] X. Zhu, W. Ertel, A. Ayala, M. H. Morrison, M. M. Perrin, and I. H. Chaudry, "Chloroquine inhibits macrophage tumour necrosis factor-α mRNA transcription," *Immunology*, vol. 80, no. 1, pp. 122–126, 1993.

[114] D. E. Macfarlane and L. Manzel, "Antagonism of immunostimulatory CpG-oligodeoxynucleotides by quinacrine, chloroquine, and structurally related compounds," *Journal of Immunology*, vol. 160, no. 3, pp. 1122–1131, 1998.

[115] S. M. Weber and S. M. Levitz, "Chloroquine interferes with lipopolysaccharide-induced TNF-α gene expression by a nonlysosomotropic mechanism," *Journal of Immunology*, vol. 165, no. 3, pp. 1534–1540, 2000.

[116] M. Rutz, J. Metzger, and T. Gellert et al., "Toll-like receptor 9 binds single-stranded CpG-DNA in a sequence- and pH-dependent manner," *European Journal of Immunology*, vol. 34, no. 9, pp. 2541–2550, 2004.

[117] A. Wozniacka, A. Lesiak, J. Narbutt, D. P. McCauliffe, and A. Sysa-Jedrzejowska, "Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients," *Lupus*, vol. 15, no. 5, pp. 268–275, 2006.

[118] P. López, J. Gómez, C. Prado, C. Gutiérrez, and A. Suárez, "Influence of functional interleukin 10/tumor necrosis factor-α polymorphisms on interferon-α, IL-10, and regulatory T cell population in patients with systemic lupus erythematosus receiving antimalarial treatment," *Journal of Rheumatology*, vol. 35, no. 8, pp. 1559–1566, 2008.

[119] M. Aringer and M. K. Crow, "A bridge between interferon-α and tumor necrosis factor in lupus," *Journal of Rheumatology*, vol. 35, no. 8, pp. 1473–1476, 2008.