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Systemic Lupus Erythematosus: Old and New Susceptibility Genes *versus* Clinical Manifestations

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Abstract: Systemic Lupus Erythematosus (SLE) is one of the most relevant world-wide autoimmune disorders. The formation of autoantibodies and the deposition of antibody-containing immune complexes in blood vessels throughout the body is the main pathogenic mechanism of SLE leading to heterogeneous clinical manifestations and target tissue damage. The complexity of etiology and pathogenesis in SLE, enclosing genetic and environmental factors, apparently is one of the greatest challenges for both researchers and clinicians. Strong indications for a genetic background in SLE come from studies in families as well as in monozygotic and dizygotic twins, discovering several SLE-associated *loci* and genes (*e.g. IRF5, PTPN22, CTLA4, STAT4 and BANK1).* As SLE has a complex genetic background, none of these genes is likely to be entirely responsible for triggering autoimmune response in SLE even if they disclosure a potentially novel molecular mechanisms in the pathogenesis' disease. The clinical manifestations and disease severity varies greatly among patients, thus several studies try to associate clinical heterogeneity and prognosis with specific genetic polymorphisms in SLE associated genes. The continue effort to describe new predisposing or modulating genes in SLE is justified by the limited knowledge about the pathogenesis, assorted clinical manifestation and the possible prevention strategies. In this review we describe newly discovered, as well as the most studied genes associated to SLE susceptibility, and relate them to clinical manifestations of the disease.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a heterogeneous clinical featured disorder characterized by B and T cell hyperactivity, formation of autoantibodies and the deposition of antibody-containing immune complexes in blood vessels throughout the body [1]. In addition SLE diverse presentations range from malar rash and arthritis through anemia and thrombocytopenia to serositis, nephritis, seizures and psychosis [2, 3]. The heterogeneous clinical manifestations in SLE patients led to the establishment of 11 criteria of diagnosis by the American College of Rheumatology (ACR), in which the simultaneously presence of at least four criteria are able to confirm the SLE diagnosis [4]. The pathogenesis of SLE is mainly due to the deficiency of several immunological mechanisms, including inappropriate function of the innate immune system, altered self-tolerance mechanisms and apoptotic cell clearance [3]. Even though the pathogenesis of SLE remains not fully understood, it is known to depend upon the interaction of genetic, environmental and hormonal factors. Indeed, SLE is a complex multisystem autoimmune disorder with a strong sex bias, affecting substantially more women (the female-to-male ratio is 15:1) of child-bearing age than any other age group [5].

Nevertheless, the genetic component has a pivotal role in SLE etiology with several genes contributing in disease´s triggering. The majority of genetic variations, including single nucleotide polymorphisms (SNPs), associated with SLE are within immune response–related genes and *HLA* (Human leukocyte antigen) gene variants, with the last one being the most well-known genetic risk factor not only for SLE but for autoimmune diseases in general [6, 7]. The SNPs associated to SLE can be clustered according to the gene function and their influence on disease´s susceptibility. The Genome Wide Association Studies (GWAS) have been providing an increase in the number of newly associated genes to SLE outside the *HLA* range and the genetic association studies are powerful tools in confirming these associations, including analysis with disease´s clinical features as depicted in Table **1**. In this review we describe SLE old and new susceptibility genes as well as the associations to the disease´s heterogeneous clinical manifestations.

THE ROLE B AND T CELLS FUNCTION RELATED GENES IN SLE

The involvement of several genes in SLE etiology has been widely examined and many of those genes that encode relevant proteins for the function of T and B cells have been considered as candidates for susceptibility to SLE and its

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Table 1. Susceptibility Genes Associated to SLE Clinical Manifestations

Clinical Manifestations and Susceptibility Genes			
SLE Features	**Definition**	**Gene**	**Referencies**
Skin Lesions	A rash on the face (cheeks and nose), often in a butterfly shape	*IL-10, RASGRP3, VDR, CTLA-4, XRCC1, STK17A, TYK2.*	[24, 78, 100, 105, 111, 114, 119, 146].
Photosensitivity	Reaction to sunlight leading to a new rash or worsen a present one	*XRCC1, TYK2.*	[111, 114, 146].
Oral ulcers	Ulcers inside the mouth or naso-pharyngeal ulcers.	*STAT4.*	[159].
Arthritis	Joint pain and swelling of two or more joints	*TNFSF4, VDR, STK17A.*	[69, 74, 100, 119].
Serositis	Pleuritis or pericarditis	*RASGRP3.*	[78].
Renal Disorders	Persistent protein or cellular casts in the urine	*PDCD1, PTPN22, TNFSF4, VDR, CTLA-4, IRF5,TLRs, STAT4.*	[33, 34, 45, 49, 73, 74, 96, 99, 105, 142, 153, 154, 159].
Neurologic disorder	Seizures or psychosis	*IL-10, XRCC1, XRCC3, XRCC4.*	[21, 25, 107].
Hematological Disorders	Anemia, leukopenia, lymphopenia or thrombocytopenia	*FYB.*	[61].
Immunologic disorder	Positivity for anti–dsDNA, anti-Sm, or antiphospholipid antibodies	*IL-10, PRL, FYB, TNFSF4, RASGRP3, BANK1, VDR, XRCC1, XRCC3 and XRCC4, STK17A, IRF5, STAT4.*	[21, 26, 27, 39, 61, 65, 78, 84, 88, 100, 107, 119, 139, 159].
Disease´s Severity and activity	Active phase modulation with symptoms worsening	*IFIH1, VDR, IRF5 and STAT4.*	[67, 100, 138, 159].

clinical manifestations. Certain variants in these genes have been identified and may contribute to abnormal lymphocytes function and, as consequence, in autoantibody production and immune complex deposition, being one of the key points in the pathogenesis of SLE.

IL-10

IL-10 (Interleukin-10) is an important immunoregulatory cytokine produced by almost all leukocytes, especially macrophages, dendritic cells (DCS) and T helper (Th) cells [8, 9]. This cytokine inhibits T cell function by suppressing the expression of proinflammatory cytokines such as TNF*α*, IL-1, IL-6, IL-8, and IL-12 [10, 11] and enhances survival, proliferation, differentiation and antibody production of B cells [12].

The *IL-10* gene is located at chromosome 1 (1q31-q32) and a number of genetic polymorphisms at its promoter region have been reported: the microsatellites IL10.G and IL10.R, a CA dinucleotide repeats at position -4000 and -1100 of *IL-10* gene, respectively [13, 14] and three single nucleotide polymorphisms (SNPs) located at −1082 (G/A), −819 (C/T) and −592 (C/A) positions. Since IL-10 biosynthesis has been demonstrated to be regulated at transcriptional level, polymorphic forms of its promoter gene may modify binding transcription factors and affect its serum levels [15-17].

Different alleles and haplotypes of these polymorphisms have been reported to be associated with SLE susceptibility both in Caucasian [18-20] as well as in Asiatic [21-23] populations and several studies also revealed the association of these polymorphisms with various clinical manifestations in SLE patients: discoid lesions [24], neurological manifestations development [21, 25], and anti-DNA [26], anti-Smith [27] and anti-cardiolipin antibodies production [21]. We can hypothesize that an abnormal production of IL-10 may cause exacerbated autoantibodies release and inflammatory processes establishment, which may favor SLE and its manifestations incidence.

PDCD1

PDCD1 (Programmed cell death 1), expressed by T and B lymphocytes, is a member of the CD28 family of receptors, which have important function in modulating lymphocyte activation. This receptor has an immunoinhibitory domain in its intracellular tail forming an immunoreceptor tyrosine–based inhibition motif (ITIMs). During cellular activation, tyrosine residues of the ITIMs are phosphorylated by the Src homology 2 protein tyrosine phosphatase 2, leading to deactivation of downstream signaling molecules. Consequently, when PDCD1 binds to its ligands, PD-L1 and PD-L2, which are expressed in many tissues, it attenuates T and B cell responses [28, 29].

PDCD1 is localized at chromosome 2 (2q37.3). Since this gene has an immunoregulatory function, genetic studies have been performed to verify the association between *PDCD1* gene polymorphisms and SLE. Several polymorphisms in intron 4 of *PDCD1* gene, such as SNPs G>A at 7146 position and C>T at 7209 position, have been reported as associated to SLE: the SNP G>A (7146), also called PD1.3, has been described as contributing to SLE susceptibility in Mexicans [30] and in different populations from Europe [30-32] and also associated to renal manifestations in SLE patients from Sweden [33, 34]. The SNP C>T (7209) demonstrated to be associated to SLE occurrences in populations from Taiwan [35] and Poland [36]. These polymorphisms affect the binding affinity and activity of the transcription factors NFkB and RUNX1 with impact on gene transcription [30]. Therefore, these associations may be due to lower binding affinity of NFkB and RUNX1 and, consequently, decreased expression of PD-1, contributing to deregulated self-tolerance and lymphocyte hyperactivity characteristic of SLE.

PRL

Sex hormones present a key role in regulating the immune response and are often associated to the sex bias in SLE patients. The prolactin (*PRL*) gene is located at chromosome 6 (6p22.2- p21.3) and encodes the prolactin hormone synthesized mainly by the anterior pituitary gland and by extrapituitary tissues, particularly immune cells, such as T lymphocytes. The *PRL* gene acts through innate and adaptive immune system by regulating the differentiation of $CD4^-$ $CD8^-$ thymocytes to $CD4^+$ or $CD8^+$ T cells and its levels are correlated to B and $CD4^+$ T lymphocytes production [37].

A biallelic polymorphism (−1149 G/T) in the promoter gene demonstrated to be responsible to modulate prolactin expression and associated with SLE, including its clinical features. Stevens *et al.*, 2001, showed that G allele consistently causes higher promoter activity, inducing an increment of prolactin mRNA from patients with the G/G genotype in relation to T/T genotype [38]. The G allele of this SNP was also associated with the presence of anti–dsDNA antibodies in serum of Mexican SLE patients [39].

PTPN22

The *PTPN22* (Protein tyrosine phosphatase non-receptor type 22) gene, located at chromosome 1 (1p13), encodes a lymphoid-specific tyrosine phosphatase known as Lyp, which is a negative regulator in T cell signaling through direct dephosphorylation of Lck, Fyn and ZAP70 kinases. Lyp also interacts with the tyrosine kinase CSK by binding its first C-terminal poly-proline (P1) region with SH3 domain of CSK [40-43]. A mutation (1858C>T) in the P1 region, which causes an amino acid change from arginine to tryptophan at position 620 (R620W), disrupts this physiological interaction and results in a gain of function that inhibits T cell receptor signaling [44]. Associations between this polymorphism and SLE susceptibility have been reported in different populations from Europe such as Sweden [45], Spain [46], Crete [47] and Poland [48] and also in populations from Egypt [49], North America [50] and Colombia [51]. Furthermore, it was observed the association of the mutation R620W with renal manifestations occurrence in SLE patients from Sweden [45] and Egypt [49]. Another variant (R263Q), located within the catalytic domain of the tyrosine phosphatase and identified as a loss-of-function mutation, was found to reduce the risk of SLE in a multiethnic cohort from Spain, Italy, Argentina and North America [52]. Individuals carrying the variant alleles of *PTPN22* are thought to have changes in T cell signaling, affecting disease predisposition by multiple mechanisms, including altered thymic selection, T-helper activity and number/function of regulatory T-cells [53]. A gain of function of PTPN22 could increase the threshold required for effective thymic selection, resulting in the permanence of autoreactive cells during the autotolerance process of immune system, allowing its participation in autoantibodies release. It could increase the formation and deposition of immune complexes, which will trigger an inflammatory response resulting in possible development of SLE and its clinical manifestations. Another mechanism involving PTPN22 gain of function with autoimmunity relates to regulatory T cells function, one of the main mechanisms to prevent autoimmune processes [54]. These cells activity depends on IL2 and a reduced production of this cytokine by peripheral T cells was observed in individuals carrying the variant R620W [55].

Although a regulatory role for Lyp in T-cell activation has been established, the effect of the R620W variant on T lymphocyte responses remains unclear, since functional studies have showed contradictory findings. Zhang *et al.*, 2011, studying knockin mice expressing PEP-R619W, the murine mutant analogous to LYP-R620W, observed the enlargement of spleens and thymuses, expansion of memory/effector T cells and lymphocyte and dendritic cell hyperresponsiveness. Also, the authors found a reduction in PEP protein levels in these mice and observed that both PEP-R619W and LYP-R620W have reduced half-lives and increased sensitivity to calpain-mediated degradation *in vitro*. The studied knockin mice in the C57BL/6J genetic background did not develop autoimmunity [56]. Dai *et al.*, 2013, also studying PEP-R619W knockin mice, observed some of the findings reported by Zhang *et al.*, such as expansion of effector and memory T cell and lymphocyte hiperresponsiveness. However, they observed that PEP-R619W and LYP-R620W have normal protein stability *in vivo* and *in vitro* and aged knockin mice on a mixed C57BL/6J and 129/Sv genetic background developed characteristics of autoimmunity [57].

FYB

Another gene involved in T cell signal transduction pathway is *FYB* (Fyn binding protein) gene, located at chromosome 5 (5p13.1) and encoding an adaptor protein implied in positive regulation of T cells [58, 59]. This gene has been shown to be downregulated in active and inactive SLE patients [60] and to have different SNPs associated to SLE and its clinical manifestations. Addobbati *et al.*, 2013 reported the association of rs6863066 (C>T) and rs358501 (T>C) SNPs with increased risk for SLE in a population from Southern Brazil. These SNPs, located at the 5' and 3' region of *FYB*, respectively, may affect the mRNA synthesis or stability and consequently protein expression. Additionally it was demonstrated the association between rs379707 (A>C)

and rs2161612 (A>G) SNPs and anti-dsDNA production and protection to hematological alterations, respectively. The SNP rs379707, in exon 15 of *FYB* gene, causes the substitution of a phenylanine to a valine amino acid, which could cause an impaired function of the Fyb protein, leading to anti-DNA antibodies production, while SNP rs2161612 is located in the 5'UTR of the gene and may protect SLE patients from excessive inflammation [61].

TNFSF4

TNFSF4 (Tumor necrosis factor ligand superfamily, member 4), also known as TNFRSF4/OX40 ligand, belongs to the tumor necrosis factor ligand family and is found to be involved in proliferation and differentiation of T and B lymphocytes. Moreover, it has a crucial role in regulating the development and survival of $CD4^+$ T cells at sites of inflammation and in inducing proinflammatory cytokines production [62-64]. Considering the role of *TNFSF4* in the immune system and its possible involvement in autoimmunity process, various genetic studies have been performed to evaluate the association between *TNFSF4* gene polymorphisms and SLE. Several SNPs in the upstream region of the gene (rs2205960, rs844648, rs844644, rs10489265 and rs1234315) have been reported to be associated with increased risk of SLE development in Asiatic [65-69], Caucasian [70, 71] and African-American [72] populations. Additionally, it has been found an association of rs2205960 SNP with both anti-Ro antibodies production [65] and renal disorders occurrence [73] in Chinese and European-derived SLE patients, respectively, and the association between rs1234315 SNP and arthritis development in Asiatic patients [69]. Since these polymorphisms are upstream of the promoter region of *TNFSF4*, they could be involved in alterations of gene regulation and, in consequence, predispose to SLE. Rajabi *et al.*, 2012 also found that mRNA expression level in SLE patients was significantly higher than in healthy controls and demonstrated the association between this increased transcripts number and the development of nephritis, arthritis and atherosclerosis in SLE patients [74].

RASGRP3

RASGRP3 (Ras guanyl nucleotide releasing proteins 3), expressed in B cells, is one of the proteins responsible for the regulation of Ras, a small membrane-bound GTPase implicated in immune B cell receptor signaling. Conversion of Ras-GDP to Ras-GTP leads to stimulation of various downstream pathways such as the Raf-Erk kinase cascade, with ensuing changes in transcription and other cellular responses [75]. RasGRP3–deficient B cells having reduced basal and BCR-regulated Ras-Erk signaling *in vitro* indicated modestly impaired proliferation in response to stimulation with anti-IgM antibodies and costimulation with anti-CD40 antibodies [76]. The polymorphism rs13385731, located in an intronic region of *RASGRP3* gene, showed association with SLE susceptibility in both populations from China [67] and Sweden [77]. Moreover, He *et al.*, 2010 reported the association of this SNP with malar rash, discoid lesion and serositis occurrence and antinuclear antibody (ANA) release in Chinese SLE patients [78].

BANK 1

Another protein involved in B cell signaling pathway is BANK1 (B-cell scaffold protein with ankyrin repeats 1), an adaptor protein that is phosphorylated upon BCR stimulation and thereafter promotes phosphorylation of inositol 1,4,5-trisphosphate receptors (IP3R) by the Src tyrosine kinase Lyn, leading to Ca^{2+} mobilization from intracellular stores [79, 80]. In addition the stimulation of the B cell receptor enhances the binding of BANK1 and BLK, an interaction mediated by cellular kinases [81]. Three *BANK1* gene polymorphisms (rs10516487, rs17266594 and rs3733197) were firstly reported to be associated to SLE in a Swedish population and in a combined analysis with populations from Scandinavia, Argentina, Germany, Italy and Spain [82]. This result has been replicated in African-Americans [83], Asians [64, 83] and other European populations [84, 85]. SNP rs10516487, in exon 2 of *BANK1* gene, leads to a non-synonymous substitution of arginine by histidine at position 61 (R61H) of the protein. The above mentioned amino acid change influences mRNA splicing and, consequently, the quantity of protein and causes a protein isoform with increased potential for multimerization [81, 86]. SNP rs17266594, located in a putative branch-point site at intron 1, is able to modify the splicing efficiency of *BANK1*; and SNP rs3733197 causes an amino acid substitution in the ankyrin domain (A383T), affecting cytoplasmic calcium mobilization [82].

The SNPs rs10516487 and rs17266594 were associated with high-title of ANA and anti-SSA antibodies production in SLE patients from a Chinese Han population [83]. SNP rs10516487 also showed to be associated to anti-DNA antibody production in European-derived SLE patients [87]. Another *BANK1* gene polymorphism associated with SLE is the rs4522865 SNP, which is located at its first intron and may have a role in the expression of the gene [65, 68]. *BANK1* mutations may contribute to sustained B-cell receptor signaling and subsequent B-cell hyperactivity, contributing to SLE development and autoantibodies production.

VDR

Vitamin D receptor (*VDR*) gene was firstly described more than three decades ago and since then over 50 targets has been identified for vitamin D, providing a broader role for this vitamin function [89]. The immunologic effect of vitamin D includes: downregulation of Th1 immune responses, depressing activated B cells proliferation, up regulation of regulatory T cells and particularly, preserving immune response [90]. Decreased levels of vitamin D are associated to immune disorders including SLE in several populations as well as its clinical manifestations [91-94]. Vitamin D acts through various immune cells, among them T and B lymphocytes and dendritic cells. These cells express VDR and 1α- hydroxylase and are able to produce vitamin D locally, which makes its deficiency a key factor in the immune system balance. When vitamin D complexes with VDR leads to pro-inflammatory cytokines suppression, such as IFN-γ and IL-12, which are interestedly elevated in SLE patient serum levels [95].

VDR gene is highly polymorphic but only four SNPs are frequently studied: *BmsI* (rs1544410), *ApaI* (rs7975232),

TaqI (rs731236) and *FokI* (rs2228570). The functional role of *BmsI*, *ApaI* and *TaqI* polymorphisms is associated with increased stability of the messenger RNA. *FokI* polymorphism can alter VDR transcription start site and synthesizes a truncated version of the VDR protein with less three amino acids [90, 95]. Studies associating *VDR* polymorphisms with SLE provided heterogeneous results mainly due cohort ethnical differences. Luo *et al.*, 2012, tested the association between *VDR* gene *BsmI* polymorphism and the genetic susceptibility to SLE in a Chinese population. The results indicated that the B allele was influencing disease susceptibility. Additionally, *VDR* B allele was associated with the development of lupus nephritis and the downregulation of *VDR* mRNA expression in SLE [96]. Renal disorders are a common feature in SLE patients and are considered as an indicator of diseases' activity [97]. This might be due to the deposition of anti-dsDNA, which is the main pathogenic event in renal failure in SLE patients [98]. *VDR FokI* (rs2228570) polymorphism is a T>C change producing a truncated VDR protein, is one of the most studied SNPs and has been associated with renal manifestation [99]. De Azevêdo Silva, *et al.*, 2013, assessed the possible association of five Tag-SNPs, which covered most of *VDR* gene by linkage disequilibrium (LD), and SLE as well as its clinical manifestations´ susceptibility in a Brazilian Population [100]. The authors described association of rs11168268 with cutaneous alterations, rs3890733 with arthritis, rs2248098 with immunological alterations and the rs4760648 with anti-dsDNA antibody. However, the study lacked association to the disease' susceptibility itself.

CTLA-4

Cytotoxic T-lymphocyte-associated antigen-4 (*CTLA-4*) is a cell surface molecule involved in the regulation of T cells through a pathway of proliferative unresponsiveness and tolerance. CTLA-4 signaling mediates antigen-specific apoptosis of T cells and suppresses autoreactive proliferation of T lymphocytes. Therefore, this immunomodulatory protein is able to regulate as well as to maintain self-tolerance [101]. CTLA-4 shares sequence homology with T cell co-stimulatory protein CD28 and both bind to the same ligands, B7.1 (CD80) and B7.2 (CD86), however with opposing functions. While CD28 promotes T-cell activity, CTLA-4 is a negative regulator of T cell responses [102]. The human *CTLA-4* gene is located at chromosome 2 (2q33) [103] and several studies have reported an association between *CTLA-4* gene polymorphisms and autoimmune diseases including SLE.

CTLA-4 SNPs have been associated to SLE in several populations and according to Ulker *et al.*, 2009, one of the most studied SNP in *CTLA-4* exon 1 at position +49 A/G has been associated with SLE susceptibility but not with disease activity or clinical manifestations in Turkish population [104]. The study performed by Sugimoyo *et al.*, 2008, presented interesting data about SLE clinical manifestations and *CTLA-4* at exon1 (+49 A/G). Two Japanese families with SLE were studied: in family 1, a boy (5-years old at SLE diagnosis) showed cardiovascular complications associated with heart failure, and his mother, also with clinically active SLE, presented lupus nephritis. In family 2, a boy (13-years old at SLE diagnosis) developed severe renal complications and peripheral vasculitis, along with skin alterations in the lower extremities. *CTLA-4* polymorphism analysis indicated that both boys and the mother of family 2 presented G/G genotype in *CTLA-4* exon 1 at +49 with a 106-bp fragment length of the 3' untranslated region (UTR) in exon 4 [105]. Ahmed *et al.*, 2001, observed that *CTLA-4* exon 1 at +49 SNP is associated to SLE but not CD28 SNPs, suggesting that *CTLA-4* SNPs might be directly linked to SLE developmental pathway [106].

DNA REPAIR GENES IN SLE

Many environmental stimuli have been associated to SLE triggering, in particular ultraviolet light exposure, which might be capable to produce Double Strand Breaks (DSBs) and DNA oxidative damage [107]. The DNA molecule itself is poorly immunogenic, however DSBs might induce immunogenicity and lead to immune response. Particularly, defects in the repair of DSBs may cause accumulation of genomic alterations and promote apoptosis [108]. In SLE patients, DSBs are ineffectively repaired which lead to apoptosis and once the clearance mechanism is not efficiently performed in SLE patients, it may contribute to the self-tolerance breakdown [107, 109]. In addition, polymorphic sites in DNA repair genes were associated with a predisposition of SLE clinical manifestations and anti-DNA antibody, supporting the role of DNA repair genes in autoimmunity [107, 110].

XRCC1, 3 and 4

Proteins encoded by the X-ray repair cross-complementing (*XRCC*) gene family protect DNA against damage from ionizing radiation [111]. Alterations in *XRCC* gene have been shown to be associated not only to SLE, but with other autoimmune disorders due to its presence at DNA damage sites [112]. *XRCC1* gene is located at chromosome 19 (19q13.2–13.3), it encodes a scaffold protein to complex with several enzymes involved with DNA repair, being the most studied XRCC family member on SLE [113]. Even though there are over 300 SNPs described in *XRCC1* gene, only three are frequently studied: the amino acid substitutions at codon 194 (at position 26304 on exon 6, rs1799782), codon 280 (at position 27466 on exon 9, rs25489) and codon 399 (at position 28152 on exon 10, rs25487), these non-conservative amino acid changes may alter XRCC1 function [113]. These three particular SNPs may lead to a diminished repair kinetic influencing on the immune response balance. The *XRCC1* Arg399Gln minor allele showed relatively high frequency in the Polish population and is associated to SLE increased risk. Interestedly, the SLE clinical manifestations associated to *XRCC1* Arg399Gln are malar rash and photosensitivity, features expressed and/or exacerbated after sun light exposure and related to the reduced ability to respond UV irradiation [111]. In the Chinese Han population, the *XRCC1* Arg399Gln also confers risk to SLE development and to the same clinical manifestations observed in the Polish population: malar rash and photosensitivity [114].

The *XRCC4* is an important player in genome stability, and *XRCC3* is suggested to play a pivotal role in the development of carcinogenesis [115-117]. Even though their functions are so important in DNA stability, these genes are not

enough studied regarding autoimmune disorder, in particular SLE. In the Brazilian population, a study evaluated SNPs from *XRCC1*, *3* and *4* genes and SLE susceptibility and its clinical manifestations. Bassi *et al.*, 2008, also investigated the efficiency of SLE peripheral blood leucocytes in repairing DNA damage induced by ionizing radiation. SLE patients' leucocytes present decreased efficiency of DNA repair after irradiation and *XRCC1* Arg399Gln SNP was associated with the presence of anti-dsDNA antibody. In addition, the three assessed SNPs taken together (*XRCC1* Arg399Gln, *XRCC3* Thr241Met and *XRCC4* Ile401Thr) were associated with the presence of neuropsychiatric disorders and antiphospholipid antibody syndrome [107]. Furthermore, in SLE patients even with presence of XRCC4, one of the most important protein in Non Homologous End Joining (NHEJ), the action of this protein is delayed when compared with healthy individuals [110]. Finally, the UV irradiation may damage DNA and decreased DNA repair may induce an autoimmune response; DNA damage might produce nucleoprotein complexes containing stimulate autoreactive T lymphocytes and so induce SLE in susceptible individuals [108, 111].

STK17A

Another study, based on microarray data analysis, pointed towards three DNA repair genes (*LIG4*, *RAD52* and *STK17A*) as associated to SLE development [60]. Although no association was found between *LIG4* and *RAD52* and SLE susceptibility [118], *STK17A* was associated not only to SLE but to several clinical features including arthritis, cutaneous and immunological alterations [119]. *STK17A,* localized at chromosome 7 (7p13), is involved in the regulation of nuclear processes, DNA damage response, positive regulation of apoptotic process, intracellular protein kinase cascade [120] and regulation of reactive oxygen species (ROS) metabolic process [121]. *STK17A* can be activated in reply to the external stimuli such as UV radiation and certain drugs. The activity of serine/threonine kinase has been requested by the DNA PKs (DNA dependent protein kinase catalytic subunit) for DNA repair of double strand breaks (DSBs) [122], consequently STK17A may have a central role in DSBs repair, caused by endogenous damage and/or environmental agents [120, 123]. Thus, DNA repair genes are potential SLE markers since their altered function are so closely related not only to the disease clinical features but in the maintenance of immune balance in those patients.

INTERFERON REGULATORY GENES

When increased expression of type I IFN regulated genes, known as IFN signature, was first described in lupus [124, 125], the interest for the potential involvement of type I IFN system in SLE etiopathogenesis raised in the scientific community. Later studies revealed that the IFN signature is not exclusive for SLE, but can also be found in others autoimmune diseases. Since IFN-α therapy can induce autoimmunity and considering that other autoimmune disorders have a noticeable IFN signature, it has been accepted that the type I IFN system has a pivotal role in the etiopathogenesis of these diseases [126]. IFN I include interferon alpha (IFN-α) and interferon beta (IFN-β), and both of them signal through type I interferon receptor [127]. The IFNs are cytokines which mediate the Th1 response, sustain activated T cells and B cells survival [1]. Th1 responses are able to broadcast proinflammatory cytokines, contributing to chronic inflammation and tissue damage [1, 127]. High IFN-α levels are associated with more a severe disease and presence of particular autoantibodies and a variety of genetic polymorphisms in genes related to IFN-α pathway have been associated with SLE susceptibility and activity.

IFIH1

The Interferon-induced Helicase C domain 1 (*IFIH1*) gene is located at chromosome 2 (2q24) and the encoded protein participates in the activation of apoptosis in viral dsRNA infected cells, modulating type 1 IFN response, production of pro-inflammatory cytokines and apoptotic processes [128]. The erroneous activation of these virus-sensitive proteins by self-derived and intracellular nucleic acids might be able to alter immune balance. IFN-1 plays a key role on SLE pathogenesis enhancing autoimmune processes and disease's complications [129, 130].

Studies on the *IFIH1* gene are limited, although those involving INF-induced genes could be used to comprehend the regulatory mechanisms involved in activity and development of SLE [131]. The deletion of the ATP-binding domain, which includes the SNP rs10930046, is associated to apoptosis in melanoma cells. The other SNP frequently studied in autoimmune diseases is rs1990760, which is located at HNF-3b binding site within exon 15, encoding an alanine to threonine change. This protein region is highly conserved in mammals and may have other unknown functions or may influence the active domains through effects on tertiary structure [131]. Rs10930046 studies in autoimmune diseases have been inconclusive because this SNP is in linkage disequilibrium (LD) with other *IFIH1* gene polymorphisms (rs2068330, rs2111485 and rs984971) and also because of the heterogeneity of frequency distribution in different populations [129, 131].

Gateva, *et al.*, 2009, reported the first association between *IFIH1* SNPs and susceptibility to SLE: the authors identified the altered risk A946T polymorphism (rs1990760) for SLE susceptibility in Sweden and US populations [70]. The results were confirmed by a study of Han *et al.*, 2009 [67]. The rs1990760 was also associated to IFN-α increased levels from SLE patients with positivity for anti-dsDNA antibody and the meta-analysis performed by Moura *et al.*, 2013, reinforced the association of this SNP to SLE onset [132]. The rs1990760 is the most associated *IFIH1* SNP in SLE and it increases gene expression, which may lead to an IFN cascade initiated by nucleic acids which is highly related to SLE pathogenesis and disease´s severity.

IRF-5

Interferon regulatory factor (*IRF*) 5, a member of the IRF family, is a transcription factor that regulates the expression of a wide range of genes. *IRF-5* is located at chromosome 7 (7q32) and expressed in B and dendritic cells. IRF-5 is able to induce transcription of IFN-α mRNA and is involved in the induction of IFN and proinflammatory cytokines [133]. Some studies report that *IRF5* gene polymorphisms are a risk factor for SLE patients in different populations [134, 135].

The first association study with *IRF5* and SLE was performed in Nordic patients (Swedish, Finnish and Icelandic) by using the SNP rs2004640 [136]. Thereafter, another study replicated the association of this SNP with SLE in cohorts with different ancestry. The rs2004640 risk allele indicated a new splice site for alternate splicing of the first exon (1A, 1B, and 1C) and was the unique polymorphism responsible for mRNAs containing exon 1B [137]. The rs2004640 forms a haplotype with the SNPs rs2004640, rs10954213 and rs10499631 and is associated to IRF5 expression levels. These SNPs are within the IRF5-SLE risk haplotype, which consists of two copies of the 4xCGGGG promoter indel, the T-allele of SNP rs2004640, the A-allele of SNP rs10954213, and C-allele of SNP rs10488631, which is associated to disease's activity [138].

The genetic variations in *IRF5* are associated with risk of developing SLE and closely related with anti-Ro autoantibodies, which are among the most frequently detected autoantibodies against nuclear antigens and also associated with SLE Sjögren's syndrome (SS) [139]. The formation of autoantibodies in SLE anticipates the disease´s active phase once it may stimulate IFNα production in humans *in vivo* via activation of the endosomal TLR system. In addition, subjects who present anti-Ro antibodies but have no clinical autoimmunity also have no high serum levels of IFNα [140]. SLE patients' homozygotes or heterozygotes for *IRF5* risk haplotype have higher serum levels of INF-α than the ones with the protective haplotype and this effect is more noticeable in patients positive for anti-ribosomal P antibody (anti-RBP) or anti-dsDNA autoantibodies [140]. Autoantibodies play a crucial role in the induction of glomerular inflammation, especially anti-dsDNA antibodies, which have been frequently associated with lupus nephritis (LN) [141]. Lupus nephritis (LN) is a common feature in SLE clinical manifestations and one of the worst organ damage in SLE leading to worse prognosis. The study performed by Qin *et al.*, 2010, in a Chinese population was the first one to describe the association between *IRF5* rs2004640 and lupus nephritis [142].

TYK2

Tyrosine Kinase 2 (*TYK2*) is located at chromosome 19 (19p13.2), a linkage locus for SLE. TYK2 phosphorylates the receptor subunits of cytokine receptors, including type-I IFN receptors, leading to increased production of IFN-1 responsive genes [130]. Serum levels of IFN-α in SLE patients follow the flares of disease activity and expression of external manifestations, such as skin rash and fever [143]. TYK2 is part of the Janus kinase (JAK) which binds to the interferon (IFN)-α receptor, IFNAR, on the cell surface of IFN-producing cells. This binding leads to phosphorylation and TYK2 activation. Active TYK2 then phosphorylates IFNAR to allow binding of STAT3 and STAT5. The production of type I IFN and the regulation of IFN- inducible genes play a crucial role in SLE etiology. In addition, an increased level of IFN- α is a well-known phenotype in SLE patients and is strongly correlated with both disease activity and severity [143].

In the meta-analysis performed by Lee *et al.*, 2012, the authors investigated four *TYK2* SNPs namely: rs2304256, rs12720270, rs280519 and rs12720356 in SLE. In the meta-analysis, the *TYK2* rs2304256 presented a significant association with SLE. However, when stratifying by ethnicity the study identified a significant association with SLE in Europeans, but not in Asians. In addition, no association was found for *TYK2* rs12720270, rs280519 and rs12720356 polymorphisms and SLE susceptibility by the meta-analysis [144]. Importantly, most of the studies were performed in European descent populations, and only two studies [143, 144] were conducted on Asians populations.

Very few studies aimed at correlating *TYK2* polymorphisms with the SLE disease´s clinical manifestations. Nevertheless, the study of Li *et al.*, 2011, investigated the role of *TYK2* SNPs including rs12720270, rs2304356 and rs2304255 without finding any association with SLE susceptibility, however associations of rs2304256 and rs12720270 with photosensitivity and discoid rash in SLE patients have been observed [146].

TLR7, 8 and 9

The Toll like Receptor (TLR) family plays a pivotal role in the mammalian innate immune system and has been considered in autoimmunity balance since activates autoreactive B cells and plasmacytoid dendritic cells by TLR ligands [147]. TLRs are very well studied pattern-recognition receptors and *TLR7/8/9* gene alterations are frequently associated to SLE mainly because their activation of INF-α production as an antiviral response. TLR7 and TLR8 recognize RNA and TLR9 recognize DNA [148, 149]. TLR7 and 9 are expressed in B and plasmacytoid dendritic cells (pDC) and TLR8 is expressed in monocyte-derived cells, such as macrophages and myeloid DC (mDC) [148].

TLR7 gene is located at X chromosome (Xp22.3-p22.2) and contains the SNP rs179008, resulting in a change from a Gln (A allele) to a Leu (T allele) at position 11 in the peptide. This exchange abbreviates the *TLR7* protein N region and extends the hydrophobic region within the signal sequence, altering *TLR7* processing. *TLR8* is located at chromosome X, 16kb from TLR7, and appears to be a linkage disequilibrium between them [150]. *TLR8* encodes two splice variants (TLR8v1 and TLR8v2) with alternative translation start sites. In fact, *TLR7* and *TLR8* are homologues and have *TLR9* as their closest evolutionary relative [147, 150]. The *TLR9* gene is located at chromosome 3 (3p21.3) and has two polymorphisms able to form the four common *TLR9* haplotypes: rs5743836 and rs352140 [151]. TLR9 protein expression is regulated by rs3764880, this particular SNP leads to an A to G exchange at the first codon, and the G allele is responsible for increasing TLR8v1 translation with no changes in mRNA levels or even protein function [152].

TLRs recognizing self-derived nucleic acids may contribute to the pathogenesis of autoimmune diseases including SLE and particularly lupus nephritis. TLRs are expressed within the kidney cells of patients diagnosed with SLE. In lupus nephritis, immunologic injury, originated by autoantibodies attack, immune complex deposition and cell-mediated injury, leads to kidneys infiltration by leukocytes. The study performed by Papadimitraki *et al.*, 2009, assessed the expression of *TLR9* in the renal tissue of patients with lupus in comparison with healthy individuals. The study showed for the first time the up-regulation of *TLR9* within the glomeru-

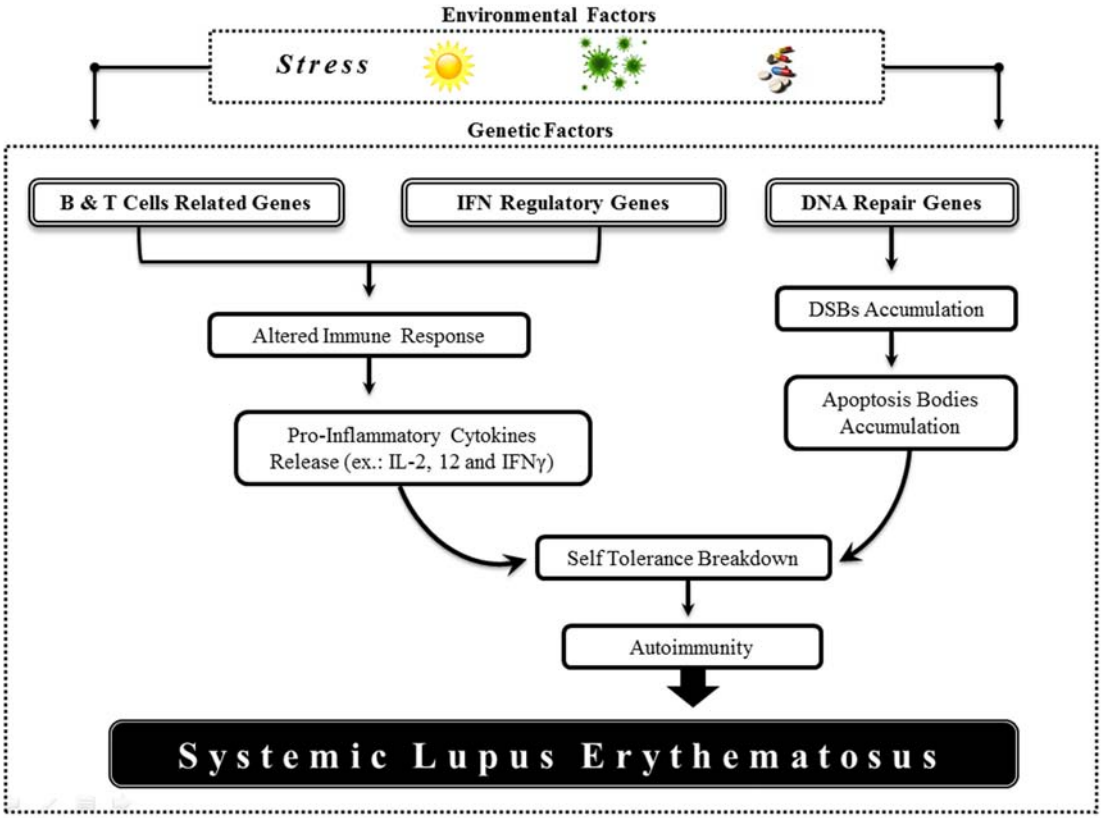

Fig. (1). Environmental factors are able to trigger the immune response and the genetic factors play a key role in this activation. The gene clusterization regarding their role in immune system indicates the major functions and general path leading to self-tolerance breakdown, autoimmunity and SLE development.

lus from lupus nephritis patients [153]. In the review of Conti *et al.*, 2011, it was shown that TLRs signaling are key components in lupus nephritis in several animal models [154].

STAT4

STAT4 (Signal Transducer and Activator of Transcription 4) belongs to the STAT family and is expressed in T and B lymphocytes, monocytes, macrophages, natural killer cells and dendritic cells. Its expression may be related to the differentiation of immune cells to inflammatory subsets, production of inflammatory cytokines and autoantibodies, prevention of apoptosis and presentation of autoantigens, which may stimulate the development of autoimmune diseases [155]. *STAT4* gene lies adjacent to *STAT1* at chromosome 2 (2q32.2–2q32.3). In murine lupus model, STAT4-deficiency is associated with acute renal disease and increased mortality, but with protective effects for arthritis in knockout mice [156].

Remmers *et al.*, 2007, identified *STAT4* as a new susceptibility gene for rheumatoid arthritis (RA) and SLE [157]. In addition, *STAT4* gene polymorphisms have been shown to be associated with other autoimmune diseases such as Systemic Sclerosis (SSc) and primary Sjogren's Syndrome (pSS), suggesting that *STAT4* polymorphisms share a common pathway for multiple autoimmune diseases [158]. One of the most associated SNPs in *STAT4* gene is rs7574865, which is located within the third intron and shows the strongest association with autoimmunity. There is no evidence indicating that this intronic SNP is responsible for any gene changes, instead any other from the many SNPs in linkage disequilibrium (LD) with it could be one explaining the disease´s association [158]. *STAT4* rs7574865 is not only associated to SLE susceptibility but with a more severe SLE clinical manifestations, particularly nephritis and the production of autoantibodies against dsDNA. In addition, in this study *STAT4* rs7574865 was associated to severe nephritis, renal disease and oral ulcers [159].

CONCLUDING REMARKS

SLE is quite known for being the prototype of the autoimmune diseases. Indeed, it displays a sophisticated intricate pathway, yet to be fully understood, leading to autoimmunity triggering and disease´s establishment. In this review we report several genes in SLE etiology encoding relevant proteins for T and B cells proper function. Actually, the most striking immune alterations in lupus patients rely on T and B cells. Therefore, the genes involved somehow to its perfect action and balance are often associated to autoimmune disorders in general. In this regard, from the "newly" associated genes batch in this review, *VDR*, for instance, seems to be a promising genetic marker in SLE and its clinical manifestations. *VDR* is very tangled in SLE etiology once it is a hor-

mone able to modulate the immune response it can be linked to the mainly lupus symptoms in skin and kidney. The association with *FYB* gene revealed the importance of the T cell activation cascade to the autoimmunity development, since the altered activation may result in an inefficient autotolerance process and, in consequence, in the autoreactive cells release, a major event in SLE.

Far from less important, the genes associated to IFN pathway are often responsible for SLE activity and worsen of clinical conditions. However, the IFN signature is not exclusive for SLE patients being frequent in other autoimmune diseases. Most of the IFN pathway genes are already well known, but *IFIH1* raises as a prominent genetic marker in autoimmune disorders. Environmental factors such as UV light exposition and stress are also a major aspect to be aware of. Additionally, genes related to DNA repair are often not working properly in SLE patients, leading to DSB accumulation, recognition of the DNA as a potential immunogenic molecule and pulling the trigger of autoimmune attack in those susceptible individuals. In this review, we described newly associated *STK17A* gene which plays a key role in DSBs repair and also a promising genetic marker in SLE. Finally, we casted for this review several genes, clustered by their function, role in SLE and most importantly, their association with SLE clinical manifestations. In conclusion, the key message in this review is that several genes are not merely associated to SLE but to its clinical manifestations as well, what may strengthens the standpoint on those genes not only to researchers but to clinicians as well toward patient´s benefit.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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