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Pathogenic mechanisms in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease characterized by the dysfunction of T cells, B cells, and dendritic cells and by the production of antinuclear autoantibodies. This editorial provides a synopsis of newly discovered genetic factors and signaling pathways in lupus pathogenesis that are documented in 11 state-of-the-art reviews and original articles. Mitochondrial hyperpolarization underlies mitochondrial dysfunction, depletion of ATP, oxidative stress, abnormal activation, and death signal processing in lupus T cells. The mammalian target of rapamycin, which is a sensor of the mitochondrial transmembrane potential, has been successfully targeted for treatment of SLE with rapamycin or sirolimus in both patients and animal models. Inhibition of oxidative stress, nitric oxide production, expression of endogenous retroviral and repetitive elements such as HRES-1, the long interspersed nuclear elements 1, Trex1, interferon alpha (IFN-α), toll-like receptors 7 and 9 (TLR-7/9), high-mobility group B1 protein, extracellular signal-regulated kinase, DNA methyl transferase 1, histone deacetylase, spleen tyrosine kinase, proteasome function, lysosome function, endosome recycling, actin cytoskeleton formation, the nuclear factor kappa B pathway, and activation of cytotoxic T cells showed efficacy in animal models of lupus. Although B cell depletion and blockade of anti-DNA antibodies and T–B cell interaction have shown success in animal models, human studies are currently ongoing to establish the value of several target molecules for treatment of patients with lupus. Ongoing oxidative stress and inflammation lead to accelerated atherosclerosis that emerged as a significant cause of mortality in SLE.

Keywords

lupus; genetics; mitochondria; nitric oxide; endosome traffic

Introduction

Systemic lupus erythematosus (SLE) is an auto-immune inflammatory diseases attributed to genetic and environmental factors causing the dysfunction of T cells, B cells, and dendritic

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cells and the production of antinuclear autoantibodies [1–3]. The pathogenesis of SLE is incompletely understood and current therapies largely relying on the use of corticosteroids and cytotoxic anti-proliferative drugs have limited efficacy and carry significant risks of toxicity. A rational approach for therapeutic design requires a detailed understanding of disease pathogenesis. Independent lines of evidence have implicated environmental factors and genetic determinants of the host in the causation of the disease [4].

Genome-wide association studies (GWAS) have identified numerous chromosomal loci that may harbor susceptibility genes [5]; however, the functional significance of these GWAS-derived polymorphisms is presently unknown. Therefore, a systematic characterization of the molecular and cellular basis of signaling abnormalities within the immune system that leads to autoreactivity and inflammation and their relationship to regulation of gene expression remain critical for understanding of disease pathogenesis [6]. This issue of *Autoimmunity* is dedicated to the state-of-the-art reviews and original articles providing novel insights into the pathogenesis of SLE.

Genetic and epigenetic factors contributing to the pathogenesis of SLE

Endogenous retroviruses (ERV) have long been implicated in triggering autoimmunity through structural and functional molecular mimicry with viral proteins [7–10]. The notion that ERV contribute to the pathogenesis of autoimmunity provides genetic linkages between the host genome and the environment. A polymorphic single nucleotide polymorphism of HRES-1 endogenous retrovirus was earlier associated with the development of SLE [11,12]. Recently, polymorphic haplotypes of the HRES-1 long-terminal repeat (LTR) have been associated with SLE in case-control and family studies [13]. The HRES-1 LTR harbors an enhancer that upregulates the expression of the HRES-1/Rab4 gene product, encoding a small GTPase that regulates receptor recycling through endosome traffic [14]. GST pull-down studies revealed a direct interaction of HRES-1/Rab4 with CD4, CD2AP, and the T cell receptor (TCR) chain [15].

Both the knockdown of HRES-1/Rab4 expression by siRNA and the inhibition of lysosomal function increased TCR-ζ levels in lupus T cells. These observations identified HRES-1/Rab4-dependent lysosomal degradation as a novel mechanism contributing to the critical loss of TCR in lupus T cells [16]. Thus, HRES-1/Rab4 may constitute the susceptibility gene at the 1q42 chromosomal locus previously linked to SLE by multiple laboratories [17–21]. The expression of full-length RNA encoded by a modified polytropic ERV in the Sgp3 (serum gp70 production 3) locus has been implicated in the pathogenesis of murine lupus [22].

GWAS studies provided strong new evidence for the genetic linkage of SLE with STAT4 [23] and IRF-5 [24], which are involved in cytokine signaling. The associations with these novel genetic loci remain less robust than the impact of the HLA locus [25]. Another interesting polymorphism that has been linked to lupus results in a non-conserved R77H substitution of the ITGAM gene that encodes the α chain of CD11b [5], which is expressed on macrophages and may contribute to the dysfunction of these cells in SLE. Additionally, a polymorphism of interleukin-1 receptor-associated kinase-1 (IRAK1) has been identified as

an X chromosome-encoded risk factor for SLESLE [26]. Importantly, deficiency of IRAK1 protects against the development of auto-reactivity and nephritis in lupus-prone mice, suggesting that the increased activity of this gene may also be relevant for disease pathogenesis in patients with SLE (Table I).

Induction of type I interferons (IFNs) by viral DNA is a principal element of antiviral defense but can cause autoimmunity if misregulated. Cytosolic DNA detection activates a potent, cell-intrinsic antiviral response through a poorly defined pathway. A screen for proteins relevant to this IFN-stimulatory DNA response identified the 3′ –5′ repair exonuclease 1 (Trex1). Mutations in the human Trex1 gene are associated with Aicardi–Goutieres syndrome and chilblain lupus [27]. Trex1 metabolizes single-stranded DNA reverse transcribed from endogenous retroelements. Single-stranded DNA accumulates and stimulates IFN-α production in Trex1-deficient cells. Thus, Trex1 deficiency is identified as a novel cell-intrinsic mechanism for initiation of autoimmunity by endogenous retroviral elements [28]. Lupus-linked polymorphisms of PTPN22 [29] lead to sustained signaling through the TCR and B cell receptor [30]. STAT4 and IRF5 polymorphisms facilitate IFN signaling in lupus [31]. In addition to linkages with nuclear genes, polymorphisms of the mitochondrial DNA (mtDNA) have also been associated with SLE [32].

Crow provides a highly innovative concept that a unique class endogenous retroelements, the long interspersed nuclear elements (LINE-1, L1), contribute to autoimmunity via stimulating the production of IFNs [33]. She proposes that increased expression of L1 transcripts or decreased degradation of L1 DNA or RNA could provide potent stimuli for an innate immune response, priming of the immune system, and inducing autoimmunity and inflammation in SLE. Genomic and genetic variations among individuals, sex-related differences in L1 regulation, and environmental triggers are among the potential mechanisms that might account for increased L1 expression. Induction of type I IFN by L1-enriched nucleic acids through Toll-like receptor-independent pathways could represent a first step in the complex series of events leading to systemic autoimmune disease.

Alternatively, epigenetic mechanisms may contribute to T and B cell hyperreactivity in SLE. In particular, drug-induced lupus has been associated with inhibition of DNA methyltransferase 1 (Dnmt1) and demethylation and activation of T cell genes, such as leukocyte function-associated antigen 1 and CD70 [34]. Procainamide and hydralazine inhibit phosphorylation and activity of extracellular signal-regulated kinase, which is proposed by Gorelik and Richardson to be a key mechanism causing the downregulation of the Dnmt1 gene [34]. Earlier studies suggest that increased activity of histone deacetylases is involved in T cell hyperreactivity in murine lupus [35]. Epigenetic mechanisms may directly contribute to the production of pathogenic anti-dsDNA immunoglobulin G (IgG) autoantibodies by B cells [36]. These autoantibodies are mutated and class switched, mainly to IgG, indicating that Ig gene somatic hypermutation (SHM) and class-switched DNA recombination (CSR) are important in their generation. The significant upregulation of SHM and CSR is associated with increased expression of activation-induced cytidine deaminase [36].

New insights into signaling abnormalities in SLE

Defective activation of T cells, B cells, DCs, and macrophages has been observed in both human and animal models of SLE [2]. Diminished IL-2 production [37] and impaired T cell-mediated cytotoxic (CTL) activity have long been recognized as biomarkers of T cell dysfunction in SLE [38,39]. Diminished IL-2 production has been attributed to defective expression of the TCR/CD3 chain [37]. Via and Shearer offer new evidence that lupus-associated defects in IL-2 synthesis and CTL responses mediate T cell-driven B cell hyperactivity [40]. Using the parent-into-F1 (P_F1) model of graft-versus-host disease-induced lupus, they have demonstrated the early appearance of diminished IL-2 production and defective CTL activity which in turn account for the subsequent B cell activation and autoantibody production. They propose that *in vitro* assessment of IL-2 production may serve as a sensitive measure of lupus disease severity [40].

Perl et al. reviewed the mechanism and consequences of the activation of the mammalian target of rapamycin (mTOR) that plays a central role in T cell dysfunction, including the diminished production of the TCR/CD3 chain, in patients with SLE [41]. mTOR serves as a sensor of the mitochondrial transmembrane potential ($\Delta\psi_m$) [42] and it is activated by NO in human T cells [15]. mTOR promotes the endosomal recycling of TCR? and targets this protein for lysosomal degradation via activation of HRES-1/Rab4 [15]. Beyond its effect on endosomal traffic, the role of mTOR is likely to be more complex and cell-type dependent. Indeed, mTOR also controls the expression of Foxp3 and development of regulatory T cells [43,44] that are deficient in patients with SLE [45,46].

The activation of B cells [47] and DCs is also dependent on mTOR [48]. Therefore, the inhibition of T, B, and DC activation and expansion of Tregs may all contribute to the therapeutic efficacy of rapamycin in murine [49] and human SLE [50]. Activation of spleen tyrosine kinase (Syk) is mapped downstream of mTOR in lupus T cells [15]. R788, an orally bioavailable Syk inhibitor, was recently found to prevent the development of renal disease and to treat established nephritis in NZB/W mice [51]. R788 minimally affected autoantibody titers, while its dose dependence reduced the numbers of CD4 + activated T cells, suggesting that T cells might be the effective targets of Syk inhibition [51]. Syk is also involved in B cell dysfunction in SLE [52]. As reviewed by Ghosh and Tsokos, preclinical and early clinical studies have urged Syk inhibition for the treatment of patients with rheumatoid arthritis, whereas *ex vivo* experiments and preclinical studies point to a therapeutic potential of Syk inhibition in patients with crystal-induced arthritides [52].

Mitochondrial dysfunction, characterized by the elevation of the $\Delta\psi_m$ or mitochondrial hyperpolarization (MHP), increased mitochondrial biogenesis, increased production of reactive oxygen intermediates (ROI) or oxidative stress, and the depletion of ATP predispose T cells to death by necrosis [53]. Increased production of nitric oxide plays key roles in MHP [54] and activation of mTOR in lupus T cells [15]. Oates emphasized the importance of ROI in modulating the effect of NO on cellular processes, the activation of innate immune responses, autoimmunity and organ damage in SLE [55]. The release of necrotic materials, DNA, RNA, and, in particular, high-mobility group B1 (HMGB1) protein stimulates DCs and B cells [56]. HMGB1, an abundant DNA-binding protein,

remains immobilized on chromatin of apoptotic bodies; however, it is released from necrotic cells [56]. Necrotic but not apoptotic cells also release heat shock proteins (HSPs), HSPgp96, hsp90. hsp70, and calreticulin [57]. pDCs are important sources of increased IL-10 [58] and promote plasma cell differentiation through production of IL-6 [59]. IFN-matured mDCs activate autoreactive T cells [60].

Wickramarachchi et al. provide insight into the modulation of T cell activation through remodeling of cytoskeletal actin filaments by coronins, which control the disassembly of actin filaments [61]. In particular, coronin-1A deficiency is associated with diminished antigen receptor-mediated T cell activation and Ca^{2+} flux, loss of mitochondrial membrane potential, and spontaneous apoptosis, primarily in the single-positive thymocyte and naïve T cell subsets [62]. A function-impairing mutation of coronin-1A has also been recently identified as the genetic alteration responsible for the lupus-associated *Lmb3* locus in mice [85]. This *Coro1a* allele was unexpectedly derived from the non-autoimmune strain, and therefore, it was a lupus-suppressing variant. This finding raised the possibility that allelic variants of other actin regulatory genes may also influence immune responses and susceptibility to SLE [61].

Avalos et al. provide new evidence that HMGB1, which is released from necrotic T cells, can also directly activate B cells [63]. IgG2a-reactive BCR transgenic AM14 B cells proliferate in response to endogenous chromatin immune complexes (ICs), in the form of the anti-nucleosome antibody PL2-3 and cell debris, in a TLR9-dependent manner, and that these ICs contain HMGB1. Activation of AM14 B cells by these chromatin ICs was inhibited by a soluble form of the HMGB1 receptor, RAGE-Fc, suggesting HMGB1–RAGE interaction was important for this response. Avalos et al. found that HMGB1 bound both CG-rich and CG-poor DNA. However, HMGB1/DNA complexes could not activate AM14 B cells unless HMGB1 was bound by IgG2a and thereby able to engage the BCR. Using RAGE-deficient mice, DNA ICs were found to activate $RAGE^{+}$ and $RAGE^{-}$ AM14 B cells to a comparable extent.

These results suggest that HMGB1 promotes B cell responses to endogenous TLR9 ligands through a RAGE-independent mechanism. Avalos et al. also reviewed the role of TLR9 and TLR-7 in B cell responses to DNA- and RNA-associated autoantigens [64]. Recent evidence suggests that B cell activation by BCR/TLR pathways depends on the balance of stimulatory and inhibitory signals. Either IFN-α engagement of the type I IFN receptor or loss of IgG ligation of the inhibitory Fc(RIIB receptor promotes B cell activation by weakly stimulatory DNA and RNA TLR ligands. These mechanisms have important implications for the role of B cells *in vivo* in the pathology of SLE [64].

Jacob and Stohl illuminate the newly appreciated role of B cells in antigen presentation and T cell activation through the expression of co-stimulatory molecules and the production of cytokines. With these points in mind, they focus on the exploitation of autoantibody-dependent and autoantibody-independent roles of B cells for the treatment of SLE [65]. Sherer et al. reviewed the pathogenesis of accelerated atherosclerosis in SLE, its role in morbidity and mortality, as well as the importance of early detection and treatment [66]. Oxidized low-density lipoprotein (oxLDL) is prone to undergo uptake by macrophages,

which turns them into the foam cells detectable in atherosclerotic lesions. Although anti-oxLDL antibodies are associated with the extent of atherosclerosis in patients, induction of anti-oxLDL antibodies with malondialdehyde-oxLDL inhibited the development of atherogenesis in animal models [67]. These results support the notion that oxidative stress also contributes to atherogenesis, and certain anti-oxLDL antibodies may protect against atherosclerosis in SLE.

References

1. Perl, A. Pathogenesis and spectrum of autoimmunity. In: Perl, A., editor. Autoimmunity, methods and protocols. Totowa, NJ: Humana Press; 2004. p. 1-8.
2. Kyttaris VC, Juang YT, Tsokos GC. Immune cells and cytokines in systemic lupus erythematosus: An update. Curr Opin Rheumatol. 2005; 17:518–522. [see comment]. [Review] [29 refs]. [PubMed: 16093827]
3. Fox RI. Sjogren's syndrome: Immunobiology of exocrine gland dysfunction. Adv Dent Res. 1996; 10:35–40. [60 refs]. [PubMed: 8934921]
4. Steinberg AD, Gourley MF, Klinman DM, Tsokos GC, Scott DE, Krieg AM. Systemic lupus erythematosus. Ann Intern Med. 1991; 115:548–559. [PubMed: 1883125]
5. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet. 2008; 40(2):204–210. [PubMed: 18204446]
6. Kyttaris VC, Krishnan S, Tsokos GC. Systems biology in systemic lupus erythematosus: Integrating genes, biology and immune function. Autoimmunity. 2006; 39(8):705–709. [PubMed: 17178567]
7. Perl A, Banki K. Human endogenous retroviral elements and autoimmunity: Data and concepts. Trends Microbiol. 1993; 1:153–156. [PubMed: 8143131]
8. Perl A. Editorial. Endogenous retroviruses in pathogenesis of autoimmunity. J Rheumatol. 2001; 28:461–464. [PubMed: 11296941]
9. Perl A. Role of endogenous retroviruses in autoimmune diseases. Rheum Dis Clin North Am. 2003; 29(1):123–143. [177 refs]. [PubMed: 12635504]
10. Perl A, Nagy G, Koncz A, Gergely P, Fernandez D, Doherty E, et al. Molecular mimicry and immunomodulation by the HRES-1 endogenous retrovirus in SLE. Autoimmunity. 2008; 41(4): 287–297. [PubMed: 18432409]
11. Magistrelli C, Banki K, Ferrante P, Perl A. Mapping and cloning of polymorphic genotypes of the HRES-1 LTR. Arth Rheum. 1994; 37:S316.
12. Magistrelli C, Samoilova E, Agarwal RK, Banki K, Ferrante P, Vladutiu A, et al. Polymorphic genotypes of the HRES-1 human endogenous retrovirus locus correlate with systemic lupus erythematosus and autoreactivity. Immunogenetics. 1999; 49:829–834. [PubMed: 10436175]
13. Pullmann R Jr, Bonilla E, Phillips PE, Middleton FA, Perl A. Haplotypes of the HRES-1 endogenous retrovirus are associated with development and disease manifestations of systemic lupus erythematosus. Arth Rheum. 2008; 58:532–540. [PubMed: 18240231]
14. Nagy G, Ward J, Mosser DD, Koncz A, Gergely P, Stancato C, et al. Regulation of CD4 expression via recycling by HRES-1/ RAB4 controls susceptibility to HIV infection. J Biol Chem. 2006; 281:34574–34591. [PubMed: 16935861]
15. Fernandez DR, Telarico T, Bonilla E, Li Q, Banerjee S, Middleton FA, et al. Activation of mTOR controls the loss of TCR. in lupus T cells through HRES-1/Rab4-regulated lysosomal degradation. J Immunol. 2009; 182:2063–2073. [PubMed: 19201859]
16. Kyttaris VC, Tsokos GC. T lymphocytes in systemic lupus erythematosus: An update. Curr Opin Rheumatol. 2004; 16:548–552. [36 refs]. [PubMed: 15314492]
17. Tsao BP, Cantor RM, Kalunian KC, Chen C-J, Badsha H, Singh R, et al. Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. J Clin Invest. 1997; 99:725–731. [PubMed: 9045876]

18. Gaffney PM, Kearns GM, Shark KB, Ortmann WA, Selby SA, Malmgren ML, et al. A genome-wide search for susceptibility genes in human systemic lupus erythematosus sib-pair families. Proc Natl Acad Sci USA. 1998; 95:14875–14879. [PubMed: 9843983]
19. Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, et al. Genome scan of human systemic lupus erythematosus: Evidence for linkage on chromosome 1q in African-American pedigrees. Proc Natl Acad Sci USA. 1998; 95:14869–14874. [PubMed: 9843982]
20. Tsao BP, Cantor RM, Grossman JM, Shen N, Teophilov NT, Wallace DJ, et al. PARP alleles with the linked chromosomal region are associated with systemic lupus erythematosus. J Clin Invest. 1999; 103:1135–1140. [PubMed: 10207165]
21. Shai R, Quismorio FP Jr, Li L, Kwon OJ, Morrison J, Wallace DJ, et al. Genome-wide screen for systemic lupus erythematosus susceptibility genes in multiplex families. Hum Mol Genet. 1999; 8(4):639–644. [PubMed: 10072432]
22. Yoshinobu K, Baudino L, Santiago-Raber ML, Morito N, Dunand-Sauthier I, Morley BJ, et al. Selective up-regulation of intact, but not defective env RNAs of endogenous modified polytropic retrovirus by the Sgp3 locus of lupus-prone mice. J Immunol. 2009; 182(12):8094–8103. [PubMed: 19494335]
23. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med. 2007; 357(10):977–986. [PubMed: 17804842]
24. Sigurdsson S, Nordmark G, G÷ring HHH, Lindroos K, Wiman AC, Sturfelt G, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory Factor 5 Genes are associated with systemic lupus erythematosus. Am J Hum Genet. 2005; 76(3):528–537. [PubMed: 15657875]
25. Harley JB, Moser KL, Gaffney PM, Behrens TW. The genetics of human systemic lupus erythematosus. Curr Op Immunol. 1998; 10:690–696. [63 refs].
26. Jacob CO, Zhu J, Armstrong DL, Yan M, Han J, Zhou XJ, et al. Identification of IRAK1 as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. Proc Natl Acad Sci USA. 2009; 106(15):6256–6261. [PubMed: 19329491]
27. Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, et al. Mutations in the gene encoding the 3[prime]-5[prime] DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet. 2007; 39(9):1065–1067. [PubMed: 17660818]
28. Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell. 2008; 134(4):587–598. [PubMed: 18724932]
29. Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: The PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet. 2005; 76(4):561–571. [PubMed: 15719322]
30. Rieck M, Arechiga A, Onengut-Gumuscu S, Greenbaum C, Concannon P, Buckner JH. Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. J Immunol. 2007; 179(7):4704–4710. [PubMed: 17878369]
31. Abelson AK, Delgado-Vega AM, Kozyrev SV, Sanchez E, Velazquez-Cruz R, Eriksson N, et al. STAT4 Associates with SLE through two independent effects that correlate with gene expression and act additively with IRF5 to increase risk. Ann Rheum Dis. 2009; 68:1746–1753. [PubMed: 19019891]
32. Vyshkina T, Sylvester A, Sadiq S, Bonilla E, Canter JA, Perl A, et al. Association of common mitochondrial DNA variants with multiple sclerosis and systemic lupus erythematosus. Clin Immunol. 2008; 129:31–35. [PubMed: 18708297]
33. Crow MK. Long interspersed nuclear elements (LINE-1): Potential triggers of systemic autoimmune disease. Autoimmunity. 2009; 43(1):7–16. [PubMed: 19961365]
34. Gorelik G, Richardson B. Key role of ERK pathway signaling in lupus. Autoimmunity. 2009a
35. Mishra N, Reilly CM, Brown DR, Ruiz P, Gilkeson GS. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. J Clin Invest. 2003; 111(4):539–552. [PubMed: 12588892]
36. Zan H, Zhang J, Ardeshna S, Xu Z, Park SR, Casali P. Lupus-prone MRL/faslpr/lpr mice display increased AID expression and extensive DNA lesions, comprising deletions and insertions, in the

immunoglobulin locus: Concurrent up-regulation of somatic hypermutation and class switch DNA recombination. Autoimmunity. 2009:89–103. [PubMed: 19156553]

37. Nambiar MP, Fisher CU, Warke VG, Krishnan S, Mitchell JP, Delaney N, et al. Reconstitution of deficient T cell receptor zeta chain restores T cell signaling and augments T cell receptor/CD3-induced interleukin-2 production in patients with systemic lupus erythematosus. Arth Rheum. 2003; 48:1948–1955. [PubMed: 12847689]
38. Perl A, Gonzalez-Cabello R, Lang I, Gergely P. Depressed natural and lectin-dependent cell-mediated cytotoxicity against adherent HEp-2 cells in patients with systemic lupus erythematosus. Immunol Commun. 1982; 11:431–440. [PubMed: 7169224]
39. Perl A, Gonzalez-Cabello R, Gergely P. Depressed effector activity of OKT4 + and OKT8 + T cell subsets in lectin-dependent cell-mediated cytotoxicity to HEP-2 cells in patients with systemic lupus erythematosus. J Clin Lab Immunol. 1984; 15:95–100. [PubMed: 6240539]
40. Via CS, Shearer GM. Defective *in vitro* IL-2 production in lupus is an early but secondary event paralleling disease activity: Evidence from the murine parent-into-F1 model supports staging of IL-2 defects in human lupus. Autoimmunity. 2009
41. Perl A. Systems biology of lupus: mapping the impact of genomic and environmental factors on gene expression signatures, cellular signaling, metabolic pathways, hormonal and cytokine imbalance and selecting targets for treatment. Autoimmunity. 2009; 43(1):32–47. [PubMed: 20001421]
42. Desai BN, Myers BR, Schreiber SL. FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. Proc Natl Acad Sci USA. 2002; 99:4319–4324. [PubMed: 11930000]
43. Haxhinasto S, Mathis D, Benoist C. The AKT-mTOR axis regulates de novo differentiation of CD4 + Foxp3 + cells. J Exp Med. 2008; 205(3):565–574. [PubMed: 18283119]
44. Sauer S, Bruno L, Hertweck A, Finlay D, Leleu M, Spivakov M, et al. T cell receptor signaling controls Foxp3 expression via PI3K. Akt, and mTOR. Proc Natl Acad Sci USA. 2008; 105(22): 7797–7802. [PubMed: 18509048]
45. Valencia X, Yarboro C, Illei G, Lipsky PE. Deficient CD4 + CD25 high T regulatory cell function in patients with active systemic lupus erythematosus. J Immunol. 2007; 178(4):2579–2588. [PubMed: 17277168]
46. Hahn BH, Anderson M, Le E, La Cava A. Anti-DNA Ig peptides promote Treg cell activity in systemic lupus erythematosus patients. Arth Rheum. 2008; 58(8):2488–2497. [PubMed: 18668553]
47. Wu T, Qin X, Kurepa Z, Kumar KR, Liu K, Kanta H, et al. Shared signaling networks active in B cells isolated from genetically distinct mouse models of lupus. J Clin Invest. 2007; 117(8):2186–2196. [PubMed: 17641780]
48. Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. Nat Rev Immunol. 2009; 9(5):324–337. [PubMed: 19390566]
49. Warner LM, Adams LM, Sehgal SN. Rapamycin prolongs survival and arrests pathophysiologic changes in murine systemic lupus erythematosus. Arth Rheum. 1994; 37:289–297. [PubMed: 8129783]
50. Fernandez D, Bonilla E, Mirza N, Perl A. Rapamycin reduces disease activity and normalizes T-cell activation-induced calcium fluxing in patients with systemic lupus erythematosus. Arth Rheum. 2006; 54(9):2983–2988. [PubMed: 16947529]
51. Bahjat FR, Pine PR, Reitsma A, Cassafer G, Baluom M, Grillo S, et al. An orally bioavailable spleen tyrosine kinase inhibitor delays disease progression and prolongs survival in murine lupus. Arth Rheum. 2008; 58(5):1433–1444. [PubMed: 18438845]
52. Ghosh D, Tsokos GC. Spleen tyrosine kinase (Syk): A src family of non-receptor kinase has multiple functions and represents a valuable therapeutic target in the treatment of autoimmune and inflammatory disease. Autoimmunity. 2009a
53. Gergely PJ, Grossman C, Niland B, Puskas F, Neupane H, Allam F, et al. Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. Arth Rheum. 2002; 46:175–90. [PubMed: 11817589]

54. Nagy G, Barcza M, Gonchoroff N, Phillips PE, Perl A. Nitric oxide-dependent mitochondrial biogenesis generates Ca^{2+} signaling profile of lupus T cells. J Immunol. 2004; 173(6):3676–3683. [PubMed: 15356113]
55. Oates JC. The biology of reactive intermediates in systemic lupus erythematosus. Autoimmunity. 2009a:16.
56. Perl A, Gergely P Jr, Nagy G, Koncz A, Banki K. Mitochondrial hyperpolarization: A checkpoint of T cell life, death, and autoimmunity. Trends Immunol. 2004; 25:360–367. [PubMed: 15207503]
57. Basu S, Binder RJ, Suto R, Anderson KM, Srivastava PK. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-{kappa}B pathway. Int Immunol. 2000; 12(11):1539–1546. [PubMed: 11058573]
58. Urbonaviciute V, Furnrohr BG, Meister S, Munoz L, Heyder P, De Marchis F, et al. Induction of inflammatory and immune responses by HMGB1-nucleosome complexes: Implications for the pathogenesis of SLE. J Exp Med. 2008; 205(13):3007–3018. [PubMed: 19064698]
59. Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity. 1919; (2):225–234.
60. Banchereau J, Pascual V, Type I. interferon in systemic lupus erythematosus an other autoimmune diseases. Immunity. 2006; 25:383–392. [100 refs]. [PubMed: 16979570]
61. Wickramarachchi D, Theofilopoulos AN, Kono DH. Immune pathology associated with altered actin cytoskeleton regulation. Autoimmunity. 2009; 43(1):64–75. [PubMed: 20001423]
62. Haraldsson MK, Louis-Dit-Sully CA, Lawson BR, Sternik G, Santiago-Raber ML, Gascoigne NRJ, et al. The lupus-related Lmb3 locus contains a disease-suppressing Coronin-1A gene mutation. Immunity. 2008; 28(1):40–51. [PubMed: 18199416]
63. Avalos AM, Kiefer K, Tian J, Christensen S, Shlomchik MJ, Coyle AJ, et al. RAGE-independent autoreactive B cell activation in response to chromatin and HMGB1/DNA immune complexes. Autommunity. 2009a
64. Avalos AM, Busconi L, Marshak-Rothstein A. Regulation of autoreactive B cell responses to endogenous TLR ligands. Autoimmunity. 2009a
65. Jacob N, Stohl W. Autoantibody-dependent and autoantibody-independent roles for B cells in systemic lupus erythematosus: Past, present, and future. Autoimmunity. 2009
66. Sherer Y, Zinger H, Shoenfeld Y. Atherosclerosis in systemic lupus erythematosus. Autoimmunity. 2009
67. George J, Afek A, Gilburd B, Levkovitz H, Shaish A, Goldberg I, et al. Hyperimmunization of apo-E-deficient mice with homologous malondialdehyde low-density lipoprotein suppresses early atherogenesis. Atherosclerosis. 1998; 138(1):147–152. [PubMed: 9678780]
68. Kozyrev SV, Abelson AK, Wojcik J, Zaghlool A, Linga Reddy MVP, Sanchez E, et al. Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. Nat Genet. 2008; 40(2):211–216. [PubMed: 18204447]
69. Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX [see comment]. New Engl J Med. 2008; 358(9):900–909. [PubMed: 18204098]

Table I

New genetic factors associated with SLE.

Gene	Pathway	Reference
ITGAM/CD11b	Macrophage activation	[5]
IRAK1	NF-kappaB activation	[26]
TREX1	IFN-α production	[27,28]
STAT4	Cytokine signaling	[23]
IRF-5	Cytokine signaling	[24]
PTPN22	Sustained TCR/BCR signaling	[29,30]
BANK1	Sustained BCR signaling	[68]
B-lymphocyte kinase	B cell activation	[69]
HRES-1/Rab4	Receptor recycling	[13,15]
Coronin-1A	Actin depolymerization	[62]
MtDNA	Electron transport	[32]