Published in final edited form as:

Curr Opin Rheumatol. 2009 September ; 21(5): 443–447. doi:10.1097/BOR.0b013e32832efe6b.

Emerging new pathways of pathogenesis and targets for treatment in systemic lupus erythematosus and Sjogren's syndrome

Andras Perl

Division of Rheumatology, Departments of Medicine and Microbiology and Immunology, State University of New York, Upstate Medical University, College of Medicine, Syracuse, New York, USA

Abstract

Purpose of review—Systemic lupus erythematosus (SLE) and Sjogren's syndrome are chronic inflammatory diseases characterized by the dysfunction of T cells, B cells, and dendritic cells and the production of antinuclear autoantibodies. Here, we evaluate newly discovered molecular and cellular targets for the treatment of SLE and Sjogren's syndrome.

Recent findings—The mammalian target of rapamycin in T and B cells has been successfully targeted for treatment of SLE with rapamycin or sirolimus both in patients and animal models. Inhibition of oxidative stress, nitric oxide production, interferon alpha, toll-like receptors 7 and 9, histone deacetylase, spleen tyrosine kinase, proteasome function, lysosome function, endosome recycling, and the nuclear factor kappa B pathway showed efficacy in animal models of lupus. B-cell depletion and blockade of anti-DNA antibodies and T–B cell interaction have shown success in animal models, whereas human studies have so far failed to accomplish clinical endpoints, possibly due to inadequacies in study design.

Summary—Discovery of novel genes and signaling pathways in lupus pathogenesis offers novel biomarker-targeted approaches for treatment of SLE and Sjogren's syndrome.

Keywords

endosome recycling; glutathione; interferon; lupus; lysosome; mammalian target of rapamycin; nuclear factor-kappa B; nitric oxide; oxidative stress; Sjogren's syndrome

Introduction

Systemic lupus erythematosus (SLE) and Sjogren's syndrome (SjS) are autoimmune inflammatory diseases attributed to genetic and environmental factors causing the dysfunction of T cells, B cells, and dendritic cells and production of antinuclear autoantibodies [1–3]. Although the inflammatory process of SLE typically involves multiple organ systems, SjS is confined to exocrine glands, particularly salivary glands [3]. The cause

of SLE and SjS is incompletely understood, and current therapies largely relying on the use of corticosteroids and cytotoxic antiproliferative drugs have limited efficacy and carry significant risks of toxicity. A more 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]. Concordance rates for SLE are approximately 25% in monozygotic twins [5]. Alternatively, the discordance rate may be as high as 70% among monozygotic twins [6], suggesting a significant role for exogenous agents [7,8]. Genome-wide association studies (GWAS) have identified numerous chromosomal loci that may harbor susceptibility genes [9]; however, the functional significance of these GWAS-derived polymorphisms is currently unknown. Therefore, a systematic characterization of the molecular and cellular basis of signaling abnormalities within the immune system that lead to autoreactivity and inflammation and their relationship with regulation of gene expression remain critical for understanding of disease pathogenesis [10].

Identification of new genes and pathways of pathogenesis that can be targeted for treatment in systemic lupus erythematosus and Sjogren's syndrome

In the first study of this special issue of SLE and SjS, Scofield [11] provides an update of novel genes with a focus on signal transducer and activator of transcription 4 (*STAT4*) and interferon regulatory factor (*IRF5*), which are involved in cytokine signaling. The associations with these novel genetic loci remain less robust than the impact of the human leukocyte antigen (HLA) locus [5]. Another interesting polymorphism that has been linked to lupus results in a nonconserved R77H substitution of the integrin, alpha M (*ITGAM*) gene that encodes the alpha chain of CD11b [9], 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 SLE [12**]. Importantly, deficiency of *IRAK1* protects against the development of autoreactivity 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 1 [9,12**,13*,14–18,19*,20,21*,22]).

Endogenous retroviruses have long been implicated in triggering autoimmunity through structural and functional molecular mimicry with viral proteins [23–26]. A polymorphic single-nucleotide polymorphism (SNP) of human T-cell leukemia virus-related endogenous sequence (HRES-1) endogenous retrovirus was earlier associated with the development of SLE [27,28]. Recently, polymorphic haplotypes of the HRES-1 long terminal repeat (LTR) have been associated with SLE in case–control and family studies [20]. The HRES-1 LTR harbors an enhancer that upregulates the expression of the *HRES-1/Rab4* gene product, encoding a small guanosine triphosphate (GTP)ase that regulates receptor recycling through endosome traffic [29]. Glutathione S-transferase (GST) pull-down studies revealed a direct interaction of HRES-1/Rab4 with CD4, CD2AP, and the T-cell receptor (TCR) ζ chain [21*]. Both the knockdown of HRES-1/Rab4 expression by small interfering RNA (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 ζ in lupus T cells [30]. Thus, *HRES-1/Rab4* may constitute the susceptibility gene at the 1q42 chromosomal locus previously linked to SLE by multiple laboratories [31–35].

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 (ISD) response identified the 3′–5′ repair exonuclease 1 (Trex1). Mutations in the human *Trex1* gene are associated with Aicardi–Goutieres syndrome (AGS) and chilblain lupus [14]. Trex1 metabolizes single-stranded DNA reverse transcribed from endogenous retroelements. Single-stranded DNA accumulates and stimulates IFN alpha (IFN α) production in Trex1-deficient cells. Thus, TREX-1 deficiency is identified as a novel cell-intrinsic mechanism for initiation of autoimmunity by endogenous retroviral elements [13^{*}]. Lupus-linked polymorphisms of protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) [17] lead to sustained signaling through the TCR and B-cell receptor [18]. STAT4 and IRF5 polymorphisms facilitate IFN signaling in lupus [36].

Nikolov and Illei [37] identified the activation of IFN α , B-cell-activating factor (BAFF), and antibodies to muscarinic acetylcholine receptor as critical new steps on the road to the development of SjS. Increased production of IFN α [38] and BAFF represents common pathways of SLE and SjS pathogenesis [39]. As described by Ronnblom *et al.* [40], plasmacytoid dendritic cells (pDCs) are a major source of increased IFN α production in SLE. Activation of pDC is attributed to stimulation of toll-like receptor (TLR)-7 and TLR-9 by endocytosed immune complexes [40]. A specific inhibitor of TLR-7 and TLR-9, called immunoregulatory sequence (IRS) 954, can block IFN α production by human pDC in response to DNA and RNA viruses and immune complexes from lupus patients. IRS 954 also prevented the production of autoantibodies, decreased proteinuria, glomerulonephritis, and end-organ damage and increased survival in the lupus prone [New Zealand black $\times$ New Zealand white (NZB $\times$ NZW)] F1 mice [41].

Alternatively, activation of pDC may be caused by the release of necrotic materials from T cells [42]. In particular, high mobility group B1 (HMGB1) protein, an abundant DNA-binding protein, remains immobilized on chromatin of apoptotic bodies; however, it is released from necrotic cells [42]. Necrotic but not apoptotic cells also release heat shock proteins (HSPs), HSPgp96, HSP90, HSP70, and calreticulin [43]. pDCs are also important sources of increased interleukin (IL)-10 [44] and promote plasma cell differentiation through production of IL-6 [45]. IFN-matured myeloid dendritic cells (mDCs) activate autoreactive T cells [46]. Clinical trials with type I IFN-neutralizing antibodies are currently ongoing in patients with SLE, which will ultimately determine the safety of IFN blockade and further clarify the relative importance of type I IFN and dendritic cell activation in SLE.

Perl *et al.* [47] reviewed the mechanism and consequences of the activation of mammalian target of rapamycin (mTOR) that plays a central role in dysfunction of T cells and B cells in patients with SLE. Rapamycin improves disease activity and normalizes enhanced T-cell

activation-induced calcium fluxing in lupus T cells [48]. mTOR promotes the endosomal recycling of TCR ζ and targets this protein for lysosomal degradation via activation of HRES-1/Rab4 [21^{*}]. 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 forkhead box P3 (Foxp3) and development of regulatory T cells (Tregs) [49^{*},50^{*}], which are deficient in patients with SLE [51,52]. The function of dendritic cells is also dependent on mTOR [53]. Therefore, the inhibition of T-cell, B-cell, and dendritic cell activation and expansion of Tregs may all contribute to the therapeutic efficacy of rapamycin in murine [54] and human SLE [48]. A prospective, open-label, phase II study is currently underway to further assess the efficacy of rapamycin in SLE (<http://clinicaltrials.gov/ct2/show/NCT00779194>). mTOR is a sensor of the mitochondrial transmembrane potential, and its activation is a result of mitochondrial hyperpolarization caused by depletion of glutathione and increased nitric oxide production [21^{*}]. A prospective, double-blind, placebo-controlled phase I/II study is currently underway to evaluate the safety and efficacy of *N*-acetylcysteine, an antioxidant and precursor of glutathione in SLE (<http://clinicaltrials.gov/ct2/show/NCT00775476>). Blockade of nitric oxide production improved the outcome of nephritis in lupus-prone mice [55]; however, the safety of such an approach for long-term treatment in humans remains to be established. Activation of spleen tyrosine kinase (Syk) is mapped downstream of mTOR in lupus T cells [21^{*}]. R788, an orally bioavailable Syk inhibitor, was recently found to prevent the development of renal disease and to treat established nephritis in NZB/NZW mice [56]. R788 minimally affected autoantibody titers, whereas its dose-dependent effect reduced the numbers of CD4⁺-activated T cells, suggesting that T cells might be the effective targets of Syk inhibition [56].

Coca and Sanz [57] reviewed the current state of B-cell depletion (BCD) in SLE. Although the largest trials employing BCD with rituximab in patients with lupus have not achieved any of the targeted clinical endpoints, the failure may be due to problematic study design. BCD remains efficacious in pediatric patients and in a subset of adult lupus patients with antibody-mediated cytopenias [57]. The proteasome inhibitor bortezomib depletes plasma cells, possibly due to their high rate of protein synthesis, and blocks nephritis in Murphy Roths Large (MRL)/lpr and (NZB/NZW) F1 mice [58]. Selective removal of plasma cells may be a particularly worthwhile target in patients with SLE.

Mevorach *et al.* [59] reviewed exciting new developments in the detection of heart conduction defects in fetuses exposed to maternal anti-SjS A (SSA)/Ro or anti-SjS B (SSB)/La, or both antibodies neonatal lupus using tissue velocity fetal kinetocardiogram (FKCG). In comparison to traditional Doppler, FKCG has superior sensitivity to detect first-degree atrioventricular block (AVB). This allows timely and effective treatment with fluorinated steroids, which prevents third-degree AVB and obviates the need for permanent pacemaker.

Conclusion

Both GWAS and hypothesis-driven studies identified a series of novel genes and signaling pathways that contribute to the pathogenesis of lupus and SjS. Despite the setback with the BCD, there are increasing numbers of promising molecular targets for human clinical trials

(Table 2 [21*,48,58,60–68]). FKCG needs to be independently validated, and perhaps simplified, which could then become a useful diagnostic tool for detecting first-degree AVB and preventing irreversible third-degree AVB in neonatal lupus.

Acknowledgments

This work was supported in part by grants #AI 048079, AI 061066, and AI 072648 from the National Institutes of Health and the Central New York Community Foundation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Perl, A. Pathogenesis and spectrum of autoimmunity. In: Perl, A., editor. *Autoimmunity Methods and protocols*. 1. Totowa, New Jersey: 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. [PubMed: 16093827]
3. Fox RI. Sjogren's syndrome: immunobiology of exocrine gland dysfunction [review]. *Adv Dent Res*. 1996; 10:35–40. [PubMed: 8934921]
4. Steinberg AD, Gourley MF, Klinman DM, et al. Systemic lupus erythematosus. *Ann Intern Med*. 1991; 115:548–559. [PubMed: 1883125]
5. Harley JB, Moser KL, Gaffney PM, Behrens TW. The genetics of human systemic lupus erythematosus [review]. *Curr Op Immunol*. 1998; 10:690–696.
6. Arnett FC, Reveille JD. Genetics of systemic lupus erythematosus. *Rheum Dis Clin North Am*. 1992; 18:865–892. [PubMed: 1455048]
7. Perl A. Mechanisms of viral pathogenesis in rheumatic diseases (invited review). *Ann Rheum Dis*. 1999; 58:454–461. [PubMed: 10419862]
8. Harley JB, Harley IT, Guthridge JM, James JA. The curiously suspicious: a role for Epstein-Barr virus in lupus [review]. *Lupus*. 2006; 15:768–777. [PubMed: 17153849]
9. Harley JB, Alarcon-Riquelme ME, Criswell LA, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXX, KIAA1542 and other loci. *Nat Genet*. 2008; 40:204–210. [PubMed: 18204446]
10. Kyttaris VC, Krishnan S, Tsokos GC. Systems biology in systemic lupus erythematosus: Integrating genes, biology and immune function. *Autoimmunity*. 2006; 39:705–709. [PubMed: 17178567]
11. Scofield RH. Genetics of systemic lupus erythematosus and Sjögren's syndrome. *Curr Opin Rheumatol*. (in press).
- 12••. Jacob CO, Zhu J, Armstrong DL, et al. Identification of IRAK1 as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. *Proc Natl Acad Sci U S A*. 2009; 106:6256–6261. An original article documenting a genetic role as well as a mechanistic role for IRAK1 in lupus. [PubMed: 19329491]
- 13•. Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. *Cell*. 2008; 134:587–598. An original article documenting the role of TREX1 in controlling a cell-intrinsic IFN response, revealing a novel mechanism of autoimmune pathogenesis due to the activation of endogenous retroviral elements. [PubMed: 18724932]
14. Lee-Kirsch MA, Gong M, Chowdhury D, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. *Nat Genet*. 2007; 39:1065–1067. [PubMed: 17660818]

15. Remmers EF, Plenge RM, Lee AT, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med*. 2007; 357:977–986. [PubMed: 17804842]
16. Sigurdsson S, Nordmark G, Göring HHH, 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; 76:528–537. [PubMed: 15657875]
17. Criswell LA, Pfeiffer KA, Lum RF, 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; 76:561–571. [PubMed: 15719322]
18. Rieck M, Arechiga A, Onengut-Gumuscu S, et al. Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. *J Immunol*. 2007; 179:4704–4710. [PubMed: 17878369]
19. Kozyrev SV, Abelson AK, Wojcik J, et al. Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. *Nat Genet*. 2008; 40:211–216. An original article, documenting the genetic association of a B-cell activation-related gene, B-cell scaffold protein with ankyrin repeats 1 (*BANK1*), in SLE. [PubMed: 18204447]
20. Pullmann R Jr, Bonilla E, Phillips PE, et al. Haplotypes of the HRES-1 endogenous retrovirus are associated with development and disease manifestations of systemic lupus erythematosus. *Arthritis Rheum*. 2008; 58:532–540. [PubMed: 18240231]
21. Fernandez DR, Telarico T, Bonilla E, 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. An original article documenting the activation of the mTOR by nitric oxide in lupus T cells that promotes the lysosomal degradation of TCR ζ via stimulating expression of HRES-1/Rab4. [PubMed: 19201859]
22. Vyshkina T, Sylvester A, Sadiq S, et al. Association of common mitochondrial DNA variants with multiple sclerosis and systemic lupus erythematosus. *Clin Immunol*. 2008; 129:31–35. [PubMed: 18708297]
23. Perl A, Banki K. Human endogenous retroviral elements and autoimmunity: data and concepts. *Trends Microbiol*. 1993; 1:153–156. [PubMed: 8143131]
24. Perl A. Endogenous retroviruses in pathogenesis of autoimmunity [editorial]. *J Rheumatol*. 2001; 28:461–464. [PubMed: 11296941]
25. Perl A. Role of endogenous retroviruses in autoimmune diseases [review]. *Rheum Dis Clin North Am*. 2003; 29:123–143. [PubMed: 12635504]
26. Perl A, Nagy G, Koncz A, et al. Molecular mimicry and immunomodulation by the HRES-1 endogenous retrovirus in SLE. *Autoimmunity*. 2008; 41:287–297. [PubMed: 18432409]
27. Magistrelli C, Banki K, Ferrante P, Perl A. Mapping and cloning of polymorphic genotypes of the HRES-1 LTR. *Arthritis Rheum*. 1994; 37:S316.
28. Magistrelli C, Samoilova E, Agarwal RK, 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]
29. Nagy G, Ward J, Mosser DD, 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]
30. Kyttaris VC, Tsokos GC. T lymphocytes in systemic lupus erythematosus: an update [review]. *Curr Opin Rheumatol*. 2004; 16:548–552. [PubMed: 15314492]
31. Tsao BP, Cantor RM, Kalunian KC, 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]
32. Gaffney PM, Kearns GM, Shark KB, et al. A genome-wide search for susceptibility genes in human systemic lupus erythematosus sib-pair families. *Proc Natl Acad Sci U S A*. 1998; 95:14875–14879. [PubMed: 9843983]
33. Moser KL, Neas BR, Salmon JE, et al. Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. *Proc Natl Acad Sci U S A*. 1998; 95:14869–14874. [PubMed: 9843982]

34. Tsao BP, Cantor RM, Grossman JM, et al. PARP alleles with the linked chromosomal region are associated with systemic lupus erythematosus. *J Clin Invest.* 1999; 103:1135–1140. [PubMed: 10207165]
35. Shai R, Quismorio FP Jr, Li L, et al. Genome-wide screen for systemic lupus erythematosus susceptibility genes in multiplex families. *Hum Mol Genet.* 1999; 8:639–644. [PubMed: 10072432]
36. Abelson AK, Delgado-Vega AM, Kozyrev SV, 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.* 2008 [Epub ahead of print].
37. Nikolov NP, Illei G. Pathogenesis of Sjogren's syndrome. *Curr Opin Rheumatol.* 2009 (in press).
38. Lovgren T, Eloranta ML, Kastner B, et al. Induction of interferon-alpha by immune complexes or liposomes containing systemic lupus erythematosus autoantigen- and Sjogren's syndrome autoantigen-associated RNA. *Arthritis Rheum.* 2006; 54:1917–1927. [PubMed: 16729300]
39. Stohl W, Xu D, Kim KS, et al. BAFF overexpression and accelerated glomerular disease in mice with an incomplete genetic predisposition to systemic lupus erythematosus. *Arthritis Rheum.* 2005; 52:2080–2091. [PubMed: 15986357]
40. Ronnblom L, Alm GV, Eloranta ML. Type I interferon and lupus. *Curr Opin Rheumatol.* (in press).
41. Barrat FJ, Meeker T, Chan JH, et al. Treatment of lupus-prone mice with a dual inhibitor of TLR7 and TLR9 leads to reduction of autoantibody production and amelioration of disease symptoms. *Eur J Immunol.* 2007; 37:3582–3586. [PubMed: 18034431]
42. Perl A, Gergely P Jr, Nagy G, et al. Mitochondrial hyperpolarization: a checkpoint of T cell life, death, and autoimmunity. *Trends Immunol.* 2004; 25:360–367. [PubMed: 15207503]
43. Basu S, Binder RJ, Suto R, et al. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF- κ B pathway. *Int Immunol.* 2000; 12:1539–1546. [PubMed: 11058573]
44. Urbonaviciute V, Furnrohr BG, Meister S, et al. Induction of inflammatory and immune responses by HMGB1-nucleosome complexes: implications for the pathogenesis of SLE. *J Exp Med.* 2008; 205:3007–3018. [PubMed: 19064698]
45. Jeco G, Palucka AK, Blanck JP, et al. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity.* 2003; 19:225–234. [PubMed: 12932356]
46. Banchereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases [review]. *Immunity.* 2006; 25:383–392. [PubMed: 16979570]
47. Perl A, Fernandez D, Telarico T, et al. T- and B-cell signaling biomarkers and treatment targets in lupus. *Curr Opin Rheumatol.* (in press).
48. 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. *Arthritis Rheum.* 2006; 54:2983–2988. [PubMed: 16947529]
49. Haxhinasto S, Mathis D, Benoist C. The AKT-mTOR axis regulates de novo differentiation of CD4⁺Foxp3⁺ cells. *J Exp Med.* 2008; 205:565–574. An original article documenting the role of mTOR in expression of Foxp3, a transcription factor required for differentiation of Tregs. [PubMed: 18283119]
50. Sauer S, Bruno L, Hertweck A, et al. T cell receptor signaling controls Foxp3 expression via PI3K, Akt, and mTOR. *Proc Natl Acad Sci U S A.* 2008; 105:7797–7802. An original article, documenting the role of mTOR in expression of Foxp3, a transcription factor required for differentiation of Tregs. [PubMed: 18509048]
51. 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; 178:2579–2588. [PubMed: 17277168]
52. Hahn BH, Anderson M, Le E, La Cava A. Anti-DNA Ig peptides promote Treg cell activity in systemic lupus erythematosus patients. *Arthritis Rheum.* 2008; 58:2488–2497. [PubMed: 18668553]

53. Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. *Nat Rev Immunol.* 2009; 9:324–337. [PubMed: 19390566]
54. Warner LM, Adams LM, Sehgal SN. Rapamycin prolongs survival and arrests pathophysiologic changes in murine systemic lupus erythematosus. *Arthritis Rheum.* 1994; 37:289–297. [PubMed: 8129783]
55. Weinberg JB, Granger DL, Pisetsky DS, et al. The role of nitric oxide in the pathogenesis of spontaneous murine autoimmune disease: increased nitric oxide production and nitric oxide synthase expression in MRL-lpr/lpr mice, and reduction of spontaneous glomerulonephritis and arthritis by orally administered N^G-monomethyl-L-arginine. *J Exp Med.* 1994; 179:651–660. [PubMed: 7507509]
56. Bahjat FR, Pine PR, Reitsma A, et al. An orally bioavailable spleen tyrosine kinase inhibitor delays disease progression and prolongs survival in murine lupus. *Arthritis Rheum.* 2008; 58:1433–1444. [PubMed: 18438845]
57. Coca A, Sanz I. B cell depletion in lupus and Sjogren's syndrome: an update. *Curr Opin Rheumatol.* (in press).
58. Neubert K, Meister S, Moser K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. *Nat Med.* 2008; 14:748–755. [PubMed: 18542049]
59. Mevorach D, Elchalal U, Rein AJJT. Prevention of complete heart block in children of mothers with anti-SSA/Ro and anti-SSB/La autoantibodies; detection and treatment of first degree atrioventricular block. *Curr Opin Rheumatol.* (in press).
60. Wu T, Qin X, Kurepa Z, et al. Shared signaling networks active in B cells isolated from genetically distinct mouse models of lupus. *J Clin Invest.* 2007; 117:2186–2196. [PubMed: 17641780]
61. Gergely PJ, Grossman C, Niland B, et al. Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2002; 46:175–190. [PubMed: 11817589]
62. Ramanujam M, Wang X, Huang W, et al. Mechanism of action of transmembrane activator and calcium modulator ligand interactor-Ig in murine systemic lupus erythematosus. *J Immunol.* 2004; 173:3524–3534. [PubMed: 15322217]
63. Ponce R. Preclinical support for combination therapy in the treatment of autoimmunity with atacicept. *Toxicol Pathol.* 2009; 37:89–99. [PubMed: 19171929]
64. Ding C. Belimumab, an anti-BLyS human monoclonal antibody for potential treatment of inflammatory autoimmune diseases. *Exp Opin Biol Ther.* 2008; 8:1805–1814.
65. Roll P, Tony HP. B cell-targeted therapies in the treatment of autoimmune diseases. *Z Rheumatol.* 2009; 68:255–259. [PubMed: 19384549]
66. Merrill, JT.; Burgos-Vargas, R.; Westhovens, R., et al. The efficacy and safety of abatacept in SLE: results of a 12-month exploratory study [abstract #L15]. American College of Rheumatology Annual Meeting; 2008.
67. Mihara M, Ohsugi Y, Kishimoto T. Evidence for the role of Th17 cell inhibition in the prevention of autoimmune diseases by antiinterleukin-6 receptor antibody. *Biofactors.* 2009; 35:47–51. [PubMed: 19319845]
68. Yao Y, Richman L, Higgs BW, et al. Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an antiinterferon-alpha monoclonal antibody in systemic lupus erythematosus. *Arthritis Rheum.* 2009; 60:1785–1796. [PubMed: 19479852]

Table 1

New genetic factors associated with systemic lupus erythematosus and Sjogren's syndrome

Gene	Pathway	Reference
<i>ITGAM/CD11b</i>	Macrophage activation	[9]
<i>IRAK1</i>	NF- κ B activation	[12**]
<i>TREX1</i>	IFN α production	[13*,14]
<i>STAT4</i>	Cytokine signaling	[15]
<i>IRF-5</i>	Cytokine signaling	[16]
<i>PTPN22</i>	Sustained TCR/BCR signaling	[17,18]
<i>BANK1</i>	Sustained BCR signaling	[19*]
<i>HRES-1/Rab4</i>	Receptor recycling	[20,21*]
<i>mtDNA</i>	Electron transport	[22]

BANK1, B-cell scaffold protein with ankyrin repeats 1; BCR, B-cell receptor; HRES-1, HTLV-1-related endogenous sequence; HTLV, human T-cell leukemia virus; IFN, interferon; IL, interleukin; IRAK1, IL-1 receptor-associated kinase-1; IRF-5, IFN regulatory factor 5; ITGAM, integrin alpha M; mtDNA, mitochondrial DNA; NF- κ B, nuclear factor kappa B; PTPN22, protein tyrosine phosphatase, nonreceptor type 22; TCR, T-cell receptor; TREX1, 3'-5' repair exonuclease 1.

Table 2

New molecular targets for treatment of systemic lupus erythematosus and Sjogren's syndrome

Drug	Molecular/cellular target	Reference
Rapamycin/sirolimus	mTOR/T and B cell	[21,48,60]
N-acetylcysteine	Glutathione/T cell	[61]
Atacicept	Blys/B-cell activation	[62,63]
Belimumab	Blys/B cell	[64]
Epratuzumab	CD22/B cell	[65]
CTLA4-Ig	CD28/T-cell costimulation	[62,66]
Tocilizumab	IL-6/Th17 cells	[67]
Medi-545/IFN α antibody	IFN α /T and B cells and dendritic cells	[68]
Bortezomib	Proteasome/plasma cell	[58]

CTLA4-Ig, cytotoxic T-lymphocyte antigen 4-immunoglobulin; IFN, interferon; IL-6, interleukin 6; mTOR, mammalian target of rapamycin; Th17, T helper cell 17.