HHS Public Access

Author manuscript

Crit Rev Immunol. Author manuscript; available in PMC 2017 November 20.

Published in final edited form as:

Crit Rev Immunol. 2016 ; 36(6): 485–510. doi:10.1615/CritRevImmunol.2017020284.

The role of the transcription factor Ets1 in lupus and other autoimmune diseases

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by excess B and T cell activation, the development of autoantibodies against self-antigens including nuclear antigens, and immune complex deposition in target organs which triggers an inflammatory response and tissue damage. The genetic and environmental factors that contribute to development of SLE have been extensively studied in both humans and mouse models of the disease. One of the important genetic contributions to SLE development is an alteration in the expression of the transcription factor Ets1, which regulates the functional differentiation of lymphocytes. Here we review the genetic, biochemical and immunological studies that have linked low levels of Ets1 to aberrant lymphocyte differentiation and to the pathogenesis of SLE.

Keywords

Systemic lupus erythematosus; autoantibodies; Ets1; B cell tolerance; plasma cells; T cell cytokines

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a potentially fatal chronic and systemic autoimmune disease that affects predominantly females in their childbearing years, with overall prevalence varying depending on geographic location and ethnicity.[1] SLE is associated with a loss of immune tolerance to nucleic acid containing antigens, leading to inflammation and organ damage. Multiple tissues and organ systems can be affected, including the skin, the joints, the kidneys, the cardiovascular system, and the central nervous system, leading to significant morbidity and mortality. Treatment for SLE primarily involves non-specific immunosuppression, which has undesirable side effects, and only one new therapy has been approved for SLE in the last 50 years.[2,3] Thus, a more thorough understanding of the molecular mechanisms of SLE pathogenesis is important for the

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development of more targeted therapeutic strategies. Genome-wide association studies have revealed genetic alterations in many genes that are associated with susceptibility to SLE, highlighting potential disease mechanisms.[4,5]

One such SLE-associated gene encodes the transcription factor Ets1,[6–8] which is primarily expressed in lymphocytes[9–13] and is present at reduced levels in peripheral blood mononuclear cells (PBMCs) from SLE patients.[7,14–17] Consistent with an important role for Ets1 in limiting autoimmune disease, Ets1-deficient mice accumulate plasma cells, produce autoantibodies, and develop several features of lupus-like autoimmune disease.[18,19] Here we review the interplay of Ets1 with lupus susceptibility and pathogenesis including (1) the association of Ets1 genetic variants with lupus and other autoimmune and inflammatory diseases, (2) the characterization of autoimmunity in Ets1-deficient mice and the role of Ets1 in B cell tolerance to self-antigens, (3) the signaling pathways that control Ets1 expression in B cells, and (4) functions of Ets1 in B and T cells that likely contribute to the control of autoantibody production, including limiting plasma cell differentiation and skewing T cell subsets and cytokines.

I. Systemic Lupus Erythematosus: Disease Mechanisms

Alterations in three major immune pathways have been shown to contribute to SLE pathogenesis; loss of adaptive immune tolerance, impaired clearance of apoptotic debris, and hyperactivation of the innate immune system, particularly with respect to Toll-like receptor (TLR) signaling and the type I interferon (IFN) pathway (reviewed in[20,4,21]). These defects synergize to form pro-inflammatory positive feedback loops described briefly below. A breach in adaptive immune tolerance results in an elevated frequency of autoreactive B and T cells, the activation of which is facilitated by the increased availability of nucleic acid-containing self-antigens. These antigens are particularly efficient at activating B cells as they can engage both the B-cell receptor (BCR) and the endosomal, nucleic-acid sensing TLRs such as TLR7 and TLR9. The autoantibodies produced by activated B cells form immune complexes which subsequently stimulate cells of the innate immune system via both Fc receptors and nucleic acid sensing TLRs to produce type I interferons (IFNs) and other proinflammatory cytokines. These cytokines further enhance B cell activation and autoantibody production, resulting in a more robust and sustained inflammatory milieu. In addition, immune complexes deposit in tissues and promote inflammation and subsequent organ damage via both complement and Fc receptor dependent mechanisms. CD4+ T cells also are important for the production of autoantibodies and inflammatory responses in lupus (reviewed in[21–24]). In particular, T follicular helper (Tfh) cells and Th17 cells are elevated in SLE and can promote the development of autoimmune germinal centers and autoantibodies. Th17 cells also contribute to tissue inflammation and damage. While there are conflicting data regarding the role of Treg defects in lupus, it has been suggested that a shift in the Th17 to Treg balance in favor of Th17 cells plays a role in SLE pathogenesis.[25] Alterations in both Th1 and Th2 cells and cytokines have also been reported in SLE, with both IFNγ (a Th1 cytokine)[26] and autoreactive IgE (induced by Th2 cytokines)[21] suggested to contribute to disease pathogenesis.

The central role of autoantibodies in the perpetuation of proinflammatory conditions and the damage to tissues in lupus highlights the importance of understanding how control of B cell development and differentiation is disrupted in this disease. Defects in both B cell tolerance and activation have been observed in SLE patients. A landmark study by Arbuckle et al[27] showed that autoantibodies can be detected in SLE patients prior to clinical presentation, suggesting an intrinsic defect in B cell tolerance that contributes to the initiation of disease. Indeed, single cell expression cloning of antibodies from new emigrant (recently emerged from the bone marrow) and mature naïve B cells revealed that unlike healthy controls, SLE patients fail to eliminate autoreactive B cells at this developmental transition.[28] Germinal center tolerance checkpoints are also breached; in SLE patients, autoreactive B cells are not excluded from germinal centers,[29] and DNA-reactive B cells can emerge from germinal centers as a result of somatic hypermutation.[30,31] Studies with mice congenic for various combinations of NZM2410-derived lupus susceptibility alleles have also shown that loss of adaptive immune tolerance conferred by the Sle1 allele is a critical initiating event in the development of autoimmune disease.[32]

Inappropriate B cell activation and differentiation in SLE patients is reflected by a dramatic increase in circulating plasmablasts, particularly during times of high disease activity.[33–36] Repertoire analysis has indicated that these expanded antibody-secreting cells are polyclonal, and many are derived from naïve precursors.[36] Interestingly, a partial plasmablast gene expression signature is observed in B cells from a subset of quiescent (inactive) lupus patients, even without a significant difference in peripheral blood B cell subsets in this group as measured by flow cytometry.[37] Taken together, these observations suggest that some patients may have intrinsic changes in B cell signaling and resultant gene expression that predispose them to enhanced B cell terminal differentiation.

Genome-wide association studies (GWAS) have identified dozens of genes associated with risk of developing SLE, as reviewed extensively elsewhere.[4,5,20,21] These genes fall into several functional categories, including each of the main pathways linked to SLE pathogenesis described above as well as the response of target organs to inflammation. Among these SLE risk alleles are numerous genes involved in B cell activation and differentiation, including the *HLA-DR* genes, *BANK1*, *BLK*, *RASGRP3*, *PTPN22*, *IL21R*, *IL10*, *TLR7*, *UBE2L3*, *STAT4*, *TNFAIP3*, *FCGR2B*, *LYN*, *CSK*, *PRDM1*, and *ETS1*. Here we review the role of one of these genes, the transcription factor Ets1, in B cell tolerance, plasma cell differentiation, and autoantibody production in lupus.

II. Human *ETS1* genetic variants associated with lupus

The transcription factor Ets1 is highly expressed in human and mouse lymphocytes (B cells, T cells and natural killer cells).[9–13] The genetic region encoding the human gene *ETS1* has been implicated as a susceptibility locus in numerous autoimmune and inflammatory diseases (Table I). As early as 2000, polymorphisms in the 3′ UTR of the human *ETS1* gene were associated with particular clinical phenotypes of lupus.[38] As described in more detail in the sections below, a few years later, *Ets1*$^{-/-}$ mice were discovered to develop a lupus-like autoimmune disease,[19] supporting a role for Ets1 in regulating immune tolerance to self-antigens. More recently, three independent genome-wide association studies in Chinese and

Korean populations have identified genetic variants in and around *ETS1* gene as increasing the lupus risk.[6–8] These initial genome-wide association studies were later replicated in independent populations of Chinese[39] and Malaysian[40] origin. As indicated in Table 1, the SNPs associated with lupus in these particular studies all map near the 3′ end of the gene, either in the final intron, in the 3′UTR or downstream of the gene. Exome sequencing in healthy donors and lupus patients has identified a single nucleotide polymorphism (SNP rs34846069) in the final exon of the gene that is associated with lupus, although this SNP does not change the encoded amino acid (Asp440→Asp).[41] This SNP may be in linkage disequilibrium with other genetic changes that promote lupus. In addition to lupus, SNPs in or near the *ETS1* gene have also been identified as susceptibility alleles in many other autoimmune and inflammatory diseases (Table 1), including rheumatoid arthritis,[42–47] psoriasis,[48–50] multiple sclerosis,[51,52] ankylosing spondylitis,[15] uveitis,[16] allergy,[53] atopic dermatitis,[54] and celiac disease.[55,56]

The association of *ETS1* with lupus in European populations is less well-replicated than it is in Asian populations. In 2013, a study showed that one of the SNPs in *ETS1* (rs6590330) that had been identified in Asian lupus populations was also associated with lupus in people of European ancestry, although it did not reach the statistical threshold of genome wide significance ($p<5\times10^{-8}$).[57] Another study with European lupus patients demonstrated that a different SNP in the *ETS1* gene (rs7941765, located about 100 kb upstream of the gene) was associated with lupus susceptibility.[58] A meta-analysis of GWAS studies of Chinese and European lupus patients confirmed this association of SNP rs7941765 with lupus susceptibility in European populations and the same SNP was also associated weakly with lupus in Asian patients.[59] Another SNP (rs61432431) located downstream of *ETS1* was associated with lupus susceptibility in both European and Asian cohorts, but the *p* value was more significant in the Asian cohort.[59] Altogether, the data suggest that *ETS1* is a lupus susceptibility locus in both European and Asian populations, but the causal variants might well be different.

Genetic variants (including SNPs) in *ETS1* have also been associated with disease phenotypes in lupus and other autoimmune diseases. Particular allelic variants of *ETS1* have been associated with a variety of clinical phenotypes in lupus, including early age of diagnosis,[39, 60] levels of anti-DNA and antinuclear autoantibodies in the serum,[17,39] serum IL-17 concentration,[61] discoid and malar rash,[38,39] photosensitivity,[39] arthritis,[39] serositis,[39] vasculitis,[38] hematologic disorders,[39] immunologic disorders,[39] and renal involvement.[39] In rheumatoid arthritis, *ETS1* SNPs have also been associated with particular clinical phenotypes including DAS28 (rheumatoid arthritis disease activity score 28) level and serum C-reactive protein level.[45] In addition, SNPs in both *ETS1* and the *IL21* gene form epistatic interactions to cooperatively promote lupus susceptibility.[62]

Several studies have shown that Ets1 mRNA levels are reduced in PBMCs from autoimmune patients, suggesting that the effects of these genetic variants are to decrease Ets1 expression.[7,14–17] Ets1 mRNA is also reduced in regulatory T cells (Tregs) from lupus patients and in bulk CD4+ T cells from multiple sclerosis patients.[51,63] Indeed, using pyrosequencing, mRNA levels of Ets1 were measured in patients carrying one copy of a disease-associated allele and one copy of a protective allele in the 3′UTR of Ets1.[7]

Expression from the allele with the disease-associated SNP (rs1128334) was reduced as compared to the protective allele.

In order to understand how genetic variants in the human *ETS1* locus might influence gene transcription, statistical analysis was used to map disease-associated SNPs and identify the most likely causal variants.[64] One of these SNPs (rs6590330) showed differential binding in electrophoretic mobility shift assays when comparing the disease-associated allele to the protective allele. Further analysis showed that the disease-associated allele results in enhanced binding of the transcription factor *Stat1*, which is associated with reduced *ETS1* transcription.[64] Therefore, interferon signaling, which is prominent in lupus, may decrease the levels of Ets1 in patient PBMCs and promote autoimmunity.

One thing that should be kept in mind when evaluating the role of genetic variants in the *ETS1* locus is the *ETS1* is located in a head-to-head orientation with another Ets gene family member *FLI1*. The transcriptional start sites of *ETS1* and *FLI1* are located about 170 kb apart and some of the SNPs listed in Table I are between the *ETS1* and *FLI1* genes. Therefore, at least some of the *ETS1* SNPs may affect *FLI1* expression in addition to or instead of affecting *ETS1* expression. In mice, *Fli1* has opposite effects as that of *Ets1* (i.e., over-expression of *Fli1* promotes autoimmunity, while loss of *Ets1* promotes autoimmunity).[65–67] Accordingly, any changes to *FLI1* expression as a result of SNPs in the *ETS1*/*FLI1* locus may affect susceptibility to lupus.

III. Ets1 knockout mice develop autoimmune disease

Analysis of Ets1 knockout mice has demonstrated the critical role of Ets1 in the development and continued proper function of the immune system. Ets1 knockout mice exhibit a variety of lymphocyte abnormalities, including increased B and T cell activation and excessive B cell differentiation to plasma cells (discussed in detail in the section below). These immune abnormalities result in an autoimmune phenotype, reminiscent of human SLE. The phenotype of Ets1 knockout mice shares some similarities with mice deficient for BCR inhibitory signaling components, such as the kinase Lyn or phosphatase SHP1, although the autoimmunity is less severe in Ets1-deficient mice than in Lyn-deficient or SHP1-deficient mice.[19,68–73]

The phenotype of Ets1 knockout mice was first described by Bories and Muthusamy, using mutant alleles that lacked either the final two exons that encode the Ets DNA binding domain or the second and third exons that encode a conserved region known as the Pointed domain, respectively.[74,75] The first allele is a complete null, while the second allele was also originally described as a null allele, but later shown to produce a very small amount of internally deleted Ets1 protein.[19] However, both alleles result in similar phenotypic manifestations, including decreased cellularity of the thymus and lymph nodes, reduced T cell populations in the thymus, lymph node and spleen, and markedly increased populations of IgM-secreting plasma cells.[74,75] These observations were later confirmed and expanded upon.

Marginal zone B cells are lacking in Ets1 knockout mice,[19,76] while follicular B cells have an activated cell phenotype, with increased surface staining of MHC II, CD23, CD80 and

CD86,[19] and undergo increased differentiation to IgM- and IgG-secreting plasma cells.[74,77] The dramatic expansion of the plasma cell population in Ets1 knockout mice correlates with increased serum levels of secreted immunoglobulin, even in the absence of any overt stimulus.[18,74,78,79] The titer of circulating IgM in Ets1 deficient mice has been observed to be 4–10 times that of wild type counterparts and levels of IgG1 and IgE have also been shown to be elevated.[18,79] Conversely, these mice have a significant decrease in circulating IgG2a, due to the role of Ets1 in positively regulating expression of T-bet, a transcription factor integral in class switching to the IgG2a isotype.[79]

Of particular interest are the antigen specificities of the circulating immunoglobulin. The serum of Ets1 knockout mice has high titers of autoantibodies of both IgM and IgG isotypes that bind to double-stranded DNA and histones.[18,19] Notably, anti-nuclear autoantibodies (including those that bind to DNA and histones) are considered hallmarks of human SLE and correlate with disease activity and severity in SLE patients.[80,81] Antibodies against cardiolipin, another autoantigen frequently associated with SLE, are also increased in Ets1 knockout mice.[19] Furthermore, these mice also have high titers of rheumatoid factor autoantibodies targeting IgG,[19] which are found in about 10% of lupus patients,[82] but are more commonly associated with rheumatoid arthritis. Ets1-deficient mice also develop autoantibodies against myelin basic protein,[19] an antigen that is frequently targeted in multiple sclerosis,[83,84] but is not characteristic of human lupus. The similarities of the serological autoantibody compositions of human autoimmune disease patients and Ets1 knockout mice suggest that the mice are a suitable model for understanding aspects of human autoimmune disease pathogenesis.

Enhanced B cell activation in Ets1$^{-/-}$ mice and excessive secretion of antibodies could be a defect intrinsic to B cells, but could alternatively be reflective of defects in the T cell compartment. Adoptive transfer of Ets1-deficient B cells to wild-type recipients or wild-type B cells to Ets1 knockout recipients demonstrated that the activated B cell phenotype is heavily influenced by its environment.[19] However, mixed bone marrow chimeras generated with allotype-labeled wildtype and Ets1 deficient fetal liver cells showed that the Ets1-deficient B cells give rise to increased numbers of plasma cells as compared with wild-type B cells developing in the same host.[85] Therefore, there are likely both B cell-intrinsic and B cell-extrinsic functions of Ets1 that together promote B cell activation and autoantibody secretion. These will be described in detail below.

Mice deficient for Ets1 also display autoimmune-related organ pathology. The spleens are often enlarged in these mice compared to wild-type counterparts.[18] There are infiltrates of lymphocytes in the lung, liver and other tissues and these infiltrates worsen as the mice age ([19] and unpublished data). In the kidneys, there is extensive deposition of IgG and IgM immune complexes,[19] reflective of a classic renal pathology associated with SLE. Although these immune complexes effectively activate complement and C3 is deposited in the glomeruli, Ets1$^{-/-}$ mice display weak proteinuria, suggesting that kidney function is largely preserved.[19] Despite the weak proteinuria, Ets1$^{-/-}$ mice have a shortened lifespan (median 18 months) in comparison with wild-type littermates (median 28 months) (unpublished data), presumably due to organ damage caused by autoimmune disease. Overall, the autoimmune disease that develops in Ets1$^{-/-}$ mice shares many features with human lupus

(activated B cells and T cells, increased numbers of plasma cells and high titers of autoantibodies, deposition of immune complexes in the kidney, infiltration of lymphocytes into target organs and a shortened lifespan). As described above, reductions in Ets1 levels are found in human lupus leukocytes and are associated with disease pathogenesis. Below we review studies of Ets1 function in B and T cells with an emphasis on their relationship to autoimmune disease development and progression.

IV. Ets1 maintains B cell quiescence and preserves peripheral tolerance

Ets1 levels are high in quiescent mouse B cells, but are downregulated upon antigen stimulation at both the mRNA and protein levels prior to differentiation.[85] In mice lacking Ets1, B cells are hyper-activated as shown by increased expression of activation markers,[19] increased isotype-switching to IgG1 and IgE[18,79] and increased propensity to terminally differentiate into plasma cells secreting IgM and IgG.[19,74,77,78] These observations suggest that Ets1 may play a role in retaining B cells in a resting state.

The *in vitro* behavior of Ets1-deficient B cells reflects the more activated phenotype observed *in vivo*. Even when left unstimulated, B cells isolated from Ets1 knockouts undergo a low level of differentiation into plasma cells.[19] Purified $Ets1^{-/-}$ B cells also undergo increased differentiation to plasma cells when cultured with TLR ligands such as oligonucleotides containing unmethylated CpG sequences (TLR9 ligand)[19] or bacterial lipopolysaccharide (TLR4 ligand).[85] This suggests that Ets1 may be particularly important in regulating TLR responses. Nguyen *et al.* also noted a significant increase in the secretion of IgM and IgG2b by $Ets1^{-/-}$ B cells in response to LPS, consistent with increased IgM and IgG-secreting plasma cells in these cultures.[79] The enhanced *in vitro* differentiation and Ig secretion of $Ets1^{-/-}$ B cells can be suppressed by enforced expression of Ets1 via a retroviral construct.[74,77,85,86] Taken together, it is clear that Ets1 expression is a critical block to plasma cell differentiation and it has B cell-intrinsic roles in regulating this process.

Appropriately maintaining the resting state of B cells is crucial, particularly for the autoreactive B cells that escape central tolerance checkpoints to persist in the periphery. Using BCR transgenic mice, we have demonstrated that peripheral B cell tolerance is compromised in the absence of Ets1, while central B cell tolerance mediated by clonal deletion is intact. In transgenic mice (Ets1 wild-type) that express a hen egg lysozyme (HEL)-specific BCR and membrane-bound HEL antigen, immature B cells undergo clonal deletion in the bone marrow in response to strong BCR crosslinking.[87,88] B cells from $Ets1^{-/-}$ transgenic mice carrying the same HEL-specific BCR and membrane-bound HEL antigen also undergo clonal deletion.[89] On the other hand, when mice carrying the HEL-specific BCR are crossed to mice carrying a soluble HEL transgene, B cells are not deleted, but rather move to the periphery and become anergic in response to constant antigen binding.[90–92] In this transgenic background, $Ets1^{-/-}$ B cells develop certain properties of anergic B cells in that they express the expected surface marker phenotype and display expected defects in BCR signaling.[89] However, these mice have elevated levels of HEL-specific antibody in circulation and increased number of Ig-secreting cells in their spleens[89], indicating that despite the apparent anergic state of the B cell population, there is still a breach in self-tolerance and differentiation of B cells to antibody-secreting plasma cells.

Some B cells that recognize their ligands only with low affinity do not become anergic and instead mature similar to normal non-self-reactive B cells, a process termed clonal ignorance.[93,94] Using BCR transgenic strains, we have also shown that clonal ignorance is compromised in Ets1-deficient B cells. Transgenic expression of a rheumatoid factor BCR (AM14) that has low affinity for its ligand (IgG2a of the "a" allotype) results in clonal ignorance in a wild-type background expressing autoantigen.[93] However, when the same AM14 BCR transgene is crossed onto an Ets1-deficient background, the B cells are not tolerized, but rather become activated and differentiate into plasma cells.[89] This evidence bolsters the idea that Ets1 prevents inappropriate B cell activation and differentiation. In its absence, peripheral tolerance is breached, and B cells spontaneously undergo terminal differentiation to Ig-secreting cells, accounting for the expanded plasma cell population and elevation in circulating autoantibodies in Ets1 knockout mice.

V. Mechanisms by which Ets1 limits plasma cell differentiation

The accumulation of autoantibodies and plasma cells in the absence of Ets1 suggests that it has an important function in limiting B cell terminal differentiation under normal circumstances. Indeed, Ets1 is expressed in resting B cells where it has several activities that could contribute to such a role. Despite the importance of Ets1 in B cell biology, relatively few target genes of Ets1 in B cells are known. To address this, we recently performed chromatin immunoprecipitation-sequencing (ChIP-seq) for Ets1 in primary mouse B cells and correlated it with gene expression changes found in $Ets1^{-/-}$ B cells as compared to wild-type B cells.[95] Ets1 binds to ~10,000 sites in the B cell genome (representing ~9,000 target genes), including the promoters of many genes involved in B cell differentiation, function and activation.

Pax-5, a key B cell identity factor (Figure 1), is among the genes harboring Ets1 binding sites (in both its promoter and the intron 5 B cell-specific enhancer). We had previously shown that Ets1 can transactivate the Pax5 promoter in transient transfection assays.[86] Furthermore, retroviral transduction of Ets1 into primary B cells cultured with the TLR9 ligand CpG DNA was able to maintain Pax5 expression, whereas it would normally be downregulated during the differentiation process triggered by TLR signaling.[77,86] Conserved arginine residues (R391 and R394) in the Ets domain of Ets1 are required for both Ets1 DNA binding and its ability to upregulate Pax5.[77] Therefore, Ets1 might be an important transcription factor regulating Pax5 expression in B cells. However, RNA-sequencing shows that Pax5 mRNA is not decreased in $Ets1^{-/-}$ B cells.[95] Together, these observations suggest a model in which Ets1 has the capability of stimulating Pax5 expression, but is not uniquely required for this process, at least in resting B cells. Even under conditions where Ets1 does not directly regulate Pax5 expression, it may stimulate the ability of Pax5 to function as a transcriptional regulator. ChIP-seq data for Ets1 and Pax5 show ~45% of the target sites of each factor are also bound by the other transcription factor. Ets1 and Pax5 are known to co-regulate the CD79a (mb-1) gene, which encodes Igα by forming a cooperative DNA binding complex.[96] Ets1 and Pax-5 may interact similarly at the regulatory regions of other B cell-specific target genes to control their expression.

RNA-sequencing assays show that only about 500 genes are expressed differentially in B cells the absence of Ets1.[95] Of these genes with altered expression, approximately half have a nearby Ets1 binding motif, indicating that they may be direct targets of Ets1. About two dozen of the potential direct Ets1 targets are genes that have been implicated in autoimmune disease susceptibility by genome-wide association studies, including *Stat4* and *Ptpn22*.[95] To determine whether Stat4 and Ptpn22 contribute to the role of Ets1 in regulating development of plasma cells, we restored their expression in Ets1$^{-/-}$ B cells using retroviral constructs.[95] Unexpectedly, both Stat4 and Ptpn22 promoted the development of plasma cells, while Ets1 blocked this process. This indicates that Stat4 and Ptpn22 are not key target genes of Ets1 that modulate plasma cell formation. However, Ets1-dependent regulation of Stat4 and Ptpn22 might influence other aspects of B cell responses.

Another gene whose expression is altered in the absence of Ets1 is the *Prdm1* gene which encodes Blimp1, a key transcription factor involved in promoting the plasma cell fate (Figure 1). Blimp1 is over-expressed by ~2-fold in sorted follicular B cells from Ets1$^{-/-}$ mice[95] and is also over-expressed in Th1 cells that were cultured from Ets1$^{-/-}$ CD4+ T cell precursors.[97] Furthermore, Ets1 binds to potential regulatory sequences localized in and near the *Prdm1* gene.[95,97] Because Blimp1 is crucial for B cell differentiation to plasma cells, it would be reasonable to think that over-expression of Blimp1 in Ets1$^{-/-}$ B cells could drive plasma cell formation. However, crossing Ets1 knockout mice to mice heterozygous for a null allele of Blimp1 (which reduces Blimp1 levels in B cells to those found in wild-type B cells) does not reverse the excess production of plasma cells caused by loss of Ets1.[95] This observation indicates that the excess plasma cell phenotype of Ets1 knockout mice cannot be simply explained by over-expression of Blimp1 in the B cells.

We have found that Ets1 also functions to regulate B cell differentiation in a non-DNA-dependent fashion. In addition to regulating the *Prdm1* gene, Ets1 also binds to and inhibits the function of the product of this gene, Blimp1.[77,86] This is dependent on a direct protein/protein interaction between Ets1 and Blimp1, which prevents Blimp1 from binding to its DNA target sequences and thereby inhibits its activity.[77,86] Normally during plasma cell formation, Ets1 is downregulated, allowing Blimp1 to function properly and promote the plasma cell phenotype. This downregulation of Ets1 is important, since retrovirally-driven forced expression of Ets1 leads to a block in plasma cell generation in response to TLR stimulation.[77,85,86] We have mapped the domains of Ets1 required for interaction with Blimp1 and found that optimal interaction of Ets1 with Blimp1 requires a large fraction of the Ets1 protein, including the Ets DNA binding domain, the N terminus, the acidic transactivation domain, and the Pointed domain,[77,86] suggesting the overall 3-dimensional structure of the Ets1 protein may be important for this process. Mutants of Ets1 that fail to interact with Blimp1 are also ineffective in blocking plasma cell formation in the retroviral assay.[77,86]

In summary then, we suggest a model in which Ets1-dependent control of Blimp1 activity via a protein/protein interaction is the most important influence in regulating plasma cell formation (Figure 1). Ets1-dependent regulation of a cohort of target genes such as *Stat4* and *Ptpn22* might influence other aspects of B cell activation and functional competence and the

combined activities of these factors are important for Ets1's role in preventing autoimmune disease.

VI. Positive and negative signaling events control expression of Ets1 in B cells

Consistent with its critical role in maintaining B cell tolerance and preventing autoimmunity, Ets1 expression in B cells is under tight control. In the absence of strong activating signals, Ets1 expression is maintained in B cells by inhibitory signaling pathways.[85] A series of immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing cell surface inhibitory receptors serve to keep B cell activation in check. These include FcγRIIb, PIR-B, CD72, CD22, and SiglecG. Phosphorylation of ITIM motifs in these receptors by the tyrosine kinase Lyn results in the recruitment and activation of the inhibitory phosphatases SHIP and SHP-1 (reviewed in[98,99]). To varying degrees, mice deficient in any of these inhibitory signaling molecules accumulate plasma cells, produce autoantibodies and develop lupus-like autoimmune disease; in many cases these effects have been shown to occur in a B cell-intrinsic manner. Loss of Lyn, SHP-1, or SHIP has a more profound effect than deficiency of individual receptors, suggesting that the receptors may be partially redundant for maintaining B cell tolerance.[70,72,100–105]

B cells from $Lyn^{-/-}$ mice demonstrate a dramatic reduction in the expression of both Ets1 mRNA and protein.[85] This occurs prior to the accumulation of autoantibodies and the development of autoimmune disease manifestations[85] and is independent of the inflammatory cytokine IL-6,[106] strongly suggesting that a Lyn-dependent signaling pathway directly controls Ets1 expression in B cells. Indeed, a similar loss of Ets1 expression was observed in B cells with mutations in SHP-1, while SHIP-deficient B cells had only a mild decrease in Ets1.[85] Loss of either CD22 or SiglecG resulted in a reduction of Ets1 levels in B cells, which was more profound in CD22 and SiglecG double knockouts.[85] In contrast, individual loss of PIR-B, CD72, or FcγRIIB had no effect on Ets1 expression.[85] Thus, an inhibitory pathway involving Lyn, SHP-1, CD22 and SiglecG normally maintains Ets1 levels in B cells (Figure 2).

Upon antigen stimulation of B cells, positive signaling pathways prevail over Ets1-maintaining inhibitory signals and Ets1 mRNA and protein expression are downregulated.[85] A combination of gain- and loss-of-function approaches and the use of small molecule inhibitors of BCR signaling components in both primary murine B cells and mouse B cell lines has revealed that BCR-induced Ets1 downregulation is mediated by PI3K, Btk, IKK2, and JNK, but not Akt, p38 or MEK (Figure 2).[85] Treatment of B cells with the TLR ligands LPS (TLR4) or CpG DNA (TLR9) also downregulates Ets1 expression, and low level TLR9 signaling cooperates with low level BCR signaling to downregulate Ets1.[85] Intriguingly, nucleic acid containing antigens, a common target of autoantibodies in lupus, can activate B cells via both the BCR and endosomal nucleic acid sensing TLRs,[107–109] with dual signaling by the BCR and TLR7 being particularly efficient at driving plasma cell differentiation.[110] Nucleic acid-specific B cells may thus be particularly efficient at downregulating Ets1 and differentiating into autoantibody-secreting plasma cells even in response to low levels of antigen. In contrast, stimuli that mimic T cell help (anti-CD40, IL-4, IL-21), promote B cell survival (BAFF), or would be encountered in an inflammatory environment (IL-6) have no

effect on Ets1 levels.[85] The inability of T cell-derived signals to downregulate Ets1 may prevent the inappropriate differentiation of bystander B cells activated in a non-cognate manner.

As described above, transduction of TLR-stimulated primary murine B cells with a retrovirus expressing Ets1 prevents differentiation into plasma cells and secretion of antibody.[77,86] Similarly, enforced Ets1 expression ameliorates the enhanced terminal differentiation of Lyn-deficient or SHP-1-deficient B cells that occurs in response to TLR engagement.[85] Thus, Ets1 downregulation is likely required for plasma cell differentiation during normal humoral immune responses, and inappropriate loss of Ets1 expression likely contributes to the unrestrained accumulation of autoreactive antibody-secreting cells that occurs in mice with impaired inhibitory signaling via the Lyn/SHP-1 pathway. The development of systems to prevent Ets1 downregulation *in vivo* at various times during immunization protocols or during the development of autoimmune disease is ongoing and will formally test this hypothesis.

Other types of genetic approaches have confirmed that a strict balance of the Btk-dependent activating signals and Lyn-mediated inhibitory signals that converge on Ets1 is required to maintain normal steady-state plasma cell numbers. First, mice heterozygous for both Lyn and Ets1 have increased IgM autoantibodies compared to $Lyn^{+/-}$ or $Ets1^{+/-}$ mice alone, although they do not develop full blown autoimmune disease.[106] This indicates that Lyn and Ets1 do indeed work together in a common signaling pathway to limit B cell differentiation and that partial disruption of this pathway is sufficient for an initial break in B cell tolerance. Second, the excessive downregulation of Ets1 in the absence of inhibitory signals depends on Btk. $Lyn^{-/-}Btk^{lo}$ mice, which express a reduced level of Btk, demonstrate normal levels of Ets1 in their B cells[85] and do not accumulate plasma cells or autoantibodies.[111,112] Finally, Btk signaling to Ets1 also controls steady-state plasma cell numbers when Lyn-dependent inhibitory signaling pathways are intact. $Btk^{-/-}$ mice demonstrate reduced splenic IgM-secreting cells and low serum IgM levels; this defect is normalized in the absence of Ets1.[106] These observations suggest that manipulations that shift the balance between Ets1-downregulating activating signals and Ets1-maintaining inhibitory signals may be useful therapeutic approaches to promote or dampen antibody responses as desired.

VII. Ets1 functions in CD4+ T cells

In addition to its roles in B cells, Ets1 also regulates the function of T cells. Of particular interest is the function of Ets1 in the CD4+ T cell subset, as these cells are important in lupus pathogenesis and function in part by regulating the responses of autoreactive B cells. Ets1 is highly expressed in human and mouse T cells including CD4+ T cells.[9,113–116] Loss of Ets1 in mice results in a variety of aberrations in CD4 T cell differentiation, as we have described in previous reviews.[117,118] Here we briefly describe the major known alterations in the CD4 lineage and discuss how they may be relevant in lupus pathogenesis (summarized in Figure 3).

A. Th1 Cells—Ets1 was first implicated in the regulating the differentiation of and cytokine production by Th1 and Th2 subsets of CD4+ T cells [114]. CD4+ T cells isolated

from *Ets1*$^{-/-}$ mice and cultured *in vitro* under conditions that promote Th1 differentiation showed greatly reduced production of IFNγ.[114] IFNγ promotes lupus development and pathogenesis in multiple mouse models of the disease.[119–130] IFNγ levels are increased in human patients with lupus and are correlated with more severe disease.[131–136] Furthermore, a SNP in the IFNγ gene has been shown to be associated with lupus susceptibility.[137] Clearly Ets1-deficiency leads to a loss of self-tolerance in mice regardless of reduced IFNγ production by Th1 cells. Perhaps, as described below, the overall balance of T cell cytokines remains sufficiently inflammatory despite a reduction in Th1 responses in the absence of Ets1. Alternatively, cells other than Th1 cells may be an important source of IFNγ in the context of reduced or absent Ets1 expression. However, the fact that *Ets1*$^{-/-}$ CD4+ T cells produce reduced amounts of IFNγ may result in less tissue damage in *Ets1*$^{-/-}$ mice. *Ets1*$^{-/-}$ mice develop high titers of autoantibodies with immune complexes deposit in the kidney,[18,19] but proteinuria in this strain is weak.[19] This might be due to reduced IFNγ-mediated kidney damage, since IFNγ is required for nephritis and impaired kidney function in NZB/W and MRL/lpr lupus-prone mice.[119,129,138]

B. Th2 Cells—*Ets1*$^{-/-}$ CD4+ T cells also produce less IL-4 when cultured under Th2 conditions.[114] Further analysis indicated that secretion of the Th2 cytokines IL-5 and IL-13 was also reduced in *Ets1*$^{-/-}$ CD4+ T cells.[139] The IL-4, IL-5 and IL-13 genes are clustered in the genome and are coordinately regulated.[140,141] Ets1 binds to several sites within this Th2 locus to stimulate expression of the Th2 cytokines.[139] Although IL-4, IL-5 and IL-13 were all reduced in *Ets1*$^{-/-}$ CD4+ cells cultured under Th2 conditions, contradictory results were obtained when assessing IL-4, IL-5 and IL-13 levels in freshly-isolated CD4+ T cells from the spleens of *Ets1*$^{-/-}$ mice, where each of these cytokines was over-produced rather than reduced in levels.[18]

IL-4 and IL-5 are implicated in promoting B cell responses such as isotype switching and plasma cell formation. IL-4 contributes to disease pathogenesis in NZB/W, MRL/lpr and NZM2410 lupus-prone mice,[127,142–144] but is not required for lupus in the BXSB mouse strain.[145] Recently, IL-4 was shown to also promote autoimmunity in Lyn-deficient mice.[146] IL-4 is elevated in some human SLE patients[147,148] and SNPs in the IL-4 locus are associated with increased susceptibility to lupus.[149,150] In keeping with increased levels of Th2 cytokines *in vivo* in *Ets1*$^{-/-}$ mice, B cells from these animals show increased isotype-switching to IgG1 and IgE and increased numbers of plasma cells ([18,77] and unpublished data). Although it is not yet clear whether the IgG1 or IgE produced by Ets1$^{-/-}$ mice is pathogenic, it is interesting to note that pathogenic IgE autoantibodies have recently been described in Lyn knockout mice that share many similar phenotypic features with Ets1 knockout mice (see above).[146] IgE autoantibodies are also found in another mouse model of lupus, Fcgr2b$^{-/-}$Yaa mice,[151] and recently IgE autoantibodies have been detected in human SLE patients and are associated with more severe disease.[152]

C. IL-10—*Ets1*$^{-/-}$ CD4+ T cells cultured under either Th1 or Th2 conditions over-produce IL-10.[114,153] IL-10 suppresses autoimmune symptoms in MRL/lpr and Sle1.2.3 lupus-prone mice.[154,155] However, in NZB/W mice, anti-IL-10 antibody therapy results in reduced rather than increased disease symptoms.[156] IL-10 stimulates human B cell proliferation and

antibody secretion[157,158] and is elevated in human patients with SLE.[159–163] SNPs in the human IL-10 gene promoter are associated with lupus susceptibility.[164,165] The over-production of IL-10 in Ets1-deficient mice might contribute to their autoimmune phenotype.

D. Th17 Cells—IL-17 has been extensively implicated as a pathogenic factor in multiple autoimmune diseases.[166,167] Ets1-deficient CD4+ T cells cultured under Th17-skewing conditions or without polarizing cytokines produce increased levels of IL-17.[115,168] IL-17 mRNA levels are elevated in freshly-isolated lung tissue from Ets1$^{-/-}$ mice, consistent with an elevation of Th17 cells *in vivo* as well.[115] Viral-driven over-expression of Ets1 can also block development of IL-17 secreting cells from naïve wild-type precursors.[115] The presence of two lupus-associated SNPs in the human *ETS1* locus (rs10893872 or rs1128334) has been shown to correlate with the serum level of IL-17.[61] This is consistent with the fact that SNP rs1128334 has been shown to decrease Ets1 mRNA levels.[7] In Th17 cells, the microRNA miR155 targets Ets1 and the absence of miR155 leads to increased Ets1 protein in Th17 cells.[169] High levels of Ets1 in Th17 cells lacking miR155 inhibits their function, because knocking down Ets1 in these cells leads to improved expression of typical Th17 transcripts such as IL-17A, IL-22 and IL23R.[169]

Serum levels of IL-17 are elevated in several autoimmune prone mouse strains[170–172] and IL-17 plays important roles in the pathogenesis of lupus in BXD2 and Fcgr2b$^{-/-}$ mice[172,173] and in pristane-induced lupus.[174] Furthermore, IL-17 deficient mice are resistant to the induction of lupus nephritis caused by the injection of DNA from concanavalin A-activated lymphocytes.[170] However, IL-17 is not required for lupus nephritis in MRL/lpr or NZB/NZW mice.[175] IL-17 is also elevated in the serum of human lupus patients.[176–180] Some studies have shown a correlation between serum IL-17 levels and disease activity as measured by the Systemic Lupus Erythematosus disease activity index (SLEDAI),[176,178] but other studies have failed to find this association.[179,180] It is likely that increased IL-17 in Ets1$^{-/-}$ mice plays a role in the autoimmune disease pathogenesis.

E. Treg Cells—In addition to the defects described above, CD4+ T cells from Ets1$^{-/-}$ mice have also been shown to develop less efficiently into regulatory T cells, with a reduced percentage of CD4+CD25+FoxP3+ cells in the spleens, reduced levels of FoxP3 within those cells and reduced functional capacity in suppressing inflammation.[18] The defect in Treg production from Ets1-deficient progenitors is cell-intrinsic and *in vitro* culture of Ets1-deficient naïve CD4+ T cells under Treg skewing conditions results in reduced Treg production.[18] Finally, transferring wild-type Tregs into Ets1$^{-/-}$ mice reduces splenomegaly and reverses certain aberrations in B cells.[18] Ets1 binds to FoxP3 gene regulatory sequences.[18,181,182]

In MRL/lpr and NZB/W lupus-prone mouse models there are reduced numbers and/or functionality of Tregs.[183–187] In human lupus, the contribution of Tregs is confusing with some studies reporting reduced numbers or impaired function,[188–191] but others finding no abnormalities[192,193] or even increased numbers.[194] Effector T cells in lupus patients may also be resistant to Treg-mediated suppression.[193,195] The levels of Ets1 and FoxP3 are correlated in T cells isolated from lupus patients and patients with Hashimoto's thyroiditis, with low Ets1 and low FoxP3 in patient samples as compared to normal controls.[63,196]

F. IL-2—IL-2 is produced mainly by T cells and functions to support T cell activation and also the survival of regulatory T cells. IL-2 also suppresses the development of inflammatory Th17 cells.[197] Ets1$^{-/-}$ CD4+ T cells make less IL-2 when cultured under Th1 conditions.[114] There is also reduced IL-2 production when the cells are cultured under Th2 conditions, but this is less obvious since CD4+ T cells make relatively lower amounts of IL-2 when cultured in Th2 promoting conditions.[114] Reduced production of IL-2 by Ets1$^{-/-}$ T cells was shown to be due to a role for Ets1 in recruiting the transcription factor NFAT to the IL-2 promoter.[97] On the other hand, elevated levels of Blimp1 in Ets1$^{-/-}$ CD4+ T cells do not appear to contribute to reduced IL-2 production, since reducing T-cell expressed Blimp1 by crossing Ets1$^{-/-}$ mice to mice with a CD4-specific deletion of the *Prdm1* gene does not reverse the IL-2 defect.[97] As described above, CD4+ T cells from Ets1 knockout mice develop more robustly into Th17 cells when cultured under appropriate conditions.[115] This is in part due to reduced IL-2 production in the Ets1 knockout background and in part due to resistance of Ets1$^{-/-}$ CD4+ T cells to the effects of IL-2.[115]

Mice carrying the *lpr* mutation of Fas on a B6 background develop lupus and deletion of IL-2 from this strain results in reduced lupus development,[198] despite the fact that IL-2 is required to support Treg survival. This is likely due to the role for IL-2 in promoting T cell activation and proliferation, which are reduced in these mice. While this study indicates that some IL-2 is required for lupus, the amount of IL-2 that T cells produce can determine whether or not those T cells are pathogenic. Similar to T cells from Ets1$^{-/-}$ mice, lupus patients' T cells make less IL-2 than healthy controls.[199,200] A recent early phase and short term trial of low dose IL-2 therapy in SLE patients showed a normalization of Th17 and T follicular helper (Tfh) cell to Treg ratios (fewer Th17 and Tfh and more Tregs post treatment) and the Tregs were more functional.[201] This suggests that low levels of T-cell derived IL-2 in SLE contribute to a potentially pathogenic skewing of T cell subsets in a similar way that Ets1 deficiency does in mice.

Thus, multiple T cell defects in Ets1$^{-/-}$ mice have the potential to contribute to autoantibody production and autoimmune pathology. A comparison of B-cell and T-cell specific Ets1 knockout mice would be informative in delineating the relative importance of B-cell vs. T-cell intrinsic functions of Ets1 in the development of autoimmune disease.

VIII. Concluding remarks and future directions

As reviewed above, several lines of evidence suggest that Ets1 plays an important role in limiting autoantibody production in SLE patients. Polymorphisms in the Ets1 gene have been repeatedly identified as being associated with SLE and other autoimmune diseases, and Ets1 levels are reduced in PBMCs and Tregs from SLE patients. Mice deficient in Ets1 develop lupus-like autoimmunity, characterized by excessive plasma cell accumulation, autoantibody production against lupus associated auto-antigens, immune complex deposition in the kidneys, and infiltration of lymphocytes into several tissues. This is likely due, at least in part, to a critical role for Ets1 in maintaining B cell tolerance and preventing plasma cell differentiation by regulating the expression of a cohort of genes involved in B cell immune responses and inhibiting Blimp1 function in a B cell-intrinsic manner. Consistent with these

roles of Ets1 in limiting autoimmunity, its expression is under tight control by the balance of activating and inhibitory signaling in B cells.

Despite the substantial evidence linking Ets1 to autoantibody production in mice and the association of Ets1 polymorphisms with SLE, little is known about Ets1 expression or function in B cells from SLE patients. Intriguingly, polymorphisms and signaling defects that affect inhibitory signaling in B cells are associated with SLE in humans, suggesting that control of Ets1 expression by these pathways might be altered in lupus patients (Figure 2). For example, Lyn expression is reduced and its subcellular localization is altered in B cells from a subset of SLE patients,[202,203] and polymorphisms in *LYN* are associated with SLE.[204] An SLE-associated polymorphism in *CSK*, a negative regulator of Lyn, results in reduced Lyn activity and increased B cell activation.[205] Expression of mRNA from the *PTPN6* gene, which encodes SHP-1, is decreased in some SLE B cells.[206] Additional changes in lupus B cells that do not directly affect known Ets1-maintaining inhibitory pathways[85] may also contribute to control of Ets1 expression (Figure 2). For example, reduced expression of PTEN, an inhibitor of PI3K signaling, has also been observed in SLE B cells,[207] and PI3K mediates BCR-induced downregulation of Ets1.[85] While events downstream of IKK2 that downregulate Ets1 have not been defined, it is likely that these include NFκB.[85] Intriguingly, SLE associated polymorphisms in *UBE2L3* result in elevated NFκB activity in B cells and an increase in plasmablasts and plasma cells.[208] Thus, even in the absence of *ETS1* risk alleles, Ets1 expression may be reduced in SLE B cells by other polymorphisms or defects, increasing the propensity of autoreactive B cells to differentiate and produce potentially pathogenic autoantibodies. The elevated autoantibodies in compound heterozygotes of Lyn and Ets1[106] suggest that polymorphisms in more than one component of Ets1-regulating pathways may result in enhanced B cell defects in SLE. A subset of SLE patients have a particularly striking plasma cell phenotype;[34,37] these individuals may be more likely to have disruptions in Ets1 or its regulators. Therapeutic strategies that promote signaling through Ets1-maintaining inhibitory pathways, or block signaling through Ets1-downregulating activating pathways, may reduce pathogenic autoantibodies in SLE patients.

Ets1 may also act in T cells to promote autoantibody production or contribute to the pathogenesis of SLE, perhaps by limiting IL-2 expression, promoting Th2 or Th17 differentiation, and/or inhibiting Treg differentiation. Numerous ITIM-containing inhibitory receptors exist on T cells, including CTLA-4 and PD-1, and can recruit SHP-1 to restrain T cell activation.[209, 210] The T cell receptor (TCR) signaling pathway also involves molecules similar to that found in the BCR pathway, including Lck and Fyn (homologs of the Lyn tyrosine kinase) and Itk and Tek (homologs of Btk).[211,212] In fact, TCR signaling is already known to downregulate Ets1 in T cells.[9] These similarities suggest that corresponding pathways in T cells may regulate Ets1 levels in a fashion similar to that found in B cells. This would imply that positive signaling via the TCR and Itk/Tek would function to downregulate Ets1 in T cells, while inhibitory signaling via ITIM-containing receptors would maintain Ets1. In fact, aberrations in TCR signaling are found in SLE patients.[213] Normal levels of Ets1 may be needed to maintain normal T cell functional differentiation. Further study will be required to better define the pathways in T cells that maintain Ets1 under unstimulated conditions and lead to its downregulation upon stimulation.

Acknowledgments

Anne Satterthwaite and Lee-Ann Garrett Sinha are supported by NIH Grant AI122720. Lee-Ann Garrett-Sinha is also supported by a Novel Research Grant from the Lupus Research Alliance. Anne Satterthwaite is a Southwestern Medical Foundation Scholar in Biomedical Research and holds the Peggy Chavellier Professorship for Arthritis Research and Treatment.

Abbreviations

BCR	B cell receptor
ChIP-seq	chromatin immunoprecipitation sequencing
DAS28	rheumatoid arthritis disease activity score 28
GWAS	genome-wide association studies
HEL	hen egg lysozyme
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ITIM	immunoreceptor tyrosine-based inhibitory motif
PBMCs	peripheral blood mononuclear cells
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus disease activity index
SNP	single nucleotide polymorphism
TCR	T cell receptor
Tfh	T follicular helper
Th	T helper
TLR	Toll-like receptor
Tregs	regulatory T cells
UTR	untranslated region

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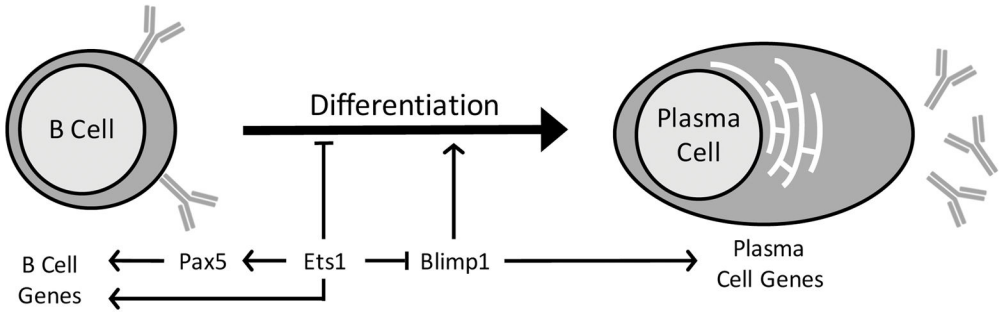

FIGURE 1. Transcriptional pathways by which Ets1 regulates B cell differentiation to plasma cells

Ets1 functions to stimulate and/or maintain the expression of the transcription factor Pax5, which is crucial for regulating B cell identity genes. Pax5 and Ets1 may also cooperate to regulate B cell genes. Ets1 also represses both the expression and the function of the transcription factor Blimp1, which is necessary to promote the plasma cell fate. Ets1 may also promote the expression of additional target genes that regulate other aspects of B cell function, like formation of germinal centers, isotype-switching and memory B cell formation.

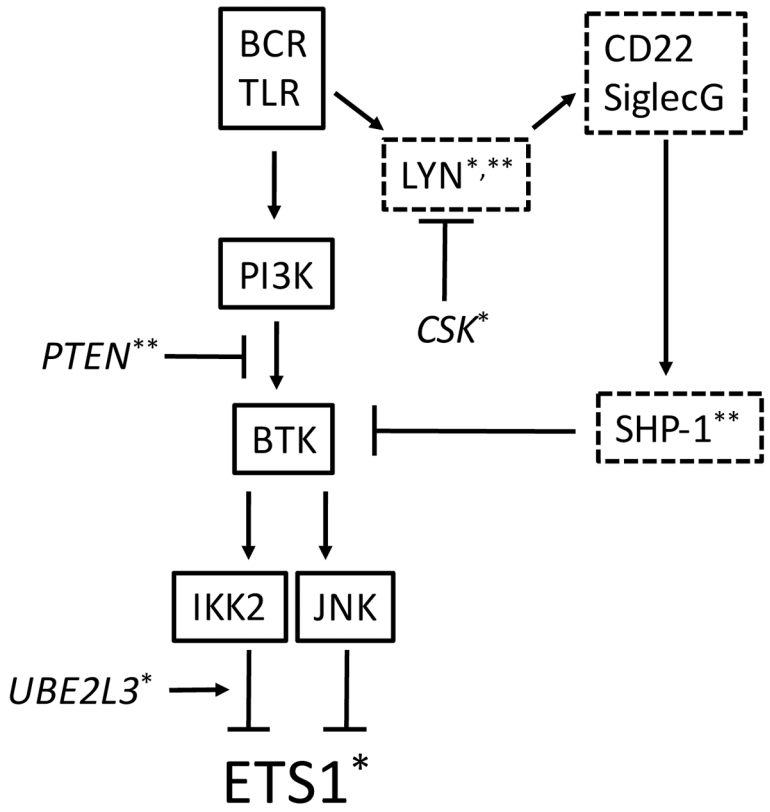

FIGURE 2. Signaling pathways controlling Ets1 expression in B cells

Signaling molecules outlined in solid lines are known to downregulate Ets1 expression, while those outlined in dotted lines have been shown to maintain Ets1 levels in B cells. Signaling molecules in italics have not been shown to control Ets1 levels, but are relevant to SLE and are likely to feed into pathways known to modulate Ets1 expression. * Polymorphisms in the gene encoding this molecule are associated with SLE. ** Expression is reduced in a subset of SLE B cells.

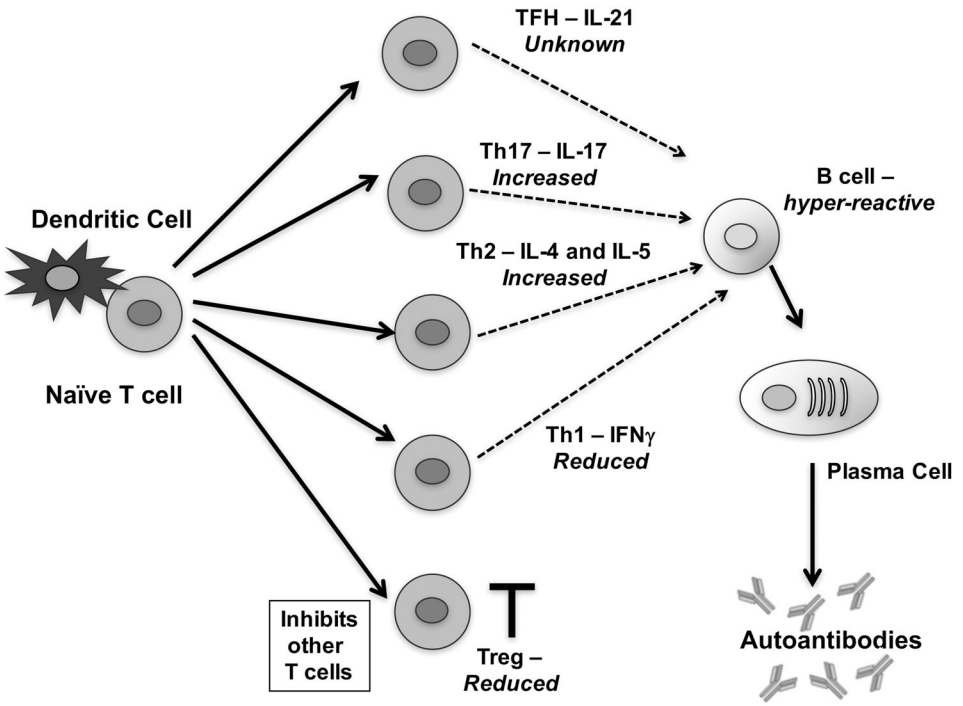

FIGURE 3. T cell aberrations in Ets1-deficient mice

Schematic of T cell differentiation with major subsets that have been implicated in lupus shown. Alterations in T cell subsets in Ets1-deficient mice are indicated in italics. Naïve autoreactive T cells interact with antigen-presenting dendritic cells and subsequently differentiate into various T cell subsets, depending on the cytokine environment in which they become activated. T cells can differentiate into T follicular helper (TFH) cells, T helper 17 (Th17) cells, T helper 2 (Th2), T helper 1 (Th1) or regulatory T cells (Treg). Tregs function to inhibit the other T cell subsets and limit autoimmune disease. Tregs are reduced in Ets1-deficient mice. The other T cell subsets produce various cytokines (as shown in the figure) and can interact with B cells to promote proliferation, germinal center formation, isotype-switching, affinity maturation and plasma cell formation. Ets1-deficiency results in skewing towards Th17 and Th2 cytokines and away from Th1 cytokines, while the effect on TFH cells is unknown. Depending on the type of T cells that interact *in vivo* with B cells, differences in B cell outcomes are possible. B cells from Ets1 knockout mice are also hyper-responsive and have an intrinsic propensity to differentiate into plasma cells.

Table I

Autoimmune or inflammatory disease-associated polymorphisms in or near the *ETS1* gene

Polymorphisms in or near *ETS1*	**Autoimmune or Inflammatory Disease**	**Reference(s)**	**Location[1]**
CA repeat polymorphisms	Lupus	Sullivan et al., 2000	3′ UTR
rs6590330	Lupus	Han et al., 2009; He et al., 2010; Yang et al., 2010; Zhong et al., 2011; Leng et al., 2013; Wang et al., 2013; Lu et al., 2015	Downstream of gene
rs10893872	Lupus, Uveitis	Yang et al., 2010; Zhang et al., 2013; Wei et al., 2014	Downstream of gene
rs4937333	Lupus, Ankylosing spondylitis	Yang et al., 2010, Zhong et al., 2011; Shan et al., 2014	3′ UTR
rs7932088	Lupus	Yang et al., 2010	Downstream of gene
rs12223943	Lupus	Yang et al., 2010	Proximal promoter
rs6590343	Rheumatoid arthritis	Freudenberg et al, 2011	Upstream of the gene
rs61907765	Celiac disease	Trynka et al., 2011	5′ UTR
rs4937362	Rheumatoid arthritis	Okada et al, 2012	Upstream of the gene
rs11221332	Rheumatoid arthritis; Celiac disease	Chatzikyriakidou 2012; Dubois et al., 2010	Intron I
rs3802826	Psoriasis	Tsoi et al., 2012	Upstream of gene
rs34846069	Lupus	Davis et al, 2013	Final exon (does not change amino acid sequence)
rs970924	Allergy	Hinds et al., 2013	Downstream of gene
rs1128334	Lupus, Ankylosing spondylitis	Zhang et al., 2013, Lessard et al., 2015; Shan et al., 2014	3′ UTR
rs76404385	Lupus	Molineros et al., 2014	Intron VII
rs4936059	Rheumatoid arthritis	Kim et al., 2014	Upstream of the gene
rs1128334	Ankylosing spondylitis	Shan et al., 2014	3′ UTR
rs73013527	Rheumatoid arthritis	Okada et al, 2014; Chen et al., 2015	Upstream of the gene
rs12576573	Lupus	Lessard et al., 2015	Downstream of gene
rs7941765	Lupus	Bentham et al., 2015; Morris et al., 2016	Upstream of gene
rs3809006	Multiple sclerosis	Lill et al., 2015	Upstream of gene
rs4520607	Psoriasis	Stuart et al., 2015	Upstream of gene
rs6590334	Psoriasis	Yin et al., 2015	Upstream of gene
rs7933433	Psoriasis	Yin et al., 2015	Downstream of gene
rs4936044	Psoriasis	Yin et al., 2015	Downstream of gene
rs55974252	Psoriasis	Yin et al., 2015	Downstream of gene
rs573624	Psoriasis	Yin et al., 2015	Downstream of gene
rs7127307	Atopic dermatitis	Paternoster et al., 2015	Downstream of gene
rs61432431	Lupus	Morris et al., 2016	Downstream of gene

[1] Introns are labeled from the first (I) to the last (VII) intron of the major isoform of Ets1