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# Infection in systemic lupus erythematosus: friend or foe?

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## Abstract

Infectious agents have long been implicated in the pathogenesis of systemic lupus erythematosus. Common viruses, such as the Epstein-Barr virus, transfusion transmitted virus, parvovirus and cytomegalovirus, have an increased prevalence in patients with systemic lupus erythematosus. They may contribute to disease pathogenesis through triggering autoimmunity via structural or functional molecular mimicry, encoding proteins that induce cross-reactive immune responses to self antigens or modulate antigen processing, activation, or apoptosis of B and T cells, macrophages or dendritic cells. Alternatively, some infectious agents, such as malaria, *Toxoplasma gondii* and *Helicobacter pylori*, may have a protective effect. Vaccinations may play dual roles by protecting against friend and foe alike.

### Keywords

autoimmunity; infections; protective; systemic lupus erythematosus; vaccination

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease and the mechanisms of the aberrant immune responses remain unclear. Several environmental factors have been implicated in the etiology of SLE. There is a concordance rate of 25% in monozygotic twins for SLE, which indicates a discordance rate of 70% contributed to by environmental factors [1].

The possibility of a viral etiology was raised by the finding of virion-like tubuloreticular structures in endothelial cells and lymphocytes, and demonstration of increased concentration of type 1 interferon (IFN) in lupus patients [1]. Many viruses have been implicated in the etiology of SLE, which includes the Epstein–Barr virus (EBV), transfusion-transmitted virus (tissue transplant virus or Torque tenovirus), retroviruses, paramyxovirus, cytomegalovirus (CMV), parvovirus B19 and corona virus (Table 1). EBV, retroviruses and parvovirus B19 may play a role in the pathogenesis of SLE, when compared with other viruses such as CMV, transfusion transmitted virus, type C oncorna virus and measles virus which play a minor role. Immunodeficiency, such as C4 or C1q deficiency, may predispose to both lupus and infection without the two being directly linked. Infectious agents may induce autoimmune disease by several mechanisms.

## Structural & functional molecular mimicry

Molecular mimicry may be structural or functional. Structural molecular mimicry occurs when a viral peptide has an amino acid sequence similar or identical to an amino acid sequence of a self peptide, resulting in cross-reactive T-cell and B-cell responses. A potentially autoreactive



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T cell, possessing T-cell receptors that recognize both a foreign (viral) peptide and a self-peptide, is activated by a virus-derived peptide. Thus, in addition to mediating an antiviral response, the T cell is also capable of mediating self-directed responses.

Peptide sequences common to a virus (e.g., EBV protein) and a target lupus autoantigen (e.g., Smith antigen [Sm]) can also induce cross-reactive autoantibodies [2,3]. There is a wide range of structural, functional and immunological similarities between HIV-1 gp120 envelope protein and host proteins. HIV-1 *tat* gene upregulates Rab4, producing functional mimicry. HIV-1 *tat* gene stimulates transcriptional activity of the *HRES-1/Rab4* promoter via transactivation of the HRES-1 long terminal repeat. There is coordinated upregulation of HRES-1/Rab4 and downregulation of $CD4^+$ expression in HIV-infected peripheral blood mononuclear cells and $CD4^+$ T cells. Enhanced expression of HRES-1/Rab4 may contribute to downregulation of $CD4^+$ recycling to the cell surface, thus preventing infection by HIV-1 and protecting virus-infected cells against death by cytotoxic T cells. [4]. EBV protein regulates apoptosis by encoding a bcl-2-like protein (BHRF1-Bam HI fragment H rightward open reading frame 1), which is also an example of functional mimicry (Figure 1) [5].

## Stimulation of pathogen recognition receptors

Exogenous stimuli are products of bacteria and viruses and have been termed pathogen-associated molecular patterns (PAMPs) [6]. Dendritic cells recognize PAMPs using pathogen recognition receptors, such as Toll-like receptors (TLRs). Necrotic debris from the cell death pathways, bacterial lipopolysaccharide, viral RNA and viral DNA act on TLRs [7]. A subset of dendritic cells, plasmacytoid dendritic cells (pDCs), is the body's major producer of type 1 IFNs. IFNs are important in host defense against viruses and there is overproduction of IFNs in SLE [8]. TLRs activate pDCs leading to the release of IFN-α/β. This in turn leads to the release of proinflammatory cytokines resulting in autoimmunity. IFN-α results in the maturation of antigen presenting cells and augmented T-cell activation including excessive helper activity. Natural killer cells produce significant amounts of cytokines, for example IFN-γ, that can influence the development of T cells [7].

Viruses may affect innate immunity by the release of proinflammatory cytokines. Proteins of commonly occurring viruses could produce profound effects on the cytokine milieu, antigen recognition and lymphocyte cell survival. PAMPs play a fundamental role in the early recognition of several infectious agents, such as Gram-positive and Gram-negative bacteria and RNA and DNA viruses. These molecules include bacterial cell surface lipopolysaccharides, lipoproteins, proteins such as flagellin from bacterial flagella, viral dsRNA, the unmethylated CpG islands of bacterial and viral DNA, and are sensed by a type of TLR pattern recognition receptor (Figure 2) [9].

There are at least 11 TLRs recognized in humans. TLR7 recognizes ssRNA and TLR9 binds dsDNA and CpG motif of bacterial DNA. TLR2 serves as a receptor for peptidoglycan and bacterial lipoproteins, TLR4 for Gram-negative lipopolysaccharide and TLR5 for flagellin. TLRs that bind to DNA and RNA lead to the production of large amounts of IFN-α, mostly derived from plasmacytoid dendritic cells [9]. In animal models of lupus nephritis, some TLRs (TLR3 and TLR9) are specifically immunolocalized in the kidneys, suggesting a possible pathogenetic role in the manifestation of the disease [10].

Microbial stimulation of TLRs leads to the initiation of the IL-1 signaling loop via the activation of IL-1 receptor-associated kinase (IRAK)1, IRAK4, TNF receptor-associated factor 6 (TRAF6), NF-κB kinase (IKK) complex and NF-κB activation. IL-1β activates its own receptor, which also signals via the same TLR pathway components to produce IL-1β [11]. Molecular mimicry and immunomodulation by viral proteins may account for both cross-reactivity with autoantigens and abnormal T- and B-cell functions in autoimmune disorders

[1]. Necrotic and late apoptotic cells release material, which, when combined with immunoglobulins from SLE patients, induces the production of IFN-α from pDCs [12].

Infections can inhibit the development of autoimmune disease by several mechanisms. Some infections elicit responses to decrease the host response and thereby limit target tissue injury. The interactions of molecules derived from bacteria, fungi and parasites with TLRs and C-type lectin receptors on cells of the innate and adaptive immune system enable them to modulate the host immune responses [13]. Animal studies have demonstrated that exposure to infectious agents, or products derived from them, can inhibit the onset of autoimmune disorders through a variety of mechanisms, which includes reinforcement of regulatory networks and influencing trafficking of autoreactive T cells to sites of inflammation [13].

Meticulous exclusion of infections is essential in patients with SLE since infections may masquerade as flare-up of the disease, and immunosuppressive medications used to treat exacerbations of SLE may result in catastrophic consequences for the patient [14]. Patients with SLE appear to have an increased risk for infection due to dysregulation of the immune system. The usage of immunosuppressants, especially steroids and cyclophosphamide, are the strongest risk factors for infections in patients with SLE [15]. IFN-α is increased during a flare-up of SLE, which may reflect a viral infection or viral reactivation [8]. EBV and transfusion-transmitted virus (TTV) have an increased prevalence in SLE patients [16,17]. In SLE patients, sometimes it may be difficult to distinguish between a flare and superimposed infection. Further complicating matters, superimposed infections can lead to a flare in SLE. Parvovirus B19 [18,19] and CMV [14,20,21] have been reported to cause both induction of SLE and flare. Infections such as parvovirus B19 can mimic the symptoms of SLE [18,19].

Bacterial infections are the most common cause of infection in SLE and accounts for almost 80% of infections [22]. Most commonly identified bacteria include Staphylococcus aureus, Streptococus pyogenes, Streptococcus pneumoniae and *Escherichia coli*, which account for more than 50% of infections. Less commonly reported bacteria include Enterococcus, Klebsiella, Pseudomonas, Salmonella, Listeria, Mycobacterium tuberculosis and *Nocardia* [22]. Under these critical circumstances, it is vitally important to distinguish between lupus flare and infection. Elevated dsDNA and low C3 and C4 point towards a flare-up of lupus, whereas leukocytosis and a positive culture indicates infection requiring treatment with antibiotics.

## Epstein–Barr virus

Epstein–Barr virus is a ubiquitous human DNA virus that infects B cells and causes their polyclonal activation and produces polyclonal antibodies. Polyclonal B-cell activation may be an early step in the pathogenesis of SLE. Serologic association, cross-reactivity of select EBV-specific antibodies with SLE autoantigens, SLE-like autoimmunity after immunization with EBV peptides, increased EB viral load in SLE patients and SLE-specific alterations in EBV humoral and cellular immunity implicate EBV in the development of SLE [23–25].

### Increased prevalence of EBV infection in SLE patients

Interestingly, prevalence of EBV infection was reported to be as high as 99% in young SLE patients compared with 70% prevalence in controls [16,17]. Similar results were reported from a large study in adult patients. This study demonstrated that 99.5% of adults with SLE had seroconverted to EBV, compared with 95% of normal subjects, giving an odds ratio of 9.35 ($p = 0.014$) [26].

Peripheral blood mononuclear cells from SLE patients showed greater expression of both latent and lytic genes after infection, suggesting that EBV may participate in the etiology of SLE

through several different mechanisms. Such altered infection patterns may contribute to the increased levels of EBV and the molecular mimicry seen in sera from SLE patients [27].

## Increased viral load of EBV in patients with SLE

Several studies have demonstrated that EBV load is 10–15-fold higher in the peripheral blood of SLE patients compared with controls [28,29]. Real-time quantitative PCR showed a significant increase in the amount of EBV DNA in peripheral blood mononuclear cells from lupus patients compared with controls [30]. Studies have also demonstrated that the abnormally high frequency of EBV-infected cells in patients with SLE is associated with the occurrence of SLE disease flares [29]. Aberrant expression of viral lytic (BZLF1) and latency (latency membrane proteins 1 and 2a) genes was also detected in the blood of SLE patients. The abnormal regulation of EBV infection in SLE patients reflects the sensitivity of the virus to perturbation of the immune system [29].

## Molecular mimicry between EBV & lupus autoantigens

Infection with EBV results in the production of the viral protein EBV nuclear antigen (EBNA)-1, antibodies against which cross-react with lupus-associated autoantigens, including Ro, Sm B/B′ and SmD1, in lupus patients (Table 2) [31,32]. A region of considerable homology, comprised of 11 highly charged residues (GRGRGRGRGRG), was identified as a site of cross-reactivity between the D component of Sm and EBNA-1 (Table 3) [1,33]. Antibodies directed against SmD1 are capable of binding the EBNA-1 peptide. Immunization of animals with the 35–38 EBNA-1 peptide induces the production of antibodies that can react with EBNA-1 and Sm D1 95–119.

In patients where anti-Ro antibodies develop, the first sequence recognized usually contains the amino acids 169–180 (TKYKQRRNGWSHK). This sequence is cross-reactive with a sequence on EBNA-1 that is bound by antibodies from lupus patients [34]. Studies carried out in pediatric SLE patients have demonstrated that pediatric SLE patients and matched normal individuals make distinct antibody responses against EBNA-1, and that anti-EBNA-1 antibodies are associated with SLE.

Autoantibodies directed against the spliceosomal proteins, anti-Sm and antinuclear RNP are found in 30–50% of lupus patients' sera. The possible molecular mimicry of the EBV peptide PPPGRRP by the peptide PPPGMRPP from Sm B′/B of the human spliceosome is consistent with the possibility that EBV infection is related to the origin of SLE in some patients [35–37].

## Induction of lupus with EBV peptide

Autoantibodies from many patients with SLE bind the Sm autoantigen B/B′ polypeptide. The binding of serial serum specimens to the 233 overlapping octapeptides of Sm B/B′ has demonstrated that of the B/B′-derived octapeptides, PPPGMRPP and PPPGIRGP, are early targets of the autoimmune response in some lupus patients. Studies have demonstrated that rabbits immunized with PPPGMRPP and PPPGIRGP develop antibodies that not only bind these octapeptides, but also subsequently bind many other octapeptides of Sm *B/B′*. These peptide-immunized animals developed features of SLE, such as antinuclear antibodies, anti-Sm antibodies, antidouble-stranded DNA, thrombocytopenia, seizures and proteinuria. The immunogen used in these experiments, PPPGMRPP, was most similar to PPPGRRP from EBNA-1 of EBV, which is also bound by human sera containing anti-Sm autoantibodies [38–40].

### Prevention of apoptosis

The persistence of EBV infection in patients with SLE may be related to the antiapoptotic potential of B cells due to their infection with EBV. During primary infection, autoreactive B cells are infected by EBV; they in turn proliferate and become latently infected memory B cells that are resistant to apoptosis that occurs during normal B-cell homeostasis because they express virus-encoded antiapoptotic molecules [14].

## Cytomegalovirus

There have been several case reports of lupus associated with human CMV (HCMV) infection. In these cases, active infection with CMV determined by either the presence of anti-HCMV IgM or viral DNA has been detected at the time of flare-up of symptoms of lupus, implicating HCMV as a possible etiologic agent in lupus [20,21]. The development of SLE may be triggered by a CMV infection. Existing SLE may undergo an exacerbation following a CMV infection [14].

## Parvovirus B19

There are striking similarities between the clinical features and hematological findings of SLE and those of parvovirus B19 infection, including anemia, thrombocytopenia and arthritis. There have been several case reports of parvovirus B19 infection causing a flare-up of SLE [19]. Parvovirus B19 may be accompanied by a transient subclinical state of autoimmunity and may mimic or exacerbate SLE [18]. Elevation of rheumatoid factor, antiphospholipid, antilymphocyte and antinuclear antibodies are frequently observed during the late phase of B19 infection occurring after the peak of viremia. The concentration of these antibodies usually decline rapidly within a few days, but, occasionally, the autoimmune response persists and may be associated with manifestations, such as arthritis, vasculitis and fibromyalgia [41].

Parvovirus B19 may have the property of inducing production of autoimmune antibodies by mimicking autoantigens [19]. This, in turn, may contribute to or exacerbate the symptoms in SLE.

It depletes erythroid progenitor cells by apoptosis. Chronic parvovirus B19 infection is associated with production of a wide array of autoantibodies [1,42].

## Transfusion-transmitted virus

Transfusion-transmitted virus is a recently discovered virus of extremely high genetic diversity that commonly infects humans. SLE patients produce autoantibodies to HRES-1/p28, a human endogenous retrovirus encoded nuclear protein [16,43]. There is possible molecular mimicry between TTV and HRES-1/p28. The highest prevalence of cross-reactivity has been shown between HRES-1/p28 residues 41–55 and 156–170 and TTV peptide ORF2a. Prevalence of TTV was noted to be increased in SLE patients with respect to healthy controls [16,43].

## Retroviruses

### Exogenous retroviruses Dysregulation of apoptosis

Dysregulation of apoptosis can occur both in HIV and SLE patients. HIV infection causes a shift from a T helper (Th)1 to Th2-type cytokine profile, which is similar to those found in patients with SLE [44–46]. The *nef* and *tat* genes of HIV-1 are thought to mediate a Th1 to Th2 shift in cytokine production. $CD4^+$ T-cell decline is mediated by an increased rate of apoptosis or programmed cell death. Th1 cytokines protect against apoptosis, whereas Th2 cells increase the rate of apoptosis. The shift of Th1 to Th2 cells causes the accelerated apoptosis

in SLE patients. Anemia, leucopenia, thrombocytopenia, polymyositis and vasculitis can occur in both SLE and HIV patients. These observations suggest that there is a common mechanism mediating the increased apoptosis and autoantibody production in SLE and AIDS [44–46]. This may indicate that SLE is probably caused by a virus that has not yet been identified. In turn, SLE, which is thought to be mediated by $CD4^+$ T cells, remits in some patients after infection with HIV-1 [1,47]. The tat protein of HIV induces oxidative stress and increases surface expression of the Fas ligand, resulting in accelerated signaling through the Fas pathway (Figure 3). In addition, cleavage of bcl-2 by HIV protease may expose the cell to a variety of apoptotic signals (Figure 4) [1,48].

## Endogenous retroviruses Genetic factors

Endogenous retroviral sequences represent a link between viral and genetic factors that may influence the development of SLE [49]. HRES-1 is an endogenous retroviral element encoding a 28 kDa nuclear autoantigen, HRES-1/p28, which is expressed in a tissue-specific manner. Antibodies to HRES-1/p28 were detected in 21–50% of patients with SLE and overlap syndromes in several laboratories compared with normal donors or HIV-infected patients [50].

HRES-1 is represented as a single copy element per haploid genome that has been mapped to a common fragile site of chromosome 1 at q42 [51]. The 1q42 region is one of at least ten chromosomal loci shown in independent studies to be linked to the development of SLE [49]. The presence or absence of a polymorphic HindIII site defines two different allelic forms of the HRES-1 genomic locus. In comparison with normal blood donors, a differential segregation of polymorphic genotypes of the HRES-1 locus (i.e., a relative decrease of genotype I and increase of genotype III) were noted among patients with SLE. The q41→q42 region of chromosome 1 was found to contain susceptibility genes that confer risk for SLE in multiple ethnic groups, further supporting the notion that HRES-1 or another gene closely linked to HRES-1 may influence susceptibility to SLE [50].

**Molecular mimicry between endogenous retroviruses & lupus autoantigens—** The 70 kD protein of U1snRNP was the first lupus autoantigen shown to contain a region of homology and immunologic cross-reactivity with a p30 gag protein of most mammalian type C retroviruses. A mimicking epitope between another lupus autoantigen, Sm and HIV-1 p24 gag was defined based on cross-reactivity with monoclonal antibody 4B4. A proline-rich domain present in both the B/B′ subunit of Sm and HIV p24 *gag* was suggested to be the core of cross-reactive epitopes. Antibodies binding to HIV-1 p24 *gag* were found in 22 out of 61 patients with SLE [44].

HRES-1/p28 shows similarity to TTV proteins. Lupus sera had strong binding affinity to a peptide showing similarity to the retroviral gag-like region of 70 kD U1 snRNP lupus autoantigen, suggesting that cross-reactivity of HRES-1 p/28 with TTV and 70 kD U1 snRNP may lead to epitope spreading and contribute to generation of antinuclear antibodies.

**Regulation of $CD4^+$ expression—**HRES1/Rab4 belongs to the family of small GTPases that regulate receptor endosome recycling. Regulation of HRES-1/Rab4 expression may play an active role in the lifecycle of HIV-1. This is supported by the fact that there is coordinated upregulation of HRES-1/Rab4 and down-regulation of $CD4^+$ expression in HIV-infected $CD4^+$ T cells and PBMC. HRES-1/Rab4 promoter activities and protein levels are increased in cells infected by HIV-1 or transfected by HIV-tat. In turn, enhanced expression of HRES-1/Rab4 may contribute to downregulation of $CD4^+$ recycling to the cell surface, thus preventing reinfection by HIV-1, allowing for increased virion production and protecting virus-infected cells against killing by cytotoxic T cells. Thus, stimulation of HRES-1/Rab4 expression by

HIV-1 and regulation of HIV coreceptor $CD4^+$ recycling by HRES-1/Rab4 represent novel mechanisms of coordinate interaction between infectious viral particles and endogenous retroviruses of the human genome [4].

$CD4^+$ expression is low in $CD4^+$ lupus T cells, while HRES/Rab4 expression is high raising a possible role for a virus similar to HIV in SLE [52]. Alternatively, genetic factors may contribute to increased expression of HRES-1 in SLE [49].

**Role of 3′ repair exonuclease 1 in autoimmunity—**Detection of nucleic acids and induction of type 1 IFNs are principal elements of antiviral defence, but can result in autoimmunity if misregulated. Cytosolic DNA detection activates a potent, cell intrinsic antiviral response through a poorly defined pathway called the IFN-stimulatory DNA (ISD) pathway. Trex1 is an essential regulator of the ISD response and delineate the genetic pathway linking Trex1 deficiency to lethal autoimmunity [53].

Trex1 has been identified as an ISD inducible but negative regulator of the ISD response. Mutations in the human *trex1* gene cause Aicardi-Goutieres syndrome and chilblain lupus. Stetson *et al.* have demonstrated that single-stranded DNA derived from endogenous retro elements accumulates in Trex1-deficient cells and that Trex1 can metabolize reverse-transcribed DNA. This is a new mechanism of autoimmunity where defective metabolism of intracellular nucleic acids triggers a cell-intrinsic autoimmune response and suggests the contribution of endogenous retro elements to autoimmunity.

## RNA viruses

### Type C oncorna virus

Type C oncorna viruses have been postulated to have an association with SLE. Lymphoblastoid cell lines derived from patients with active SLE by allowing spontaneous transformation of peripheral B lymphocytes (B cells) harboring endogenous EBV or by super infecting peripheral lymphocytes with exogenous EBV. Extensive studies were conducted searching for type C oncorna viruses using electron microscopy, DNA–DNA hybridization, reverse transcriptase assays and cocultivation experiments, which revealed negative results [54]. The results of experimental studies on the role of type C viruses in SLE were conflicting. There were several reports of increased viral expression, but the attempts at type C virus isolation from the tissues of SLE patients were unsuccessful [55].

### Paramyxoviruses

Increased antibodies to measles and parainfluenza type 1 have been detected in patients with SLE. There are three possible explanations for this observation. First, they could reflect persistent viral infection. Second, the increased antibody levels might be a nonspecific result of immuno-logic hyper-reactivity. Finally, the increases in antibody may be due to antigens shared by host cell and virus (molecular mimicry) [56,57].

## Vaccinations as a trigger for SLE

Vaccines have been associated with the onset or flare-up of SLE [58]. A total of five healthy patients who received immunizations by a combination of vaccines, including typhoid, influenza, meningococcal vaccines, tetanus toxoid, measles, mumps, rubella vaccine and anthrax vaccine, developed SLE 2–3 weeks after secondary immunization [58,59]. The trigger for the onset of SLE may be either the bacterial or viral components of the vaccine or the chemical components of the solvent (adjuvant).

### Hepatitis B vaccine

There have been several case reports suggesting a temporal relation of SLE to hepatitis B vaccine, but a causal relationship has not yet been proven [58,60]. There are no studies on the safety and efficacy of HBV for patients with well-established lupus [61–64].

### Influenza vaccine

Some reports suggest a link between influenza vaccination and lupus, but these are isolated and rare associations. The efficacy and safety of influenza vaccination in lupus patients have been proven by several studies [65–67].

### Pneumococcal vaccine

In an Israeli cohort study, 24 patients with SLE who were vaccinated with pneumococcal vaccine showed no change in biological or clinical markers of disease activity 1 month after the vaccination [68,69]. A Hungarian cohort study of 18 SLE patients showed good tolerability of the pneumococcal vaccine [69,70].

## Ethnicity

The prevalence and incidence of lupus is high in patients from certain ethnic groups. SLE is more common in those of Hispanic origin, those of African descent in North America, or with a Caribbean background in the UK, those of Asian descent (from India, Pakistan and China), as well as those from countries around the Pacific, including North American Indians, Australian Aborigines and New Zealand Maoris [71,72]. Hispanics, African–Americans, African–Caribbean, South Asians and Chinese tend to present with SLE at a younger age, have more renal involvement, earlier damage and often higher mortality than Caucasians [72].

Systemic lupus erythematosus is very rare in West Africa, more common in Central and Southern Africa and increases in frequency towards the west, including the Caribbean, Europe and America. One possible explanation is that malaria is very common in West Africa and the immune responses against malaria may act as a protective factor in the prevention of SLE. Most of the African–Americans in the USA originate from West Africa and the increased incidence of SLE in this group could be explained by the fact that they do not have the protective effect of malaria [73,74].

## Genetic factors predisposing to infections in SLE

Recent studies have indicated that genetic factors may increase the risk of serious infections in SLE. Mannose-binding lectin (MBL) is one of the molecules in the lectin complement activation pathway that shares many features of C1q. Human MBL is derived from a single gene located on chromosome 10 (*MBL2*) [75]. Patients who had MBL deficiency associated with homozygous MBL variant alleles have been reported to be at increased risk of infections. Patients with SLE who were homozygous for MBL variant alleles had a fourfold increase in the incidence of infections [14,15]. It has been reported that low serum MBL predisposes Chinese SLE patients to infections, especially bacterial infections [76]. The presence of anti-MBL autoantibodies in sera of SLE patients can influence MBL plasma levels and its functional activity.

At least a third of the SLE patients with C1q deficiency also suffered from recurrent bacterial infections, including otitis media, meningitides and pneumonia [77]. An increased susceptibility to bacterial infections may be present in up to 30% of C2 deficient individuals, which occurs mainly in infancy and childhood [78].

IRF-5 is a transcription factor that is expressed in B cells and dendritic cells that regulates the expression of a variety of genes and leads to the induction of IFN and proinflammatory cytokines. In mice deficient in the *IRF5* gene, the production of type 1 IFN against viral infections was decreased and there was impaired induction of proinflammatory cytokines by TLR stimulation [79,80]. In humans, overexpression of IRF5 stimulates the expression of type 1 IFN genes after viral infection, and knockdown of *IRF5* by short interfering RNA reduces the induction of type 1 IFN in response to TLR7 ligand [81–83].

Variants of the gene encoding signal transducer and activator of transcription 4 (STAT4) have also been discovered to be risk factors for SLE. The identification of these risk genes supports the hypothesis that the type 1 IFN pathway plays a key role in the pathogenesis of SLE [84, 85]. After 24 h infection with *Pseudomonas aeruginosa*, STAT4-deficient mice showed impaired production of the proinflammatory cytokines, TNF-α, IL-1β and macrophage inflammatory protein-2 [86]. Thus, STAT4 appears to contribute to *Pseudomonas aeruginosa*-induced inflammation, but it is not necessary for bacterial clearance [86].

Two new susceptibility loci for SLE have been identified: BLK-C8orf13 on chromosome 8 and *ITGAM–ITGAX* (genes encoding integrin-α M and integrin-α X) on chromosome 16 [84]. The genes most likely involved within these two loci are *BLK* (B lymphoid tyrosine kinase) and *ITGAM* (Table 4).

## Protective effect of infections in autoimmune diseases

The ‘hygiene hypothesis’ postulates that infection may protect from autoimmune diseases. Epidemiological evidence indicates that there is an alarming increase in autoimmune diseases over the last three decades in North America and Europe, which is thought to be linked to the improved socioeconomic status, better hygiene, and more specifically to the reduced microbial exposure of children, as a result of Westernized lifestyles [87–92].

However, the immunological changes induced by higher standards of hygiene during childhood are still under debate. The two possible explanations include: missing immune deviation from Th2 to Th1, caused by reduced production of Th1 polarizing cytokines by cells of the innate immunity in response to stimulation of their TLRs by microbial components; and reduced activation of T-regulatory cells caused by reduced stimulation of the immune system [92].

Studies have demonstrated that there is a north–south gradient for the distribution of autoimmune diseases – the incidence of autoimmune disease decreases from north to south in the northern hemisphere and reciprocally from south to north in the southern hemisphere. Some infections in European countries may be distributed according to a south–north gradient that is a mirror image of the gradient for autoimmune diseases [91].

It has been consistently observed that autoimmune diseases in susceptible strains of mice or rats develop earlier and at a higher rate among animals bred in a specific pathogen-free environment than among animals bred in a conventional environment. A similar effect of the use of pathogen-free conditions has been reported in rats with collagen-induced arthritis, which is an experimental model for rheumatoid arthritis (Figure 3).

Bacteria and viruses could protect against autoimmune diseases through their effect on TLRs. TLRs are receptors for various bacterial components – TLR2 serves as a receptor for peptidoglycan and bacterial lipoproteins, TLR4 for Gram-negative lipopolysaccharide, TLR5 for flagellin and TLR9 for CpG motif of bacterial DNA. When TLRs bind bacterial ligands they stimulate mononuclear cells to produce cytokines, which in turn could downregulate autoimmune responses [91].

### Toxoplasma gondii

Animal studies have demonstrated that *Toxoplasma gondii* infection may prevent the development of a lupus-like syndrome in autoimmune New Zealand black and white (NZBW) F1 mice. The pathogenic isotypes (IgG2a and IgG3) of the anti-DNA antibodies in the serum of *T. gondii*-infected mice were significantly reduced [93,94].

The level of antiself heat-shock protein 70 (anti-HSP70) IgG autoantibody in the sera of NZBW F1 mice was significantly higher than that in control mice at 9 weeks after *T. gondii* infection. Furthermore, NZBW F1 mice treated with HSP70 monoclonal antibody were substantially protected against the onset of glomerulonephritis. In addition, downregulation of intracellular expression of IFN-γ and IL-10 was shown in spleen cells of *T. gondii*-infected NZBW F1 mice. These results indicate that *T. gondii* infection is capable of preventing the development of autoimmune renal disorder in NZBW F1 mice [94].

### Helicobacter pylori

*Helicobacter pylori* infection may play a protective role against the development of SLE. Immunoregulatory events leading to *H. pylori* seropositivity correlate inversely with the risk of developing SLE. This has been suggested by the fact that there was an association between SLE and *H.pylori* seronegativity [95,96].

### Malaria

As discussed previously, SLE is very rare in West Africa, more common in Central and Southern Africa and increases in frequency towards the west, including the Caribbean, Europe and America. One possible explanation is that malaria is very common in West Africa and acts as a protective factor in the development of SLE. Most of the African–Americans originate from West Africa and the increase in incidence in SLE in this population could also be explained by the fact that there has been considerable genetic admixture since their arrival in America.

There are several mechanisms that have been postulated by which malaria protects against the development of autoimmune disease such as SLE. Malaria is a potent inducer of tumor necrosis factor (TNF) and it is now known that the pathology in malaria results from the initial induction of this cytokine. Patients who are infected with *Plasmodium falciparum* and have high levels of TNF are at higher risk of developing the more severe form of the disease – cerebral malaria. TNF-induced activation of macrophages and neutrophils controls parasite replication in the early stages of malaria, but when there is uncontrolled overproduction of this cytokine it leads to severe disease. As a consequence to reduced ability to generate TNF in low endemic areas for malaria there is a greater risk of developing autoimmune disease, such as SLE. This is a likely explanation for the higher rate of SLE in African–Americans [74].

Another mechanism that has been described is a defunctioning, SLE-associated polymorphism of the inhibitory receptor FcγRIIb in African and Asian populations, which corresponds to the areas where malaria is endemic [97]. FcγRIIb-deficient mice have increased clearance of malarial parasites and develop less severe disease. FcγRIIb deficiency or dysfunction is associated with the development of autoimmunity, especially SLE, in mice and humans [97].

## Protective effect of vaccinations

Vaccinations may have two roles in the development of autoimmune disease. They may induce autoimmunity by preventing the onset of infections, which may have a protective role in the development of autoimmune diseases. This is probably unlikely since there are very few infections implicated in the development of autoimmune diseases that are protected by

vaccinations. The second postulation is that vaccination may contribute to the development of autoimmune disease by stimulation of the immune system by the repeated injections of the vaccine along with their adjuvant [98].

Bacillus Calmette Guerin (BCG) vaccine and Q fever vaccine have been evaluated in children for the prevention of diabetes in a population of children at risk of developing the disease. The difficulty encountered was that these vaccinations were not given at repeated intervals, and isolated immune stimulations were not sufficient to produce protective mechanisms, which were obtained in experimental models [98–103].

## Protective effect of genetic factors in autoimmune disease

Susceptibility to SLE depends on cumulative interaction of many genetic loci containing polymorphic variants, and the likelihood of developing the disease is a function of the number of susceptibility genes present in the genome of the individual [104,105]. A locus on chromosome 1, Sle1, breaches immunological tolerance to chromatin, and Sle2, another locus on chromosome 4, triggers generalized B-cell hyperactivity [104]. Sle3, a locus on chromosome 7, is associated with a number of T-cell aberrations, which are mediated through myeloid cells. Genetic polymorphisms or deletions within CCR5 diminish or abrogate viral binding to the receptor, which leads to a lower susceptibility to infection and slower disease progression in persons carrying these mutations [4].

Mice with the Sle3 susceptibility locus have been demonstrated to have enhanced antibacterial responses, especially pneumonia and intra-abdominal sepsis, compared with wild-type mice. This was associated with markedly increased accumulation of neutrophils in infected tissues. Neutrophils from lupus-susceptible mice displayed markedly reduced rate of apoptosis, associated with altered expression of bcl-2 family proteins, leading to their greater accumulation. On the other hand, inhibition of apoptosis in wild-type mice increased the accumulation of neutrophils at the site of infection and resulted in an enhanced antibacterial response. These observations suggest that some of the genetic loci that mediate autoimmunity may also produce enhanced antibacterial immunity [104].

## Role of interferon in the development of autoimmune disease

Viral infections induce the production of large amounts of IFN-α and -β, which in turn modulate immune responses. IFN-α produces a positive effect by stimulating Th1 cell mediated autoimmunity. However, IFN-β produces a negative response and its immunoregulatory properties have been utilized in the treatment of multiple sclerosis.

IFN-γ may also have a protective role in the development of autoimmune diseases, which has been demonstrated in some animal models of experimental allergic encephalomyelitis and to a lesser extent in human autoimmune diseases, such as rheumatoid arthritis [98].

## Future perspective

In summary, infections play a major role in modulating the development of autoimmune diseases by performing a dual role of protection and also induction of the disease process. The underlying mechanisms are multiple and extremely complex and varies widely according to the specific pathogen involved [106].

The study of the role of infections in the development or protection of autoimmune diseases has been extremely difficult. There are several possible explanations for the difficulties in identifying infections as etiological agents in autoimmune diseases. One hypothesis is that there is a long lag time between the initial causal infection and the onset of clinical symptoms

in SLE. The causative infection may resolve quickly and the serological evidence may have disappeared by the time of clinical onset of the autoimmune disease [106].

Evidence has emerged from studies of human SLE of a role of TLR7 and TLR9 in autoimmunity. TLR signaling in T cells leads to the production of Th1 cytokines and in B cells to cell proliferation, differentiation and immunoglobulin switching. The genetic deficiency of TLR-7 may confer protection from autoimmunity in murine SLE and the deletion of TLR9 may enhance disease activity [107]. Pharmacologic modulation of TLR signaling may offer new therapeutic targets for the treatment of SLE.

Several studies are in progress that may in the future identify viruses or bacteria as etiological agents in lupus. This will expand the therapeutic perspectives for SLE in the form of anti-infectious agents in the treatment of SLE and vaccinations, which could be used for the prevention of disease onset in SLE [106].

## Executive summary

**Several viruses have been identified as possible etiological agents in systemic lupus erythematosus**

- The implicated viruses with a major role include Epstein–Barr virus, retroviruses and parvovirus B19, and those playing a less significant role include transfusion-transmitted virus, cytomegalovirus and paramyxovirus.

**Infections may have a protective role in the development of autoimmune disease**

- Animal studies have suggested that *Toxoplasma gondii* may have a protective role in the development of autoimmune disease. In the serum of *T. gondii*-infected NZBW F1 mice, the pathogenic isotypes (IgG2a and IgG3) of the anti-DNA antibodies were significantly reduced. The level of antiself heat-shock protein 70 IgG autoantibody was significantly higher in the sera and there was downregulation of intracellular expression of IFN-γ and IL-10 in spleen cells of NZBW F1 mice infected with *T. gondii*. *Helicobacter pylori* may have a protective role in the development of autoimmune disease since seropositivity for *H. pylori* has been shown to decrease the risk for developing systemic lupus erythematosus (SLE). Epidemiological studies have suggested that infection with malaria can act as a protective factor in the development of SLE.

**Vaccinations**

- Vaccinations may have a dual role in the development of autoimmune diseases, providing protection by preventing infections, but contributing to autoimmune disease by repeated injections of vaccine with their adjuvant.
- There have been isolated case reports of flare-up of SLE secondary to the administration of Hepatitis B vaccine and influenza vaccine, but no change in serological markers with pneumococcal vaccine.

**Genetics in autoimmune diseases**

- Sle1 on chromosome 1 and Sle 3/5 on chromosome 7 are perhaps the most critical lupus susceptibility loci identified in mouse models of lupus. Some of the genetic loci that mediate autoimmunity, such as Sle3, may also produce enhanced antibacterial immunity.

**Interferons in autoimmune disease**

■ Increased IFN-α production coincides with disease flare and may be proinflammatory, but IFN-β and IFN-γ have a protective effect.

■ The production of IFN-α may reflect viral infection or viral reactivation.

**Conclusion**

■ Infection can predispose to pathogenesis of SLE, can induce a flare and can also mimic a flare of SLE.

■ Meticulous exclusion of infections by improved detection of infectious agents is important in patients with SLE since they can masquerade as exacerbations of SLE.

■ The use of immunosuppressants in the presence of infection can lead to disastrous consequences.

■ Innate immunity-related receptors and signaling molecules could become therapeutic targets for treatment of SLE.

■ We need to identify an infection that can induce lupus in animals, which will prove infection to be an etiological factor in pathogenesis of SLE.

■ Future studies are required for evaluation of anti-infectious agents in treatment of SLE and vaccinations as a preventive measure for the onset of SLE.

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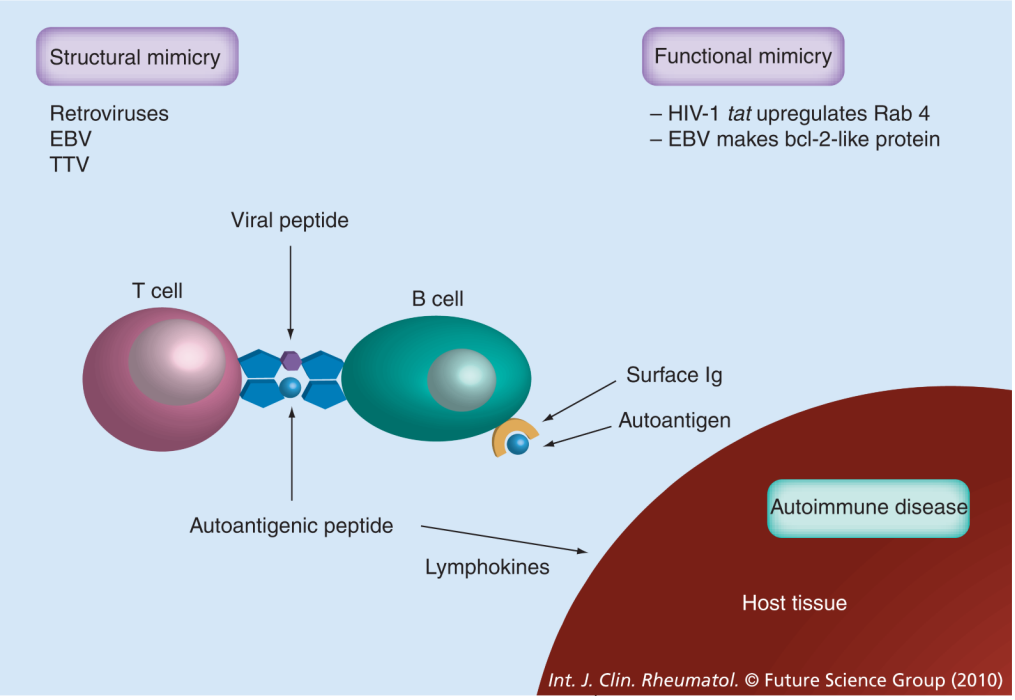



**Figure 1. Molecular mimicry in virus induced autoimmunity**

Viruses can influence adaptive immunity through molecular mimicry (i.e., homology between exogenous and endogenous epitopes). Peptide sequences common to a virus (e.g., EBV protein) and a target lupus autoantigen (e.g., Sm) can induce autoantibodies [2,3]. HIV *tat* upregulates Rab4 producing functional mimicry [4]. EBV protein regulates apoptosis by making a bcl-2-like protein, which is also an example of functional mimicry.

EBV: Epstein–Barr virus; TTV: Transfusion-transmitted virus.

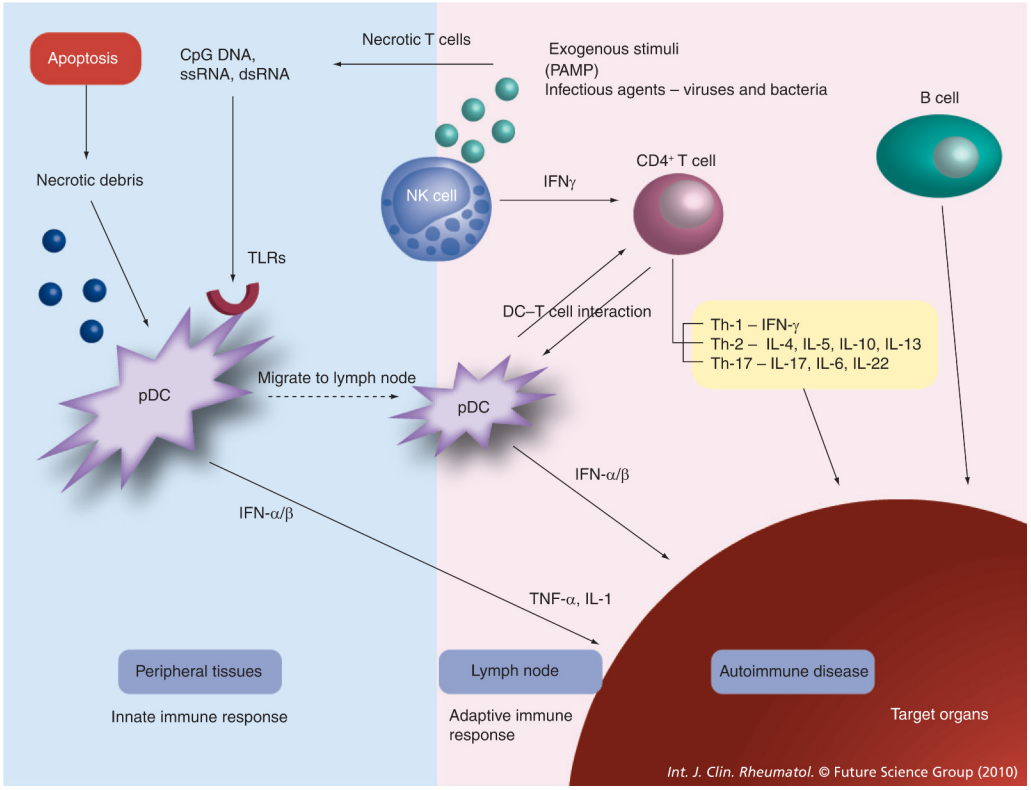



**Figure 2. Role of interferons in virus-induced autoimmune disease**

Cells recognize PAMPs using pathogen recognition receptors such as TLRs. Necrotic debris from the apoptotic pathways, bacterial lipopolysaccharide, viral RNA and viral DNA act on TLRs. Plasmacytoid dendritic cells produces type 1 IFNs, which are important in host defense against viruses, and there is overproduction of IFNs in systemic lupus erythematosus. TLRs activate plasmacytoid dendritic cells leading to the release of IFN-α/β. IFN-α results in the maturation of antigen presenting cells and augmented T-cell activation, including excessive helper activity. Natural killer cells produce significant amounts of cytokines, for example IFN-γ, that can influence the development of T cells [7].

IFN: Interferon; PAMP: Pathogen-associated molecular patterns; TLR: Toll-like receptor.

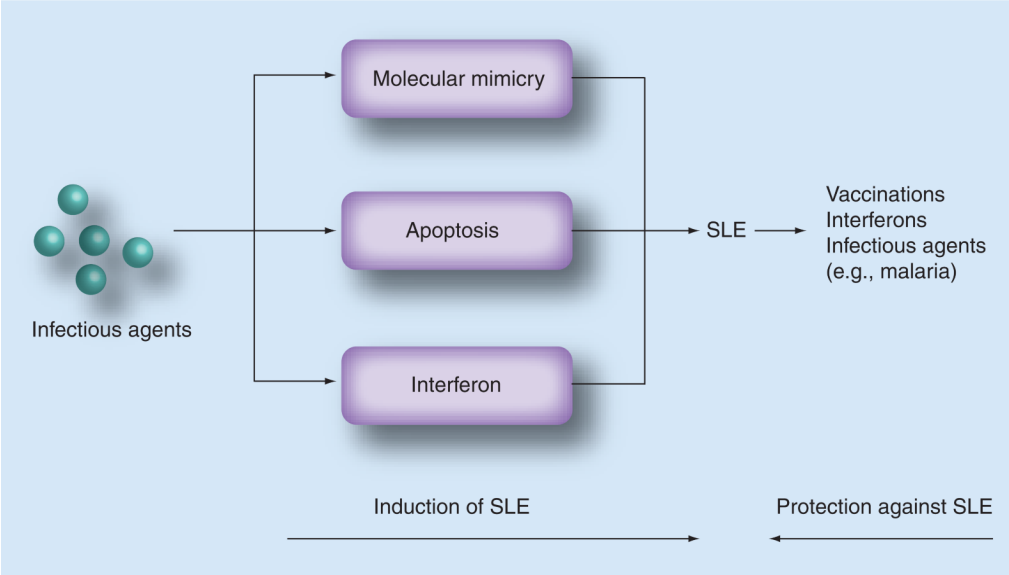



**Figure 3. Mechanisms by which infectious agents induce or protect against systemic lupus erythematosus**

Infectious agents lead to the pathogenesis of SLE through several mechanisms, including molecular mimicry, apoptosis (programmed cell death) and IFN-α. On the other hand, some infections, such as malaria, can act as protective agents. Vaccinations may act as protective agents by preventing some of the infections that can induce SLE. IFN-β and IFN-γ may also have a protective effect.

SLE: Systemic lupus erythematosus.

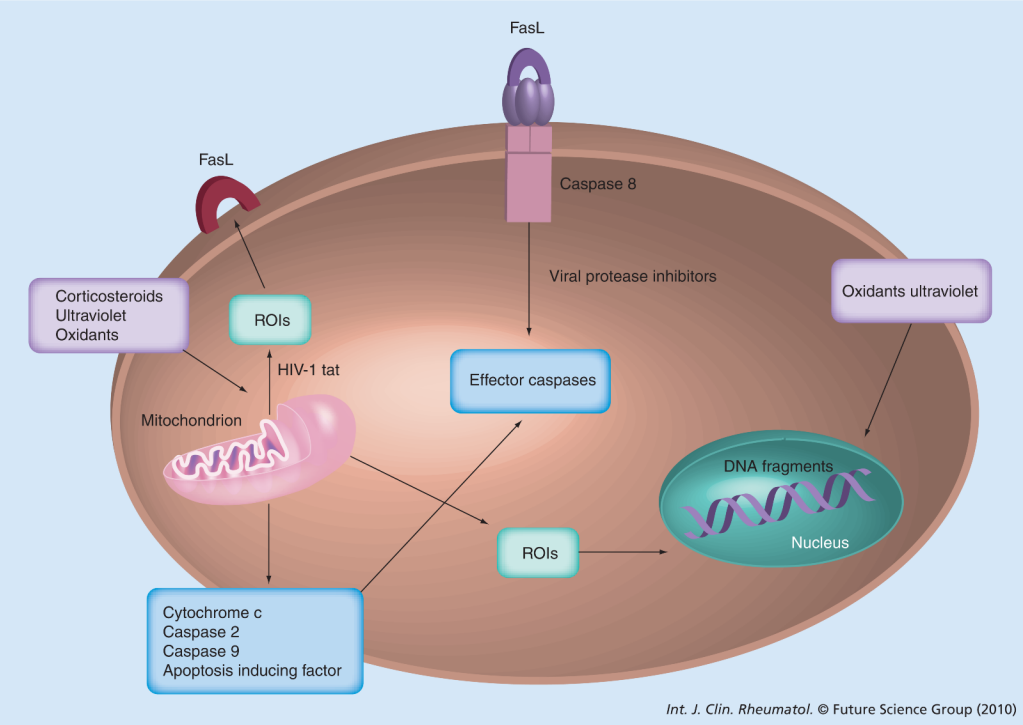



**Figure 4. Regulation of apoptosis pathways by viral proteins**

Oxidants, ultraviolet light and corticosteroids trigger apoptosis by damage of mitochondria, which in turn leads to caspase activating factors. This process is inhibited by viral bcl-2 and its homologs. Release of ROIs causes increased production of Fas ligand and DNA fragmentation. HIV-1 *tat* increases mitochondrial ROI production, thereby increasing apoptosis. The tat protein induces oxidative stress and increases surface expression of Fas ligand resulting in accelerated signaling through the Fas pathway.
ROI: Reactive oxygen intermediate.

## Table 1

Potential role of viruses in the pathogenesis of systemic lupus erythematosus.

| Virus | Evidence | Potential mechanism | Ref. |
|---|---|---|---|
| ***Herpes viruses*** | | | |
| EBV | Increased prevalence; Increased viral load | Molecular mimicry; Induction of lupus by EBV peptide; Bcl2-like protein – prevention of apoptosis | [1,16,17,33] [28,29,38–40] [5] |
| Cytomegalovirus | Increased prevalence | Induction of lupus | [14,20,21] |
| Parvovirus B19 | – | Molecular mimicry | [19] |
| Transfusion-transmitted virus | Increased prevalence | Molecular mimicry | [16] |
| ***Retroviruses*** | | | |
| HIV-1 | – | Molecular mimicry | [44] |
| HTLV-1 | – | Regulation of $CD4^+$ expression | [4,49,52] |
| ***RNA viruses*** | | | |
| Type C oncorna virus | Enhanced viral expression | – | [54,55] |
| Measles virus | Increased antibodies | Molecular mimicry | [56,57] |

EBV: Epstein–Barr virus; HTLV: Human T-lymphotropic virus.

**Table 2**

Cross-reactivity of viral antigens with self antigens.

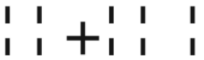
| Virus | Viral protein | Autoantigen |
|---|---|---|
| Epstein–Barr virus | EBNA-1 | Sm B/B′, Sm D1, Ro |
| | EBNA-2 | Sm B/B′, Sm D |
| Retrovirus | gagp24 | Sm B/B′, HRES-1/p28 |
| HRES-1 endogenous retrovirus | p28 | U1 70K |
| Cytomegalovirus | gB | U1 70K |

EBNA: Epstein–Barr virus nuclear antigen.

**Table 3**

Molecular mimicry between lupus-associated autoantigens and viral antigens.

| Viral/auto antigen | Amino acid sequence |
|---|---|
| ***EBV*** | |
| Sm B/B′ | PPPGMRPP |
| EBNA-1 | PPPGRRP |
| Sm D1 (95–119) | RRPGGRGRGRGR |
| EBNA-1 (35-58) | GPAGPRGGGRGRGR |
| ***TTV (homologies between HRES-1 p28 epitopes and viral sequences)*** | |
| HRES1 | PRHRHPQDPRSPGPA |
| TTVORF2A | AVLRAPQNPPPPGPQ |
| HRES1 | PRHRHPQDPRSPGPA |
| TTVORF2b | PRSRHPGGPGTPQIR |
| HRES1 | ATARRKRRWATRGPA |
| TTVORF1a | APWRRRRRWRTRRTR |

| Viral/auto antigen | Amino acid sequence |
|---|---|
| HRES1 | A T ARRKRRWATRGPA |
| |  |
| TTVORF1b | WWARRRRRWRRWKRR |
| ***CMV*** | |
| HRES-1 | PRHRHPQDPRSPGPA |
| Human herpes virus 5 |  |
| (CMV J1S) | VASRPL F P PRSPGPS |

*Position of identical residues (|) and position of functionally similar amino acids (+) are indicated* [52].

CMV: Cytomegalovirus; EBNA-1: Epstein–Barr virus nuclear antigen-1; TTV: Transfusion-transmitted virus.

## Table 4

Genetic factors predisposing to infections in systemic lupus erythematosus.

| Gene | Chromosome | SNP | Infection | Ref. |
|---|---|---|---|---|
| Mannose-binding lectin deficiency | 10 | Alleles B,C,D<br>Codons 54,57,52 | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa*<br>Community-acquired pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella*, *Mycoplasma pneumoniae*)<br>Invasive aspergillosis<br>Influenza A and B<br>Herpes simplex virus 1 and 2 | [14,15,75,76] |
| C1q deficiency | – | rs631090<br>rs292001<br>rs294183 | Recurrent bacterial infections<br>Otitis media<br>Meningitis<br>Pneumonia | [77] |
| *IRF5* | 7q32 | rs2004640 | Paramyxovirus (Newcastle disease virus)<br>Other viral infections | [79,80] |
| *STAT4* | 2 | rs7574865 | *Pseudomonas* | [86] |
| *ITGAM* | 16 | rs1143679 | – | [84] |