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Lupus and Epstein-Barr

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Abstract

Purpose of review—Systemic lupus erythematosus (SLE) is a heterogeneous human disease influenced by a complex interplay of necessary, but not individually sufficient, factors. Although many genetic and environmental factors are associated with SLE, this review will focus on the evolving evidence for key Epstein-Barr virus (EBV)-specific roles in SLE, focusing on new experimental studies published during 2009, 2010, and 2011.

Recent findings—SLE patients have a dysregulated immune response against EBV. EBV antigens exhibit structural molecular mimicry with common SLE antigens and functional molecular mimicry with critical immune-regulatory components. SLE patients, from a number of unique geographic regions, are shown to have higher rates of EBV seroconversion, especially against early EBV antigens, suggesting frequent viral reactivation. SLE patients also have increased EBV viral loads and impaired EBV-specific CD8⁺ cytotoxic T cells, with impaired cytokine responses to EBV in lupus patients. Irregular cytokine production in plasmacytoid dendritic cells and CD69⁺ CD4⁺ T cells after stimulation with EBV has also been demonstrated.

Summary—Recent advances demonstrate SLE-specific serologic responses, gene expression, viral load, T-cell responses, humoral fine specificity, and molecular mimicry with EBV, further supporting potential roles for EBV in lupus etiology and pathogenesis.

Keywords

environmental factors; Epstein-Barr virus; etiology; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus is a complex autoimmune disease with varied clinical presentations. Although advances are being made, a full understanding of the etiology and pathogenesis of this disorder does not yet exist. SLE has a genetic component and multiple genetic polymorphisms are associated and confirmed (reviewed in [1, 2]). However, genetic predisposition alone is likely insufficient for SLE development in the majority of patients. Ongoing work examines the sex bias and the hormonal influences in SLE [3]. Although a diverse list of medications, UV exposure, and infectious pathogens have been associated with SLE (reviewed in [4]), this review will focus on information regarding EBV and SLE published between 2009 and 2011.

Epstein-Barr Virus serology and lupus

New studies have focused on EBV seroconversion and SLE in a number of new geographic regions. In Turkey, sera from 198 SLE patients were tested for antibodies against various EBV proteins, including early antigen-D (EA/D), suggesting viral reactivation, Epstein-Barr nuclear antigen 1 (EBNA-1), the major latent protein of EBV infection, and the P18 peptide of the viral capsid antigen (VCA). SLE patients were found to have increased prevalence of antibodies directed against EA/D [54% compared with 17% of controls, odds ratio (OR)=5.77, 95% confidence interval (CI) 2.8–11.6 and P=0.001] [5,6]. SLE patients with anti-EA/D responses were older, had longer disease duration, were more likely to suffer from Raynaud's phenomenon, and have the presence of antiextractable nuclear antigen responses in their sera compared with anti-EA/D-negative SLE patients [5].

The seroprevalence of reactivity against a variety of pathogens was assessed in 120 SLE patients and 140 healthy controls from Columbia [7]. This group noted a significant difference in antibodies against EBV EA/D which were detected in 57% of SLE patient sera compared with 8% of controls (P<0.0001), whereas the overall rate of seroprevalence against EBNA-1 and EBV VCA were high in both patients and controls. Toxoplasma, EBV-EA/D, and EBV-VCA IgG levels were higher in SLE patients compared with controls; however, SLE patients were less likely to have antibodies directed against hepatitis B core antigen and rubella [7].

Using an antigen microarray, patient sera from Columbia and Israel were assessed for antibodies against pathogens and self-antigens to determine the patterns of antibody reactivity in SLE patients with acute lupus nephritis, SLE patients in renal remission, and SLE patients without evidence of renal disease compared to healthy controls [8]. This study detected a SLE antibody profile which persists across SLE patients, regardless of disease activity, and was comprised elevated levels of IgG antibodies directed against double-stranded DNA (dsDNA), single-stranded DNA, hyaluronic acid, and EBV antigens (sensitivity >93%, specificity >88%) [8].

Another study [9] from Taiwan focused on assessing the antibody responses against EBV in SLE patients compared to inflammatory myositis patients (polymyositis/dermatomyositis) who did or did not have nasopharyngeal carcinoma (NPC). Studying 94 SLE patients, 98 polymyositis/dermatomyositis patients and 370 healthy controls, 13% of polymyositis/dermatomyositis patients (compared with no SLE patients) had nasopharyngeal carcinoma. IgA EBNA-1 responses were detected in 30.6% of polymyositis/dermatomyositis patients, 31.9% of SLE patients, and only 4.1% of healthy controls (OR=10.44 and 11.12, both P<0.001). The IgA EBNA-1 responses, as well as EBV genome positivity, were higher in the patients with NPC compared with healthy controls or to SLE or polymyositis/dermatomyositis patients without NPC.

Finally, a follow-up murine study showed that EBNA-1 antibodies produced after immunization cross-react with dsDNA or with the spliceosomal protein, Sm [10,11]. EBNA-1 immunization leads to the generation of antibodies against dsDNA or Sm and dually reactive murine monoclonal antibodies (EBNA-1/dsDNA or EBNA-1/Sm) [10]. This study suggests that EBNA-1 carboxyl region antibodies may be most important for crossreactivity with dsDNA, whereas those against the amino terminal may cross-react with Sm [10]. These data further support the mechanisms of molecular mimicry between EBNA-1 and common lupus antigens, as previously described (reviewed in [11, *12, 13, *14, *15]).

Epstein-Barr Virus T-cell responses and lupus

SLE patients have decreased EBV-specific cytotoxic T-cell responses [17]. More recent studies have shown that SLE patients have a high frequency of EBV-specific CD69⁺CD4⁺ T cells producing IFN-gamma after EBV stimulation and a trend toward higher frequencies of EBV-specific CD69⁺CD4⁺ T cells producing tumor necrosis factor alpha [18]. Higher viral loads were associated with lower numbers of CD69⁺CD4⁺ T cells producing IFN-gamma [18]. The frequency of CD8⁺ EBV-specific cells in SLE tends to be slightly increased compared with controls (although not statistically significant, $P=0.07$) and their functional capacity to express IFN-gamma after stimulation with EBV is decreased [6]. A recent large study [19**] of 76 inactive and 42 active SLE patients demonstrated increased EBV viral loads compared with 29 age-matched and sex matched healthy controls ($P=0.003$ and $P=0.002$, respectively). Less EBV-specific CD8⁺ T cells secreted multiple cytokines in SLE patients regardless of disease activity compared with controls. These cells from SLE patients were also less cytotoxic. EBV-specific CD8⁺ T-cell impairment is a consequence of their programmed death-1 receptor upregulation. Longitudinal studies suggest that disease flares precede EBV reactivation and that CMV CD8⁺ responses are similar between SLE patients and healthy controls [19**].

Epstein-Barr Virus, Plasmacytoid Dendritic Cells and Interferon

One of the major studies published regarding EBV and SLE over the past 3 years provides direct evidence for a link between a mechanism of increased interferon expression by plasmacytoid dendritic cells and EBV [20**]. Increased interferon expression and increased interferon-inducible, gene-expression profiles have been described for over a decade in SLE. In addition, a number of lupus-associated genes are pivotal to interferon pathways. EBV is a DNA virus with small associated RNAs (EBERs) and as such could signal through TLR-9 and TLR-7 leading to increased interferon expression. This study shows that plasmacytoid dendritic cells, but not monocytoic dendritic cells, increased interferon production following stimulation by live EBV. This interferon-alpha expression by plasmacytoid dendritic cells is dependent on viral uptake, endosomal acidification, and TLR-9 engagement [20**]. Additional studies are needed to assess whether SLE patient plasmacytoid dendritic cells differentially respond to EBV with enhanced interferon production and upregulation of interferon-inducible genes. An editorial regarding this study outlines some of the directions to expand this work into human lupus investigation [21].

Epstein-Barr Virus epigenetics, microRNAs, molecular mimicry, and Lupus

Epigenetics has evolved over the past several years as an important pathway in lupus pathogenesis. SLE patients have hypomethylation and deacetylation changes leading to significant effects on T-cell functions [12]. Other viruses in addition to EBV have been associated with lupus autoimmunity, and this work has been recently reviewed [13*]. It has been suggested that some viruses may work together to lead to lupus autoimmunity and clinical disease in genetically predisposed hosts. Latent EBV infection of B cells can lead to transactivation of the HERV-K18 superantigen through human CR2 docking on primary B cells, thus leading to stimulation of a large number of cells and differentiation of EBV-infected B cells to memory cells (reviewed in [13*]). Expression of HERV-E4-1 is increased in SLE patients because of DNA hypomethylation (reviewed in [14]) and similar expression changes may be regulated by methylation status in EBV (reviewed in [15*]). Additional studies are underway to understand the methylation status and expression of latent viral proteins and their role in human lupus.

miRNAs are emerging as key regulators of gene expression, demonstrating roles to fine-tune the immune responses and activate negative feedback loops. Recent work shows that of 72

genes associated with either human or murine lupus, numerous insilico target sites for over 140 miRNAs are suggested [22]. As an example, MECP2 has over 50 miRNA target sites alone. On average each miRNA has target sites in nine lupus-associated genes [22]. miRNAs have been shown to be overexpressed in select SLE patient subsets [23,24], and further evaluation of the roles of EBV miRNA and EBV regulation of human miRNAs is warranted. Humoral molecular mimicry between early targets of lupus autoimmunity and regions of EBV latent proteins remain an underlying hypothesis for a role of EBV in SLE (reviewed in [16,25–28]). Another review of the parent-into-F1 model suggests alternate roles for EBV infection causing a loss of tolerance and lupus autoimmunity [29].

Clinical Associations and Case reports of Epstein-Barr Virus and Systemic Lupus Erythematosus

Although many studies over the past several decades have examined the potential roles for EBV in SLE cause and pathogenesis, three studies over the past 3 years have addressed previously understudied clinical aspects of this association. Ulf-Møller et al. [30*] examined the relationship between EBV-associated infectious mononucleosis and subsequent risk of SLE in a population-based cohort study. Large cohorts of Danish individuals [those tested serologically for infectious mononucleosis by heterophile antibody (1939–1989), hospitalized with infectious mononucleosis (1977–2007), and hospitalized with SLE (1977–2008)] were used to examine the risk of SLE development in these groups. Interestingly, individuals who were tested for infectious mononucleosis but found to be serologically negative (heterophile negative) had a significantly increased risk of SLE hospitalization years after the negative test (highest within 1–4 years of the negative heterophile test, SIR=6.6, 95% CI 3.3–13.2) but still significantly elevated for more than 25 years [30*]. This study demonstrates no association between the risk of having severe infectious mononucleosis (requiring hospitalization) and subsequent development of SLE requiring hospitalization; however, the majority of individuals infected with EBV never develop infectious mononucleosis. Additional evaluation of individuals who are referred for infectious mononucleosis work-up may be justified as some of their symptoms may be suggestive of early SLE autoimmunity in a subset of individuals.

For the first time, a study [31] evaluated the relationship between SLE clinical features and select EBV seroresponses. This study evaluated 120 SLE patients and 140 healthy individuals to assess whether any specific ACR SLE classification criteria were over-represented in individuals with a high concentration of antibodies against EBV-VCA (IgG and IgM), EBNA-1 (IgG), early antigen (EA-G), and heterophile IgM. Antibodies against EA-G were elevated in SLE patients with anti-Ro antibodies and cutaneous symptoms, whereas anti-VCA IgG responses were elevated in patients with polyarthritis. Heterophile IgM responses were elevated in anti-nRNP positive SLE patients. However, this study suggests that select clinical manifestations of SLE may correlate with specific EBV serologic responses and that future studies in large, multiethnic collections of patients may provide additional insights.

Finally, 88 cases of acute viral infections in adult SLE patients, including 23 new cases and reviews of the literature, were assessed for the influence of these infections on diagnosis, prognosis, and treatment of SLE. Twenty-five patients initially fulfilled ACR SLE classification criteria after acute viral infection (3 of 25 were after EBV infection, 15 of 25 occurred after parvovirus B19, and 6 of 25 occurred after CMV). In addition, 63 cases of acute viral infections in patients with established SLE were divided into three groups: those that mimic a lupus flare, those with organ-specific viral infections, and those with systemic infection. The most common infectious organism was CMV; however, EBV was found mimicking SLE flare once and in three cases of systemic infection (including two cases of

hemophagocytic syndrome). Two of the 12 viral infection-associated deaths were linked to EBV [32]. Over the past 3 years, a number of case reports have been published. These focus on unusual clinical presentations of EBV infections in SLE patients [33–37], including suspected EBV encephalitis [33], EBV-positive lymphoproliferative disorder [34], EBV large B-cell lymphoma [35], hemophagocytic syndrome and mesenteric vasculitis [36], and Kikuchi-Fujimoto disease [37]. Several case reports of EBV-associated hemophagocytic syndrome in SLE were reviewed previously [28,35,37].

Epstein-Barr Virus functional molecular mimics and gene expression profiles

Although humoral molecular mimics have been proposed and supported to play important roles in the initiation and perpetuation of SLE for a number of years (reviewed in [27,38]), new work over the past 3 years has focused on the potential functional molecular mimics in lupus autoimmunity and disease pathogenesis [39**,40,41]. Latent membrane protein-1 (LMP-1), a major latent protein of EBV which serves as an oncogenic mimic of CD40, has been detected in SLE patient PBMCs with baseline disease activity [16] or during times of disease flare [42]. Mice expressing a chimeric molecule of murine CD40 extracellular domain and the LMP-1 intracellular signaling regions induced enhanced autoreactivity, but did not develop fatal disease [43]. Bishop and colleagues have crossed these mice with a lupus-prone mouse strains, B6.Sle1 and B6.Sle 3. B6.Sle1 LMP-1 mice developed enlarged lymphoid organs with increased germinal centers, B cells, CD86⁺ B cells, and activated and memory T cells. These mice have elevated levels of antihistone antibodies and enhanced kidney pathology [39**]. TNFR-associated factor 6 (TRAF6) has also been shown to be critical for LMP-1-mediated B-cell activation [40]. This model suggests that LMP-1 expression, in a genetically predisposed host, may enhance autoreactivity and disease pathogenesis; however, additional human experiments are warranted.

Yoshida and colleagues explored the role of an EBV-inducible gene 3 (EBI3), a component in the IL27 heterodimer, in lupus pathogenesis through the use of an EBI3 knockout mouse on the MRL/lpr background. Mice lacking the WSX-1 subunit of the IL27R complex develop excessive pathological inflammation reminiscent of Th1 and Th2 responses, suggesting that the IL27 axis may have broad anti-inflammatory functions. The EBI3 knockout in the MRL/lpr model leads to the transition from diffuse proliferative glomerulonephritis to membranous glomerulonephritis and IgG1 glomerular depositions. T cells from these mice display reduced IFN-gamma production and elevated IL4 expression [41]. However, the role of EBI3 in human lupus is relatively unexplored.

Another study [16], which has been published in the past 3 years, explored the EBV gene-expression profiles in SLE patients compared to healthy controls. PBMCs from 10 unique SLE patients and 10 matched healthy controls were infected with EBV and expression levels of eight EBV genes were compared. SLE patients had elevated expression levels of mRNA for BLLF1 (3.2-fold, $P<0.004$), LMP-2 (1.7-fold, $P<0.008$), EBNA-1 (1.7-fold, $P<0.01$), and cRF1 (1.7-fold ($P<0.02$). The frequency of LMP-1 gene expression was greater in SLE patients (44% compared with 10%, $P<0.05$). PBMCs from SLE patients had greater expression of select latent and lytic genes after EBV infection, suggesting that SLE patients may have dysregulated control of EBV infection. Additional studies are underway to explore the mechanisms and potential consequences of this dysregulated control. Several mechanisms have been proposed, in which EBV latency-associated viral gene products may play critical roles in systemic autoimmunity [15*,26].

Conclusion

EBV has been identified as an environmental factor with multiple potential roles in SLE etiology and pathogenesis. SLE patients have increased seroprevalence against early antigens, suggesting more frequent viral reactivation and increased viral loads. SLE patients also have decreased functionality of EBV-specific cytotoxic T cells and plasmacytoid dendritic cells can produce increased interferon after EBV infection. Additional work will be needed to fully decipher how EBV may modulate the immune system in human SLE.

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References

1. Sestak AL, Fürnrohr BG, Harley JB, Merrill JT, et al. The genetics of systemic lupus erythematosus and implications for targeted therapy. *Ann Rheum Dis*. 2011; 70:i37–i43. [PubMed: 21339217]
2. Deng Y, Tsao BP. Genetic susceptibility to systemic lupus erythematosus in the genomic era. *Nat Rev Rheumatol*. 2010; 6:683–692. [PubMed: 21060334]
3. Lockshin MD. Sex differences in autoimmune disease. *Lupus*. 2006; 15:753–756. [PubMed: 17153846]
4. Sarzi-Puttini P, Atzeni F, Iaccarino L, Doria A. Environment and systemic lupus erythematosus: an overview. *Autoimmunity*. 2005; 38:465–472. [PubMed: 16373251]
5. Esen BA, Yilmaz G, Uzun S, Ozdamar M, et al. Serologic response to Epstein-Barr virus antigens in patients with systemic lupus erythematosus: a controlled study. *Rheumatol Int*. 2012; 32:79–83. [PubMed: 20661740]
6. Berner BR, Tary-Lehmann M, Yonkers NL, Askari AD, et al. Phenotypic and functional analysis of EBV-specific memory CD8 cells in SLE. *Cell Immunol*. 2005; 235:29–38. [PubMed: 16181618]
7. Berkun Y, Zandman-Goddard G, Barzilai O, Boaz M, et al. Infectious antibodies in systemic lupus erythematosus patients. *Lupus*. 2009; 18:1129–1135. [PubMed: 19880558]
8. Fattal I, Shental N, Mevorach D, Anaya JM, et al. An antibody profile of systemic lupus erythematosus detected by antigen microarray. *Immunology*. 2010; 130:337–343. [PubMed: 20201986]
9. Chen DY, Chen YM, Lan JL, Chen HH, et al. Polymyositis/dermatomyositis and nasopharyngeal carcinoma: the Epstein-Barr virus connection? *J Clin Virol*. 2010; 49:290–295. [PubMed: 20934910]
10. Yadav P, Tran H, Ebegbe R, Gottlieb P, et al. Antibodies elicited in response to EBNA-1 may cross-react with dsDNA. *PLoS One*. 2011; 6:e14488. [PubMed: 21245919]
11. Sundar K, Jacques S, Gottlieb P, Villars R, et al. Expression of the Epstein-Barr virus nuclear antigen-1 (EBNA-1) in the mouse can elicit the production of anti-dsDNA and anti-Sm antibodies. *J Autoimmun*. 2004; 23:127–140. [PubMed: 15324931]
12. Sawalha AH. Epigenetics and T-cell immunity. *Autoimmunity*. 2008; 41:245–252. [PubMed: 18432405]

- 13*. Francis L, Perl A. Infection in systemic lupus erythematosus: friend or foe? *Int J Clin Rheumatol*. 2010; 5:59–74. A nice recent review of viral-induced autoimmunity in susceptible individuals. [PubMed: 20209114]
14. Blank M, Shoenfeld Y, Perl A. Cross-talk of the environment with the host genome and the immune system through endogenous retroviruses in systemic lupus erythematosus. *Lupus*. 2009; 18:1136–1143. [PubMed: 19880559]
- 15*. Niller, HH.; Wolf, H.; Ay, E.; Minarovits, J. Epigenetic dysregulation of Epstein-Barr virus latency and development of autoimmune disease. In: Ballestar, E., editor. *Advances in experimental medicine and biology: epigenetic contributions in autoimmune disease*. New York, NY: Springer US; 2011. p. 82-102. This work explores the potential epigenetic-mediated mechanisms of EBV infection and the development of autoimmune disorders, including postulated epigenetic alterations or immune cell gene expression and how they may influence the immune system
16. Poole BD, Templeton AK, Guthridge JM, Brown EJ, et al. Aberrant Epstein-Barr viral infection in systemic lupus erythematosus. *Autoimmun Rev*. 2009; 8:337–342. [PubMed: 19167523]
17. Tsokos GC, Magrath IT, Balow JE. Epstein-Barr virus induces normal B cell responses but defective suppressor T cell responses in patients with systemic lupus erythematosus. *J Immunol*. 1983; 131:1797–1801. [PubMed: 6311898]
18. Kang I, Quan T, Nolasco H, Park SH, et al. Defective control of latent Epstein-Barr virus infection in systemic lupus erythematosus. *J Immunol*. 2004; 172:1287–1294. [PubMed: 14707107]
- 19**. Larsen M, Sauce D, Deback C, Arnaud L, et al. Exhausted cytotoxic control of Epstein-Barr virus in human lupus. *PLoS Pathog*. 2011; 7:e1002328. A study examining a large cohort of SLE patients compared to controls. In SLE patients, EBV-specific CD8⁺ T cells are impaired in their cytokine production and cytotoxic potential compared with healthy controls. [PubMed: 22028659]
- 20**. Quan TE, Roman RM, Rudenga BJ, Holers VM, et al. Epstein-Barr virus promotes interferon-alpha production by plasmacytoid dendritic cells. *Arthritis Rheum*. 2010; 62:1693–1701. This study examined EBV interaction with human dendritic cells and shows that plasmacytoid dendritic cells increase IFN α in response to EBV stimulation. [PubMed: 20178121]
21. Harley JB, James JA. Everyone comes from somewhere: systemic lupus erythematosus and Epstein-Barr virus induction of host interferon and humoral anti-Epstein-Barr nuclear antigen 1 immunity. *Arthritis Rheum*. 2010; 62:1571–1575. [PubMed: 20178135]
22. Vinuesa CG, Rigby RJ, Yu D. Logic and extent of miRNA-mediated control of autoimmune gene expression. *Int Rev Immunol*. 2009; 28:112–138. [PubMed: 19811318]
23. Te JL, Dozmorov IM, Guthridge JM, Nguyen KL, et al. Identification of unique microRNA signature associated with lupus nephritis. *PLoS One*. 2010; 5:e10344. [PubMed: 20485490]
24. Stagakis E, Bertsias G, Verginis P, Nakou M, et al. Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of PDCD4 expression. *Ann Rheum Dis*. 2011; 70:1496–1506. [PubMed: 21602271]
25. Agmon-Levin N, Blank M, Paz Z, Shoenfeld Y. Molecular mimicry in systemic lupus erythematosus. *Lupus*. 2009; 18:1181–1185. [PubMed: 19880565]
26. Niller HH, Wolf H, Minarovits J. Regulation and dysregulation of Epstein-Barr virus latency: Implications for the development of autoimmune diseases. *Autoimmunity*. 2008; 41:298–328. [PubMed: 18432410]
27. Poole BD, Scofield RH, Harley JB, James JA. Epstein-Barr virus and molecular mimicry in systemic lupus erythematosus. *Autoimmunity*. 2006; 39:63–70. [PubMed: 16455583]
28. James JA, Harley JB, Scofield RH. Epstein-Barr virus and systemic lupus erythematosus. *Curr Opin Rheumatol*. 2006; 18:462–467. [PubMed: 16896283]
29. Via CS. Implications of the parent-into-F1 model for human lupus pathogenesis: roles for cytotoxic T lymphocytes and viral pathogens. *Curr Opin Rheumatol*. 2010; 22:493–498. 10.1097/BOR.0b013e32833b0174 [PubMed: 20485174]
- 30*. Ulff-Moller CJ, Nielsen NM, Rostgaard K, Hjalgrim H, et al. Epstein-Barr virus associated infectious mononucleosis and risk of systemic lupus erythematosus. *Rheumatology (Oxford)*.

2010; 49:1706–1712. A longitudinal study that showed that EBV-associated infectious mononucleosis is not a risk factor for SLE; however, increased SLE risk that remained elevated for more than 25 years was found in individuals with a negative heterophile antibody test. [PubMed: 20488925]

31. Zandman-Goddard G, Berkun Y, Barzilai O, Boaz M, et al. Exposure to Epstein-Barr virus infection is associated with mild systemic lupus erythematosus disease. *Ann N Y Acad Sci.* 2009; 1173:658–663. [PubMed: 19758212]
32. Ramos-Casals M, Cuadrado MJ, Alba P, Sanna G, et al. Clinical guidelines for the management of acute viral infections in patients with systemic lupus erythematosus. *Minerva Med.* 2009; 100:437–446. [PubMed: 20010479]
33. Hongbo C, Hongzhen M, Lingzhi H, Maosheng X, et al. Secondary neuropsychiatric manifestations caused by Epstein-Barr virus encephalitis in a new onset systemic lupus erythematosus patient. *Rheumatol Int.* 2011
34. Tsukamoto N, Handa H, Yokohama A, Mitsui T, et al. Long-term follow-up of EBV-positive lymphoproliferative disorders in a patient with systemic lupus erythematosus. *Med Mol Morphol.* 2011; 44:237–241. [PubMed: 22179188]
35. Tsang HH, Trendell-Smith NJ, Wu AK, Mok MY. Diffuse large B-cell lymphoma of the central nervous system in mycophenolate mofetil-treated patients with systemic lupus erythematosus. *Lupus.* 2010; 19:330–333. [PubMed: 19897521]
36. Moon SJ, Kwok SK, Park KS, Kim WU, et al. Simultaneous presentation of hemophagocytic syndrome and mesenteric vasculitis in a patient with systemic lupus erythematosus. *Mod Rheumatol.* 2011; 21:330–333. [PubMed: 21229376]
37. Gionanlis L, Katsounaros M, Bamihas G, Frigidis S, et al. Kikuchi-Fujimoto disease and systemic lupus erythematosus: the EBV connection? *Ren Fail.* 2009; 31:144–148. [PubMed: 19212912]
38. Harley JB, Harley ITW, Guthridge JM, James JA. The curiously suspicious: a role for Epstein-Barr virus in lupus. *Lupus.* 2006; 15:768–777. [PubMed: 17153849]
- 39**. Peters AL, Stunz LL, Meyerholz DK, Mohan C, et al. Latent membrane protein 1, the EBV-encoded oncogenic mimic of CD40, accelerates autoimmunity in B6.Sle1 mice. *J Immunol.* 2010; 185:4053–4062. Latent membrane protein 1 is a functional mimic of CD40 and when expressed in mice with select autoimmune-prone loci can accelerate autoantibody production and change to a more severe clinical phenotype. [PubMed: 20810985]
40. Arcipowski KM, Stunz LL, Graham JP, Kraus ZJ, et al. Molecular mechanisms of TNFR-associated factor 6 (TRAF6) utilization by the oncogenic viral mimic of CD40, latent membrane protein 1 (LMP-1). *J Biol Chem.* 2011; 286:9948–9955. [PubMed: 21262968]
41. Igawa T, Nakashima H, Sadanaga A, Masutani K, et al. Deficiency in EBV induced gene 3 (EBI3) in MRL/lpr mice results in pathological alteration of autoimmune glomerulonephritis and sialadenitis. *Mod Rheumatol.* 2009; 19:33–41. [PubMed: 18779924]
42. Gross AJ, Hochberg D, Rand WM, Thorley-Lawson DA. EBV and systemic lupus erythematosus: a new perspective. *J Immunol.* 2005; 174:6599–6607. [PubMed: 15905498]
43. Stunz LL, Busch LK, Munroe ME, Sigmund CD, et al. Expression of the cytoplasmic tail of LMP1 in mice induces hyperactivation of B lymphocytes and disordered lymphoid architecture. *Immunity.* 2004; 21:255–266. [PubMed: 15308105]

Key Points

- SLE patients have increased frequency of antibodies against EBV early antigens and higher titers of antibodies against several common EBV antigens.
- EBV antigens exhibit structural molecular mimicry with common SLE antigens.
- Select EBV proteins are functional molecular mimics of the human immune system which can lead to impaired apoptosis and increased B cell signaling.
- SLE patients have impaired CD8⁺ cytotoxic T cells, and irregular cytokine production in plasmacytoid dendritic cells and CD69⁺ CD4⁺ T cells in response to EBV.
- SLE patients, regardless of disease activity, have increased anti-dsDNA, anti-ssDNA, anti-hyaluronic acid, and anti-EBV antigen antibodies. Some EBV protein-specific antibodies associate with clinical features of SLE.