CZYŻ, Witold, CHUNCIA-ILCZEKO, Marta, WÓJCIKIEWICZ, Michalina, ARCZEWSKI, Filip, DZIEDZIC, Karol, KULBACKA, Julia, WOJSZCZYK, Maciej, ZYS, Damian, PASEK, Piotr and RYNIECKA, Julia. Epstein-Barr virus (EBV) and systemic lupus erythematosus (SLE) association in serological studies. Quality in Sport. 2025;37:57143. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57143
https://apcz.umk.pl/QS/article/view/57143

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.12.2024. Revised: 03.01.2025. Accepted: 03.01.2025 Published: 10.01.2025.

Epstein - Barr virus (EBV) and systemic lupus erythematosus (SLE) association in serological studies

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Abstract
Over the past 50 years, a substantial body of research revealed an association between Epstein-Barr virus (EBV), and various aspects of EBV infection, with multiple autoimmune diseases. Growing evidence points to EBV as a potential co-factor in systemic lupus erythematosus (SLE) and several mechanisms have been proposed to explain this relationship, however there is as yet no conclusive proof of causality. This literature review constitutes an introduction into the subject and attempts to outline the findings on the EBV-SLE connection, focusing mostly on the evidence provided by serological studies.
Purpose of work: This literature review aims to provide general overview of research investigating the association between the Epstein-Barr virus and systemic lupus erythematosus, with primary focus on serological studies.
Materials and methods: Literature search and review.

Keywords: "Epstein-Barr", "EBV", "systemic lupus erythematosus", "SLE", "EBV seroprevalence", "viral load", "autoimmunity"

Introduction

Infectious agents have long been suspected to act as catalysts for autoimmunity, including some complex, multifactorial autoimmune diseases (1–7). Research of the past century implicated multiple viruses in rheumatic disease etiology (8–10). One of the more extensively studied case is the involvement of Epstein-Barr Virus (EBV) in systemic lupus erythematosus (SLE) (11–13). Like many other connective tissue or systemic autoimmune rheumatic diseases (SARDs), SLE is characterized by persistent inflammation as well as an impaired immune response, typically with presence of autoantibodies like antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anti-Smith, anti-RNP and anti-phospholipid antibodies (8,14–16). Polyclonal B cell activation is also observed, together with an abnormal T cell response (17). SLE is a chronic disorder with a variable presentation and most often a relapsing-remitting course of activity. It affects multiple organs, leading to significant morbidity and mortality (18). Majority of patients are female (ca. 90%) and adult (19). Despite decades of research the exact causal mechanism of SLE has not been elucidated and no cure is available. However, associations with multiple factors have been proposed, such as genetic predispositions, ultraviolet light, viruses, bacteria, alcohol, tobacco and vitamin D deficiency among others (19–22). Hormonal, estrogen-driven, upregulation of B-cell proliferation and antibody synthesis may be another factor of interest, as EBV is known to infect naïve B-cells, mimicking, in many ways, the innate mechanism of B-cell activation, where it establishes latency (21). EBV, member of the Herpesvirus family, has been linked to lymphoproliferative disorders, tumors, and autoimmune diseases (23) in which it most likely acts as a catalyst on account of the oncogenic properties of some of its proteins (most notably LMP1), whose primary role is to interfere with natural molecular pathways in order to ensure the life-long persistence of the virus once its establishes latency in its host (24–28). EBV does so by infecting naive B-cells during primary infection (most often in the oropharnyx) mimicking antigen-driven activation, and altering a natural B-cell development and maturation process into resting memory B-cells (26,27).

It utilizes a set of latency proteins and transcripts for that purpose. During latency, EBV occasionally reactivates and replicates, also lytically, in a small fraction of infected B-cells (26,27). About 90-95% people carry EBV and co-infection with multiple strains and Herpesviruses also occurs (27,29,30). Infection occurs most often in childhood and is asymptomatic, but sometimes manifests as Infectious Mononucleosis (IM), especially in adolescence (27,31–33). EBV infection and ensuing B-cell proliferation elicits immune response from host's cytotoxic T-cells, 0.1% to 3% of which (CD8+ and CD4+ T-cells) may be EBV - specific in people with a history of EBV infection (28). Higher anti-EBV antibody levels have been observed in some EBV-related tumours (28).

Since the first reports in the scientific literature, a significant body of research has confirmed the existence of a potentially causal association between Epstein-Barr Virus (EBV) infection and subsequent development of Systemic Lupus Erythomatosus (SLE). The exact nature of this complex association has remained elusive, although existing evidence indicates an underlying role of both genetic susceptibility and environmental mechanisms. This review aims to provide a general introduction into the subject as well as an overview of the literature, with a specific emphasis on serological research of EBV DNA load as well as anti-EBV antibodies in SLE patients.

Early Research

Current evidence in favor of EBV involvement in SLE can be generally divided into two categories. The first one encompasses mostly serological studies. Historically, these studies provided most evidence linking EBV to SLE by showing either higher viral load, higher seroprevalence and anti-EBV antibody levels, or abnormal EBV gene expression and EBV-specific T-cell activity in SLE patients (34). The other category can broadly be described as experimental/functional studies, mostly looking at potential mechanisms by which EBV proceeds from primary infection into long term latency, alters immunity and potentially elicits an autoimmune response in host. Such studies focus mainly on viral protein or nucleic acid properties, or their effect on the immune system, including interactions with human molecular pathways.

With the advent and refinement of immunofluorescent techniques, in the 1950s and 1960s, new research demonstrated presence of autoantibodies as well as pathogen-directed antibodies in a range of autoimmune conditions, providing new means of studying their role in disease etiology (35). Initial findings implicating EBV in autoimmune disease etiology were mostly based on patient high seroconversion rates as detected by precipitin tests and indirect immunofluorescent assays using SLE patient sera and EBV-infected cell-lines like EB-3, HRIK and Jijoye (11). The sample size was limited in those early studies, without usually exceeding a hundred individuals (12,16).

It is widely accepted that the first work indicating a possible link between high anti-EBV antibody levels and SLE was a 1969 study of pediatric lymphoma patients in Brazil using precipitin tests (11,36). This observation was first brought to the attention of the scientific community by Alfred Evans and co-researchers (1971 and 1973), who also showed elevated anti-EBV antibody titers in SLE patients by immunofluorescent assays, and proposed a working hypothesis for EBV involvement in SLE etiology (37–40).

Evans et al were the first to note that high EBV-specific antibody level was independent of the ANA antibodies and total serum IgG levels.

Nonetheless, those early findings subsequently failed to be replicated by other teams. Three studies: by Klippel et al. 1973, Phillips et al. 1973, and Stevens et al. 1972, tested sera from SLE patients for anti-EBV antibodies by indirect immunofluorescence, and found no statistical difference between cases and controls in seropositivity and antibody titers (41–43). A fourth, early case-control study (70 SLE patients and 70 healthy controls), also failed to confirm higher anti-EBV antibody seroprevalence in SLE patients, and although it showed increased mean anti-EBV titers among cases, the association strength was considered not significant enough (44).

This state of research was recapitulated by Evans in 1974 who attempted to explain the discrepancies by technical factors or variation in SLE activity at the time of testing (45). Although the subject was further explored by various researchers over the next two decades, there was no clear scientific consensus as to the EBV involvement and its role in SLE until the subject gained renewed interest in the mid - 90s (11,46). One important caveat to the early immunofluorescent studies of seroprevalence was their limited sensitivity, especially in the ability to effectively separate the ANA antibodies from the anti-EBV antibodies (11).

In 1979, a study demonstrated that antibodies directed against EBV capsid antigen (EB-VCA; VCA) are significantly higher among SLE patients than patients with active infectious mononucleosis (47). Both groups numbered however only 22 individuals, and patients with an active primary EBV infection may not be appropriate controls (due to the fact an IgM response is initially mounted during primary infection, and IgG follows) (11,47). At the same time, Catalano et al. (1979) using an immunodiffusion assay with lysates of EBV-infected lymphoid cells, found no difference in anti-EBV anti-RANA (rheumatoid arthritis nuclear antigen, which is closely related to EBV EBNA-1 antigen) antibody levels between 21 SLE patients and 48 controls (48). The authors concluded their findings support the earlier work by Stevens et al. (1973).

However, by 1988 the EBV-SLE association received further support. A case - control study by Kitagawa et al. (1988) used EBV - infected cell lines and Western blots, and compared blood sera of 65 SLE patients to 66 age- and sex-matched healthy controls, confirming significant association for three antibodies directed against EBV nuclear antigens 1, 2 and 3 (EBNA-1, 2, and 3) (49). Also, Origgi et al. (1988) using an indirect immunofluorescent assay, found higher levels of anti-VCA antibodies in 18 SLE patients vs 19 controls, while Yokochi et al. (1989) showed increased titers of anti-Membrane Antigen antibodies in SLE patient sera by flow cytometry (50).

In addition to those quantitative studies, by using EBV-infected cell line lysates, patient sera and Western blots, another group of authors showed a difference in anti-EBV antibody affinity between SLE patients and normal, EBV - infected controls, which potentially suggested abnormal immune response to viral infection in the former (51). This general conclusion was further supported by others (52). Also, case studies were published, pointing to a temporal association between IM, representing an active EBV infection with high viraemia, and early onset SLE (53,54).

The James et al. (1997&2001) studies

The link between SLE and EBV once again received much interest thanks to a study by James et al. (1997) (46). The authors attempted to circumvent three crucial limitations of early serologic studies - small sample size, ubiquitous character of EBV infection in the adult population (~90-95%) and the relatively low sensitivity of indirect immunoassays (estimated to be below 90%) (11,46). The authors used ELISA assays and confirmed seroconversion against EBV VCA in 116 of 117 young (aged 4 to 19) SLE patients (99%), compared to 107 of 153 (70%) matched controls (46). This effect was also not related to the total IgG level nor ANA and anti-spliceosomal antibody cross-reactivity. Additionally, 32 of cases were tested for EBV DNA by PCR, and all were confirmed positive in contrast to 23 out of 32 controls.

This was further replicated in the adult population, when James et al. (2001) looked at 196 SLE patients and 382 controls (55). Out of 196 cases, 195 were positive for anti-EBV antibodies (99.5%), versus 360 out 382 controls (94.2%), suggestive of EBV possibly playing a specific role in SLE etiology. Additionally, anti-VCA IgG antibody (indicative of a past EBV infection with active replication) titers were higher in SLE patients. Also, contemporarily, another group showed anti-EBNA2 IgG present in sera of some SLE patients, but not in healthy controls (HCs) (56).

These studies revived the theory of EBV being a causal factor of SLE and introduced new important concepts to explain its role in disease etiology: auto - aggression through molecular mimicry and epitope spreading in genetically predisposed individuals with increased activation and de - regulation of infected B-cells (12,57). The authors suggested that a peptide motif of the viral EBNA1 protein, PPPGRRP, may mimic a native antigen with repetitive proline sequences, PPPGMRPP, derived from the core spliceosomal protein of the major spliceosome Small Nuclear Ribonucleoprotein Polypeptides B/B' (SmB/B'), eliciting an autoimmune response possibly leading to high anti-dsDNA and anti-Sm antibody synthesis (11,16,46,58). This hypothesis received some support from animal model studies, in which autoimmunity developed acter immunization with EBNA1 (57,59,60).

Studies of seroprevalence, antibody levels and viral load - recent research

1990s and especially the 21st century brought new research and to an extent reaffirmed the findings of some previous studies, while also providing new insights. However, conflicting evidence and a considerable ambiguity emerged as to whether and which antibodies are overrepresented in SLE patients, and what their significance for disease etiology is. The next generation of studies relied mainly on ELISA assays and followed mostly two major lines of investigation looking at differences in EBV-specific antibodies and EBV DNA load.

EBV viral load

Studies focusing on the amount of the virus present in peripheral blood of SLE patients yielded more consistent results overall. An early study by Tsai et al. (1995) used DNA probes and PCR finding no viral DNA in 21 childhood - onset systemic lupus erythematosus (SLE) patients and 20 age-matched controls, except for a single patient (61). Similarly, another study Lau et al. (1998) found no evidence for active EBV replication nor statistical difference in EBV DNA quantity between 34 SLE patients and matched controls, using a PCR method (62).

Among the cases, 11 were newly diagnosed while 18 had active disease, as indicated by a score on the SLE Disease Activity Index (SLEDAI). Also, Katz et al. (2001) - found no significant viral DNA in sera from 11 out of 13 SLE adolescent patients (63). The authors stated that their findings differ from those of James et al. and concluded that serologic findings typical of SLE and suggestive of EBV infection may in fact be a by-product of SLE itself, rather than intense viral infection, whether primary or secondary, and replication. They also pointed to limitations of the James et al. (1997) study.

However, as far as the adult population was concerned, James et al received further support from Kang et al. (2004), who, by using quantitative RT-PCR found a ~40-fold increase in EBV viral loads in peripheral blood mononuclear cells (PBMCs) of 22 SLE patients when compared with 21 healthy controls as well as a higher frequency of EBV-specific CD69+ CD4+ T cells producing IFN-gamma (64). The elevation of EBV load, most likely in infected B-cells, was not related to the overall quantity of B cells, immunosuppressive therapy or disease activity. The authors also suggested downregulation and abnormal CD8+ T cell response (in contrast to $CD4^+$ T cell response) as a contributing factor towards more active lytic replication and higher EBV load, indicating that SLE patients do not control EBV latency as effectively as healthy controls due to abnormal T-cell response. Of note, a similar phenomenon was noted in patients with rheumatoid arthritis, therefore, as the authors conclude, it may be not SLE specific (64).

Another study, which yielded comparable results, quantified EBV viral DNA by RT-PCR, finding similar prevalence, but 15 fold increase in PBMCs from 24 SLE cases vs 29 controls (65). Once again, it was suggested that EBV more frequently enters active lytic cycle with high viral replication in patients with SLE, possibly due to inadequate control of the latent infection. The authors also speculated that higher numbers of infected B-cells seen in patients may promote auto-aggression. PCR and Southern Blot conducted on mouthwash samples (66 SLE patients and 63 controls) detected viral DNA in 98.5% cases and 94% controls. The latter finding replicated a finding by Strauch et al. (1974) and was also in concordance with blood serum results of James et al. (2001) (55,66)

Gross et al. (2005) first attempted to distinguish between virion-bound EBV DNA in lytical replication and viral genomes in latently EBV - infected B-cells only (containing usually 2-5 genomes per cell) (67). They attempted to quantify the latter by flow-cytometry coupled with a limiting dilution and a DNA PCR assay, finding higher viral load in 35 SLE patients as compared to 44 HCs. The authors suggested that higher viral load was associated with high amounts of latently infected B-cells. They also showed an association to SLE flares, and stated that the higher frequency of infected PMBCs was independent of immunosuppressive therapy. The study also found increased expression of BZLF1, LMP1 and LMP2a in SLE patient sera. EBNA1 was quantified in a single patient. No expression was present in healthy controls, except for LMP2a.

Subsequently, four larger studies followed up on the issue of viral DNA quantity in peripheral blood cells of SLE patients and confirmed the association. Using a PCR and Southern blot approach, Yu et al. (2005) detected EBV DNA more frequently and showed higher EBV viral load in PBMCs from 87 SLE patients, in comparison to 174 matched controls (68).

Also, Lu et al. (2007) detected EBV DNA more frequently (42% vs 3%) and confirmed higher viral loads in blood sera from 93 Taiwanese SLE patients vs 370 controls by RT-qPCR (69).

Larsen et al. (2011), found and confirmed higher seroprevalence (by ELISA) as well as higher viral load in PBMCs from 118 SLE vs 29 controls (70). No difference was observed between patients with active and inactive SLE (57,70). In addition, the authors provided evidence for impaired cytotoxicity and cytokine secretion by the EBV-specific CD8+ T cells of SLE patients, when compared to controls.

The latter findings from this study supported an earlier work by Berner et al. (2005) and were later corroborated by Draborg et al. (2014) - who also found SLE patients exhibit decreased amounts activated (CD69) T-cells upon ex vivo stimulation with EBV antigens, and decreased interferon-γ secretion (71,72). In an extension of the 2014 study, Draborg et al. (2016) showed reduction in concentrations of 7 out of 14 tested cytokines upon stimulation with EBNA1 and EBV early antigen (EA/D; EA) in SLE patient whole blood samples (73,74). Once again, these studies suggest a deficiency in EBV infection control by EBV specific cytotoxic T-cells in SLE.

More recently, by using RT-PCR, Piroozmand et al. (2017), found EBV DNA in buffy coats prepared from whole blood samples in 67.5% out of a total of 40 SLE patients, with significantly higher viral loads in patients with active disease (20 out of 40) (75).

In contrast, Broccolo et al. 2013 used a calibrated quantitative RT-PCR assay to measure viral DNA load in PBMCs, finding no difference in seropositivity and no correlation in 21 SLE cases and 38 HCs (76). The authors note concordance of their findings with the work of Moon et al. (2004) in terms of seropositivity and suggest that larger sample size may be required to detect differences in viral load (65,76). Likewise, Han et al (2018), who confirmed that lytic replication (as defined by the presence of anti-VCA IgM antibodies) is significantly higher in SLE patients than HCs, also measured EBV DNA load with RT-qPCR and found none of 46 patients with active lytic infection had EBV DNA concentrations above the adopted minimum threshold ($10^2/mm^3$) in their blood sera (20). The study did not however compare viral loads in SLE cases to HCs. Last year, Banko et al. (2023) also did not find any association between SLE status and viral load sourced from cell-free viral DNA in blood (instead of B-cells, PBMCs and blood sera), which should mostly originate during increased lytic replication (77). The authors support the conclusion of Han et al. (2018).

Present decade brought more studies which mostly confirmed higher EBV prevalence and higher viral load in SLE patients, like a 2022 work by Ming et al., who examined PBMCS from 121 untreated SLE patients and 191 that underwent treatment as well as 115 HCs (78). Association with high EBV load and renal involvement in SLE patients was also recently confirmed. Higher prevalence was also documented in a cohort of 105 SLE patients and 110 matched HCs by RT-PCR and Southern blot, with no difference between cases with active disease vs stable SLE (79). Prabir Das et al. (2022) found significant association for higher DNA load in pediatric SLE patients (52 pediatric SLE cases vs 63 pediatric HCs), and in 109 adult SLE patients compared to 215 healthy adult controls (80). At the same time, however, another group, could not find an association for DNA load in 70 juvenile SLE cases compared to 44 HCs (81).

A first prospective study investigated 51 SLE patients with active disease at two timepoints, 6 months apart. DNA prevalence was initially detected in 8 patients (15.7%), with a slight, statistically insignificant decrease at the end of the follow-up (82). The authors highlighted the high variability of EBV DNA prevalence in SLE patients, which was estimated to be ~55% vs ~21% in HCs in a 2019 meta-analysis, yet which could range from 0% to 74% in individual studies (17,81,83).

Altogether, these studies provide evidence for higher EBV DNA load in the adult SLE patient blood sera (and in fact also in several other autoimmune diseases), which has been also confirmed by a recent meta-analysis (17), but its scale and significance has not been fully explained.

Current evidence indicates the increased viral load derives mostly from the latently infected B-cells, instead of the lytic replication phase. Another study concluded that high EBV DNA association is stronger in younger patients (78). Most importantly, it is still unclear whether this phenomenon is a hallmark of a potentially causal role of the virus or is simply a by-product of an altered immune response.

Anti-EBV antibody levels and seroprevalence

Studies of antibody seroprevalence and anti-EBV antibody quantity provided more variable and often contradictory results. Table-1 lists most relevant studies of the past 25 years as well as their general findings.

Table-1: Studies of anti-EBV antibody seroprevalence and quantity (* denotes studies investigating antibody quantity instead of or in addition to seroprevalence).

Of note: the total number of cases and controls was not always used in full, in the analysis.

Study - first author (reference)	Year	Cases	Controls	Association positive for:	No or negative association:
Yokochi(84)	1989	11	14	EBNA1 IgG	VCA IgG
Westgeest(85)	1989	14	84		EBNA1 IgG
Marchini(86)	1994	40	20	EA IgG	EBNA1 IgG
Tsai(61)	1995	16	20		VCA IgG
Ngou(87)	1996	33	50	EBNA2- ,3-, 4-, 6 IgG	EBNA1 IgG
Newkirk(88)	1996	70	31	EA IgG	
James(46)	1997	**117**	153	VCA IgG	
Lau(62)	1998	34	22	VCA IgA, IgG	EA IgG
Zhang(89)	1999	36	45	VCA IgA	VCA IgG
Stratta(90)	1999	60	35	EA IgG	VCA IgG
James(55)	2001	**196**	382	VCA IgG	

Huggins(91)	2004	36	25	EA IgG	VCA IgG, IgM EBNA1 IgG, IgM
Chen(92)	2005	36	36	VCA IgA	VCA IgG, VCA IgM
Parks(93)	2005	**230**	**276**	VCA IgA (only in Black patients)	VCA IgG, VCA IgM
Lu(69)	2007	93	370	EBNA1 IgA, DNase IgG	
Mohammad(94)	2007	40	40	VCA IgA	VCA IgG, VCA IgM
Zandmann-Goddard*(95)	2009	**120**	140	EA IgG, VCA IgG	EBNA1 IgG, VCA IgM
Tazi(96)	2009	44	44		EBNA1 IgG,VCA IgG, VCA IgM
Berkun(97)	2009	**120**	140	EA IgG	EBNA1 IgG, VCA IgG, VCA IgM, heterophile IgM
Esen(98)	2010	**198**	65	EA IgG	EBNA1 IgG
Chen(99)	2010	94	370	EBNA1 IgA	
Sun(100)	2011	**108**	122		VCA IgG, EBNA1 IgG
Us(101)	2011	50	50	EA IgG	VCA IgG, VCA IgM, EBNA-IgG
Larsen(70)	2011	**118**	31	EBV IgG	
Draborg (102)	2012	60	20	EA IgA, IgG, IgM	VCA IgG, EBNA1 IgG
Broccolo*(76)	2013	22	58	EA IgG	EBNA IgG, VCA IgG, VCA IgM
Csuka*(103)	2013	**301**	345	EBNA IgG	
Hanlon(12)	2014	meta-analysis		VCA IgG, VCA IgA, EA IgG	EBNA1 IgG
Draborg(71)	2014	22	22	EBNA1 IgA, IgM, EA IgG , IgA, IgM	EBNA1 IgG
Rasmussen*(104)	2015	77	29	EA IgA, IgG, IgM	
Draborg(73,74)	2016	27	27		EBNA1 IgG
Vista*(105)	2017	**233**	221	VCA IgG, EA IgG	

Chougule* (106)	2018	87	50	VCA IgG, VCA IgM, EBNA IgG	
Han* (20)	2018	**116**	76	VCA IgM	VCA IgG, EBNA1 IgG
Sternbaek* (107)	2019	85	67	EAD IgA, IgG, IgM, VCA IgA, EBNA2 IgA (among others)	VCA IgG, IgM, EBNA1 IgA, IgG, IgM (among others)
Li (17)	2019	meta-analysis		VCA IgG, IgA, IgM, EBNA1 IgA, EA IgG, IgA, IgM	EBNA1 IgG
Das (80)	2022	**109** 52 pediatric	215 63	EA IgG	EA IgM, VCA IgM, EBNA1 IgM, VCA IgG, EBNA1 IgG
Chen (79)	2023	**105**	110	EBV IgM	
Lemus (108)	2024	55	61	EBNA1 IgG, EA-IgG	
Banko* (77)	2023	**103**	99	VCA IgM, EA IgG, EA IgM (&titers of EBNA1 IgG, VCA IgM, EA IgG, EA IgM)	VCA IgG, EBNA1 IgG

Most frequently and consistently, a higher prevalence and level of antibodies directed against viral early antigen (EA) was observed, as well as various IgA class antibodies, mainly specific to the viral capsid antigen. Anti-VCA IgG antibodies were also often correlated with SLE. In contrast, antibodies against EBNA1 usually do not reveal any association with the disease. These observations are supported by two recent meta-analyses (12,17). The first one included 25 case-control studies, conducted between 1966 to 2012, which investigated the prevalence of anti-EBV antibodies in SLE patients and healthy controls, and found statistically significant association for anti-VCA IgG, anti-EA IgG, and anti-VCA IgA, but not for anti-EBNA1 IgG. Zhao-Xia Li et al. (2019) performed a second meta-analysis of antibody seroprevalence and included 33 studies from 1966-2018 (17). Increased seroprevalence was confirmed for anti-VCA IgG, IgA and IgM and anti-EA IgG, IgA and IgM, as well as anti-EBNA IgA.

Overall, these results, especially when considered together with higher EBV DNA load in SLE cases, suggest a more pronounced, active lytic replication occurring in SLE patients. This may be explained by the association with anti-EA antibodies. This however, contrasts with findings from studies that investigated cell-free EBV DNA. Rapid clearance of viral DNA from blood could possibly offer an explanation for the discrepancy, but would require further confirmation. Also, higher prevalence for anti-VCA IgG indicates SLE patients are more often exposed to the virus. Caution has to be taken however, because of high heterogeneity of the studies and possible biases and limitations. Many of the studies relied on small sample size, with over one third of them counting less than 50 cases per study.

Hanlon et al.(2014) pointed to probable publication bias suggested by their quality control, especially in the anti-VCA antibody analysis (12).
The authors also noticed high variability in applied methods, patient sourcing and selection, control matching (including gender and age; ~50% of the included studies did not match for age) and study blinding, and stressed the fact that best quality studies tended to report no associations or possibly inconclusive results - like Parks et al. (2004) who found an association was positive for Black patients, but not for Caucasians (93). This may also hint at presence of potential confounding factors other than race and ethnicity, such as socioeconomic status. Similarly Li et al. (2019) noticed that minority of studies used appropriate community-based controls (17). Same limitations concern the studies of EBV DNA load.
Also, medication (especially glucocorticoids and immuno-suppressing agents), an active form of SLE or specific clinical subvarieties of the disease (for example with renal or joint involvement) may influence EBV reactivation rate and viral load as well as antibody seroprevalence and quantities (82,83,95,106,109).

Conclusion

Despite having been studied for decades, the association between EBV and SLE has still not been explained. Most importantly, it is unclear whether EBV plays an etiologically causal role or the often observed correlations point to some other, common cause. EBV has been implicated in several other complex, multifactorial disorders with both genetic and environmental components, and as such - even if causal, it would likely be one of multiple contributing factors. Especially given the fact it commonly infects over 90% of adult population. Multiple scenarios for EBV-induced autoimmunity have been formulated. Many of them have been recently reviewed by Robinson et al. (2024), along with the supporting literature (110).
Limited evidence from experimental studies indicates that EBV protein epitopes, in particular those of EBNA1, may induce cross-reactivity through molecular mimicry (111). Ensuing chronic inflammation could then potentially provoke the immune system into targeting other self - antigens through epitope spreading (13,57,111–113). However, the EBNA1 cross - reactivity contrasts with EBNA1 being rarely associated with SLE in serological studies. Alternatively, it has been proposed that impaired immunity and innate T-cell response permits the virus to reactivate and enter the lytic cycle more frequently (57,73). The associated persistent increase in EBV antigens elicits immune system activation, inflammatory cytokine synthesis and response that ultimately targets both the virus and the host cells with antibodies and autoantibodies (13,34), possibly through bystander activation (113,114). Also, increased expression of LMP1, or other anti-apoptotic viral proteins, coupled with B-cell proliferation could promote survival of B-cells and thus also lead to autoimmunity (11,108). One study pointed to an association between EBNA2 and SLE genetic risk loci (60). Some authors speculated on potential importance of EBV strain and protein variants (77,110).
Other researchers however, suggested that it may be the intrinsic (also genetic) susceptibility and abnormal immune response that predisposes both towards autoimmunity and SLE as well as a higher level of EBV activity, including more frequent lytic replications, due to ineffective control mechanisms (20,63). This could manifest in higher EBV DNA load as well as antibody seroprevalence.

In summary, current evidence tends to confirm the EBV-SLE association, however does not unequivocally explain the nature of the virus involvement in SLE pathogenesis. Several authors emphasised the need for further research, optimally in the form of case-control studies with a prospective design and adequately matched patients and controls (17,77,82).

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Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interests.

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