Viral Infections and Systemic Lupus Erythematosus: Pathophysiological Roles of Parvovirus and Epstein-Barr Virus Infections

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Abstract:

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by immune-mediated tissue damage affecting different organs. The pathogenesis of SLE is multifactorial and involves interaction between genetic and environmental factors, culminating in the breaking of immune self-tolerance. Viral infections such as parvovirus and Epstein–Barr virus can trigger or worsen SLE disease, stimulating the immune processes via different mechanisms.

Aim: This study was designed to investigate the possible role of parvovirus and Epstein–Barr virus in the pathogenesis of SLE and its relation to disease activity.

Patients and Methods: This study was conducted on 90 SLE female patients and 83 healthy controls. Disease activity was assessed according to the systemic lupus disease activity index (SLEDAI-2K) score. IgG antibodies against parvovirus and Epstein–Barr virus, blood parameters (hemoglobin, platelet count, and white blood cell count), serum albumin, kidney function parameters (urea, creatinine, 24-hour-urine protein, urine analysis), and immune parameters (C3, C4, and anti-dsDNA) were evaluated using appropriate methods.

Results: There was no statistically significant increase in IgG antibodies against parvovirus and Epstein–Barr virus infections in SLE patients compared to the control group. There was also no statistically significant difference between patients with positive and negative test results for IgG antibodies against parvovirus and Epstein–Barr virus infections regarding blood parameters, kidney function parameters, immune parameters, and SLE disease activity.

Conclusion: Parvovirus and Epstein–Barr virus infections have a similar frequency in SLE patients and controls. In addition, these infections did not have evident pathophysiological effects in SLE patients. More studies are required to confirm these findings.

Keywords: Systemic lupus erythematosus (SLE), Parvovirus, Epstein–Barr virus, Autoimmunity.

Introduction:

Systemic lupus erythematosus (SLE) is an autoimmune disease where dysregulated immune defenses cause tissue damage in different organs such as joints, skin, kidneys, and blood vessels. The clinical picture of SLE ranges from mild forms, such as fatigue, fever, and skin rash, to severe forms, such as

organ failure (1). SLE incidence worldwide is 0.3–31.5 cases per 100000 individuals per year (2).

Pathogenic mechanisms of SLE involve an interplay between genetic and environmental factors. Genetic factors were determined to be responsible for 43.9% of SLE susceptibility, while environmental factors are responsible for 25.8-30.3% of SLE susceptibility (2). Genetic and environmental factors culminate in immune dysregulation and inflammation (3). Dysregulated immune processes in SLE include the production of autoantibodies (e.g., antinuclear antigens (ANA), anti-double-stranded DNA (anti-dsDNA), and anti-Smith (anti-Sm)), formation and deposition of immune complexes, decreased B cell tolerance, increased cytokine and chemokine secretion, and decreased clearance of nucleic acids (3).

Viral infections have been associated with SLE for several reasons: (1) Viral infections can trigger SLE, (2) SLE onset can co-occur with viral infection, (3) SLE could develop in patients with chronic viral infection, and (4) Immunosuppressive therapy in SLE patients increases the risk of viral infection. Therefore, the relationship between SLE and viral infections is complex (3). Viral infections could contribute to dysregulated immune processes in SLE through several mechanisms, such as structural or functional molecular mimicry, formation of superantigens, interferon production, and deranged apoptotic processes (3).

Antibodies against Parvovirus (Parvovirus IgG) were more frequent in SLE patients than healthy controls (4, 5). Similarly, antibodies against Epstein–Barr virus (EBNA IgG) were higher in SLE patients than healthy controls (6). The occurrence of Epstein–Barr virus and Parvovirus infections in SLE patients may increase disease activity and worsen symptom severity by boosting autoimmune processes via molecular mimicry or activation of aberrant signaling pathways (4, 7). In this study, we investigated the frequency of Epstein–Barr virus and Parvovirus infections in SLE patients compared to healthy controls. In addition, we studied the effect of these viral infections on SLE disease activity, blood parameters, kidney function parameters, and different immune parameters.

Patients and Methods

The study included 90 female SLE patients who fulfilled the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE (8). Patients were recruited from the Rheumatology Clinic, Department of Internal Medicine, Assiut University Hospital, Assiut, Egypt. Their age ranged from 18-54 years. Patients were subjected to a complete medical history and examination to assess clinical signs and symptoms of SLE disease. Disease activity was assessed according to the systemic lupus disease activity index (SLEDAI-2K) score, and the range of possible values was 0-105 (9, 10). Patients with SLEDAI-2K score < 8 have low disease activity, and patients with SLEDAI-2K score ≥ 8 are considered to have high disease activity. SLE patients were also classified according to ACR renal criteria for diagnosis of lupus nephritis (11) into patients with and without lupus nephritis.

Eighty-three healthy females were included in the study as a control group. Their age ranged from 15-45 years.

This study was approved by the ethical committee of the Faculty of Medicine, Assiut University (IRB no: 17101182). Each subject or their parent/guardian gave informed consent before being included in the study.

Sample collection, storage, and handling:

1. Blood sample:

Six ml of venous blood was collected from each subject under complete aseptic precautions and was divided into:

a. Two mL into an EDTA-containing tube for complete blood count and reticulocyte count.
b. Four ml into a Wasserman tube, allowed to clot for 15 minutes in a water bath at 37 °C, and then centrifuged at 3000 rpm for 10 minutes. Part of the collected serum was used immediately for chemical and immunological investigations, and the rest was divided into aliquots and stored at -70 °C for later use.

2. Urine sample:

A random sample for urine analysis and a 24-hour urine sample were collected to measure 24-hour protein in urine and creatinine clearance.

Laboratory Investigations:

A complete blood count was done using Celldyn Ruby (Abbott, USA), and a reticulocyte count was performed by Brilliant cresyl blue stain (12). Serum urea, creatinine, and albumin were measured on the automated chemistry analyzer Dimension RxL Max (Siemens, USA) according to the manufacturer's instructions using Siemens flex reagent cartridge BUN (REF DF2, Siemens, USA), Siemens flex reagent cartridge CRE2 (REF DF33B, Siemens, USA), respectively.

Antinuclear antibody (ANA) was performed using an indirect immunofluorescence technique on HEp-2 cells using ANA Fluoro kits (cat.no. 1660, DiaSorin Inc., USA) according to the manufacturer's instructions. Anti-double-stranded DNA (anti-dsDNA) was performed by the indirect immunofluorescence technique on Crithidia luciliae using nDNA Fluoro Kit (cat.no. 1790, Diasorin Inc., USA) according to the manufacturer's instructions. C3 and C4 were analyzed by the nephelometric technique on BN ProSpec analyzer (Siemens, USA) according to the manufacturer's instructions using Siemens N antiserum to human C3c (REF OSAP09, Siemens USA) and Siemens N antiserum to human C4 (REF OSA009, Siemens USA), respectively.

Urine analysis was performed by urine strips comboStik 10 (DFI CO . ltd, Korea) and microscopic examination (13); the protein and creatinine in urine were measured by automated chemistry analyzer Erba XL 300 (main scientific, Pakistan) then 24 hours protein was calculated by the equation (protein in urine (mg) × volume of urine (ml) /100) (14).

Qualitative assessment of IgG antibodies against Epstein-Barr virus nuclear antigen was done by enzyme-linked immunosorbent assay (ELISA) using SERION ELISA classic Epstein-Barr Virus EBNA1 IgG kits (REF ESR1362G, Institut Virion/Serion GmbH, Germany) according to the manufacturer's instructions. Also, IgG antibodies against Parvovirus B19 were performed using SERION ELISA classic Parvovirus B19 IgG kits (REF ESR122G, Institut Virion/Serion GmbH, Germany) according to the manufacturer's instructions.

Statistical Analysis:

Data were verified, coded, and analyzed using GraphPad Prism v9 (GraphPad Software Inc., Boston, MA, USA). Descriptive statistics: mean, standard deviation, median, and range were calculated. Chi-square/Fisher's Exact test was calculated to compare the frequencies among groups for categorical variables. For continuous variables, an independent t-test analysis was carried out to compare the means of normally distributed data, while the Mann-Whitney U test was calculated to test the median differences of the data that don't follow the normal distribution. P-value was significant if ≤ 0.05.

Results

There was no statistically significant difference regarding age ($p > 0.05$) between

SLE patients (mean±SD 30.73 ± 8.47 years) and the control group (mean±SD 32.06 ± 7.28 years).

SLE patients had a significant decrease in haemoglobin level and platelet count compared to the control group (Table 1). SLE patients showed a significant increase in urea and creatinine levels and a significant decrease in albumin levels (Table 2). There was a nonsignificant difference between SLE patients and the control group regarding the frequency of Epstein–Barr virus IgG and Parvovirus B19 IgG positive test results (Table 3).

All control subjects had negative ANA tests. The ANA test was positive in 88/90 SLE patients (97.8%), and the anti-dsDNA test was positive in 34/90 SLE patients (37.8%). Two patients showed negative ANA tests, while their anti-dsDNA test was positive.

Table 1. Comparison between SLE patients and control subjects regarding Hb, platelet, and WBC levels

	Control subjects (n=83)	**SLE patients (n=90)**	**P-value**
Hb (g/dl)			
• Mean ± SD	11.83 ± 1.17	10.77 ± 1.57	< 0.0001*
• Median (Range)	11.9 (9 - 14.5)	10.9 (5.6 – 13.9)	
WBCs ($\times 10^3$ /ul)			
• Mean ± SD	7 ± 2.5	8.1 ± 5.5	= 0.9801**
• Median (Range)	6.7 (3.1 – 15)	6.3 (1.5 - 33)	
Platelet ($\times 10^3$ /ul)			
• Mean ± SD	325 ± 87	227 ± 92	< 0.0001*
• Median (Range)	328 (177 - 593)	212 (26 - 717)	

*An independent t-test was used to compare the means among groups

**Mann-Whitney U test was used to compare the medians among groups

Hb=Hemoglobin **n**=Number **SLE**=Systemic Lupus Erythematosus **WBCs**=White Blood Cells

Table 2. Comparison between SLE patients and control subjects regarding serum urea, creatinine, and albumin levels

	Control subjects (n=83)	SLE patients (n=90)	P-value
Blood Urea (mmol/l)			
• Mean ± SD	4.64 ± 1.25	7.96 ± 9.4	= 0.0002 *
• Median (Range)	4.5 (2.4 – 8.1)	6.05 (2 – 71)	
Serum Creatinine (umol/l)			
• Mean ± SD	76.56 ± 15.39	216.1 ± 758.2	< 0.0001*
• Median (Range)	76.5 (6.7 - 111)	100 (5 - 7214)	
Albumin (g/l)			
• Mean ± SD	40.58 ± 4.07	31.89 ± 7.94	< 0.0001**
• Median (Range)	39.8 (33.8 - 50)	31 (2.9 - 46)	

*Mann-Whitney U test was used to compare the medians among groups

**An independent t-test was used to compare the means among groups
n=number **SLE**=Systemic Lupus Erythematosus **SD**=Standard deviation

Table 3. Comparison between SLE patients and control subjects regarding parvovirus and EBNA IgG

	Control (n=83)	SLE patients (n=90)	P-value
Parvovirus IgG			
• Negative	11 (13.25%)	21 (23.33%)	= 0.0880 *
• Positive	72 (86.75%)	69 (76.67%)	
EBNA IgG			
• Negative	9 (10.84%)	13 (14.44%)	= 0.381*
• Positive	74 (89.16%)	77 (85.56%)	

*The Chi-square test was used to compare the proportions between groups
EBNA = EBV nuclear antigen **SLE**=Systemic Lupus Erythematosus **n**=number

Pathophysiological effects of parvovirus and Epstein–Barr virus infections in SLE patients

To investigate the potential pathophysiological effects of parvovirus and Epstein–Barr virus infections, we divided SLE patients according to their serum parvovirus IgG and EBNA IgG positivity.

SLE patients with positive parvovirus IgG (n=69) did not differ significantly from patients with negative parvovirus IgG (n=21) regarding age (mean±SD 31 ± 8.2 vs 31 ± 9.4 years) and disease duration (mean±SD 4.5 ± 3.4 vs 4.8 ± 3.2 years). Similarly, no significant difference was found between patients with positive Epstein–Barr virus EBNA IgG (n=77) compared to patients with negative Epstein–Barr virus EBNA IgG (n=13) regarding age (mean±SD 31 ± 7.9 vs 31 ± 12 years) and disease duration (mean±SD 4.8 ± 3.2 vs 3.5 ± 4 years).

Regarding blood parameters (Hb, WBC, and platelet levels), there was no significant difference between the positive and negative patient groups in either parvovirus or Epstein–Barr virus (Table 4). SLE patients with positive parvovirus IgG did not differ significantly from patients with negative parvovirus IgG regarding kidney function parameters (urea, creatinine, albumin, 24-hour urine protein, presence of RBCs, pus, and casts in the urine) (Table 5). Patients with positive Epstein–Barr EBNA IgG also showed a nonsignificant difference compared to patients with negative EBNA IgG regarding kidney function parameters.

The immune parameter, C4, showed significant differences between the two parvovirus groups, where patients with positive IgG had higher levels than those with negative IgG (Table 6). There was no significant difference between the two patient groups regarding the Epstein-Barr virus infection regarding C3, C4, and anti-dsDNA levels (Table 6).

There was no significant difference regarding the frequency of patients with high and low disease activity between patients with positive IgG and patients with negative IgG in either parvovirus or Epstein–Barr virus infections (Table 7). Similarly, no significant difference regarding the frequency of patients with lupus nephritis between patients with positive IgG and patients with negative IgG in either parvovirus or Epstein–Barr virus (Table 8).

Table 4. Comparison between SLE patients with positive and negative parvovirus infection regarding Hb, platelet, and WBC levels.

	Parvovirus B19 IgG			Epstein–Barr virus EBNA IgG		
	Positive (n=69)	**Negative (n=21)**	**P-value**	**Positive (n=77)**	**Negative (n=13)**	**P-value**
Hb (g/dl)						
• Mean ± SD	11±1.5	11 ± 1.6	= 0.1123 *	11±1.6	11±1.5	= 0.1002 *
• Median (Range)	11 (5.6-14)	12 (7.8 – 14)		11 (5.6-14)	11 (9.5-14)	
WBCs ($\times 10^3$ /ul)						
• Mean ± SD	8.2±5.8	7.7 ± 4.3	= 0.9566 **	7.9±5.5	9.6±5.2	= 0.2232 **
• Median (Range)	5.9 (2.2-33)	7.9 (1.5-20)		5.9 (1.5-33)	11 (3-21)	
Platelet ($\times 10^3$ /ul)						
• Mean ± SD	229±95	220±84	= 0.2885 *	220±94	266±68	= 0.2885 *
• Median (Range)	212 (26-717)	202 (84-373)		203 (26-717)	291 (159-373)	

*An independent t-test was used to compare the means among groups
**Mann-Whitney U test was used to compare the medians among groups
Hb=Hemoglobin **SLE**=Systemic Lupus Erythematosus **WBCs**=White Blood Cells

Table 5. Comparison between systemic lupus erythematosus (SLE) patients with positive and negative parvovirus and Epstein–
Barr virus infections regarding kidney function parameters

	Parvovirus B19 IgG			Epstein–Barr virus EBNA IgG		
	Positive (n=69)	**Negative (n=21)**	**P-value**	**Positive (n=77)**	**Negative (n=13)**	**P-value**
Blood Urea (mmol/l)						
• **Mean ± SD**	**7.3 ± 6.6**	**10 ± 16**	**= 0.9001 ***	**8.1 ± 9.8**	**6.9 ± 7.2**	**= 0.3260 ***
• **Median (Range)**	**6 (2 – 43)**	**6.1 (2.5 – 71)**		**6.1 (2 – 71)**	**4.8 (2.1 – 30)**	
Serum Creatinine (umol/l)						
• **Mean ± SD**	**132 ± 140**	**493 ± 1545**	**= 0.2002 ***	**132 ± 128**	**714 ± 1961**	**= 0.4145 ***
• **Median (Range)**	**90 (5 - 900)**	**112 (32 - 7214)**		**91 (5 - 900)**	**112 (32 - 7214)**	
Albumin (g/l)						
• **Mean ± SD**	**32 ± 7.8**	**31 ± 8.6**		**32 ± 8.4**	**31 ± 5**	
• **Median (Range)**	**32 (3.8 - 45)**	**31 (2.9 - 46)**	**= 0.7528 ****	**32 (2.9 - 46)**	**31 (21 - 41)**	**= 0.6824 ****
24 hr urine protein (mg/ 24 hr)						
• **Mean ± SD**	**891 ± 1137**	**1533 ± 2030**	**= 0.1447 ***	**932 ± 1186**	**1683 ± 2306**	**= 0.2555 ***
• **Median (Range)**	**525 (55 - 7555)**	**719 (198 - 7714)**		**581 (55 - 7555)**	**620 (311 - 7714)**	
RBCs in urine						
• **Present**	**20 (28.99%)**	**4 (19.05%)**	**= 0.367 *****	**19 (24.68%)**	**5 (38.46%)**	**= 0.298 *****
• **Absent**	**49 (71.01%)**	**17 (80.95%)**		**58 (75.32%)**	**8 (61.54%)**	
Pus in urine						
• **Present**	**21 (30.43%)**	**6 (28.57%)**	**> 0.999 *****	**22 (28.57%)**	**5 (38.46%)**	**= 0.471 *****
• **Absent**	**48 (69.57%)**	**15 (71.43%)**		**55 (71.43%)**	**8 (61.54%)**	
Casts in urine						
• **Present**	**17 (24.64%)**	**6 (28.57%)**	**= 0.717 *****	**20 (25.97%)**	**3 (23.08%)**	**= 0.824 *****
• **Absent**	**52 (75.36%)**	**15 (71.43%)**		**57 (74.03%)**	**10 (76.92%)**	

* Mann-Whitney U test was used to compare the medians among groups
** An independent t-test was used to compare the means among groups
*** The Chi-square test was used to compare the proportions between groups
SLE=Systemic Lupus Erythematosus **SD**=Standard Deviation

Table 6. Comparison between systemic lupus erythematosus (SLE) patients with positive and negative parvovirus and Epstein–
Barr virus infections regarding different immune parameters.

	Parvovirus B19 IgG			**Epstein–Barr virus EBNA IgG**		
	Positive (n=69)	**Negative (n=21)**	***P-value***	**Positive (n=77)**	**Negative (n=13)**	***P-value***
C3 (g/l)						
• Mean ± SD	0.88±0.4	0.81±0.45	= 0.5543 *	0.87±0.43	0.82±0.26	= 0.7183 *
• Median (Range)	0.8 (0.2-1.8)	0.8 (0.2-1.7)		0.8 (0.2-1.8)	0.8 (0.2-1.2)	
C4 (g/l)						
• Mean ± SD	0.25±0.12	0.18±0.11	= 0.0175 *	0.23±0.12	0.24±0.097	= 0.7701 *
• Median (Range)	0.3 (0.01-0.4)	0.11 (0.06-0.4)		0.25 (0.01-0.4)	0.3 (0.1-0.4)	
Anti-dsDNA						
• Present	28 (40.58%)	6 (28.57%)	= 0.3203 **	29 (37.66%)	5 (38.46%)	= 0.9562 **
• Absent	41 (59.42%)	15 (71.43%)		48 (62.34%)	8 (61.54%)	

* An independent t-test was used to compare the means among groups
** The Chi-square test was used to compare the proportions between groups
n=number **SD**=standard deviation

Table 7. Comparison between systemic lupus erythematosus (SLE) patients with positive and negative parvovirus and Epstein–
Barr virus infections regarding the number of patients with high and low disease activity.

	Parvovirus B19 IgG			**Epstein–Barr virus EBNA IgG**		
	Positive (n=69)	**Negative (n=21)**	**P-value**	**Positive (n=77)**	**Negative (n=13)**	**P-value**
• High activity	56 (81.16%)	16 (76.19%)	= 0.6182 *	60 (77.92%)	12 (92.31%)	= 0.2304 *
• Low activity	13 (18.84%)	5 (23.81%)		17 (22.08%)	1 (7.69%)	

*The Chi-square test was used to compare the proportions between groups. A systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 8 was used to split SLE patients into two groups.

Table 8. Comparison between systemic lupus erythematosus (SLE) patients with positive and negative parvovirus and Epstein–
Barr virus infections regarding the number of patients with lupus nephritis

	Parvovirus B19 IgG			Epstein–Barr virus EBNA IgG		
	Positive (n=69)	**Negative (n=21)**	**P-value**	**Positive (n=77)**	**Negative (n=13)**	**P-value**
• LN	35 (50.72%)	14 (66.67%)	0.1990 *	41 (53.25%)	8 (61.54%)	0.5787 *
• NLN	34 (49.28%)	7 (33.33%)		36 (46.75%)	5 (38.46%)	

*The Chi-square test was used to compare the proportions between groups. LN lupus nephritis, NLN non-lupus nephritis

Discussion

Several viruses have been linked to SLE pathogenesis, such as Epstein-Barr virus, Cytomegalovirus, parvovirus, transfusion-transmitted virus, Human Herpes Virus, Human Papilloma Virus, Dengue virus, Human T cell Lymphotropic virus, and HIV (4, 15). These viruses act as environmental primers to induce or exacerbate SLE in genetically susceptible individuals.

The association of parvovirus or Epstein-Barr virus with SLE has been controversial; while some studies reported a significant association, others reported no difference between SLE patients and controls. For example, a study at Benha University in Egypt found no evidence linking SLE to parvovirus exposure (6). A Swedish cohort reported a similar finding: SLE patients and controls had similar parvovirus prevalence (16). On the other hand, a study from Mexico reported significantly higher levels of parvovirus IgG in SLE patients compared to controls (6). Our study did not find evidence supporting the association of parvovirus with SLE.

A similar picture is reported for the Epstein-Barr virus. One study reported higher titers of anti-Epstein-Barr virus antibodies in SLE patients than in controls (17). Another study from Korea reported no significant difference between SLE patients and controls regarding Epstein-Barr virus infection (18). However, this study reported higher viral loads in peripheral blood mononuclear cells in SLE patients. Therefore, serological results don't necessarily reflect the viral status within the body (18). The current study found no significant difference in anti-Epstein-Barr virus infection among SLE patients and controls. This discrepancy in the results could be attributed to differences in the sensitivity and specificity of different bioassays that detect anti-viral antibodies (6). Also, the sample size could be another factor. A meta-analysis of 19 studies tested for Epstein-Barr virus IgG seropositivity from 1572 SLE cases and 2270 controls found no significant association between Epstein-Barr virus IgG and SLE (19).

Viral infections in SLE patients are hypothesized to boost autoimmune processes via several mechanisms and could worsen SLE clinical symptoms. For example, parvovirus increases cytokine secretion, stimulates the release of autoantibodies, activates T cells, and stimulates abnormal apoptosis (4). Similarly, the Epstein-Barr virus stimulates antibody-producing B cells and acts as a superantigen to stimulate T cells, which secrete large amounts of cytokines (4). These immunological responses result in an inflammatory microenvironment, which could contribute to tissue damage and clinical manifestations in SLE patients. For

example, parvovirus infection mimics SLE clinical symptoms; in both cases, patients present with skin rash, fevers, and rheumatic manifestations (20). Clinical symptoms of Epstein-Barr virus are similar to SLE disease (5). Also, SLE disease activity has been associated with viral load in peripheral B cells (5). In our study, parvovirus infection significantly increased C4 levels with a nonsignificant effect on C3 and anti-dsDNA levels, while Epstein-Barr virus did not affect immune parameters significantly. SLE Patients with either positive parvovirus IgG or Epstein-Barr virus EBNA IgG had a clinical picture similar to SLE patients with negative test results, where blood parameters, kidney function parameters, and SLE disease activity were similar between the two groups. This could be explained by the fact that the measured antibodies in this study are IgG, which reflects previous infections, as opposed to IgM antibodies, which reflect recent infections. Therefore, the clinical manifestations of patients enrolled in this study could have occurred after their viral infections had resolved, and therefore no major differences were found between the two groups. Hence, future studies could investigate the relationship between anti-viral IgM antibodies and SLE disease activity. In addition, biomarkers other than serological investigations should be used to better reflect viral activity such as viral loads, and its association with SLE disease severity.

In conclusion, this study investigated the potential pathophysiological effects of parvovirus and Epstein-Barr virus infections in SLE patients. We did not find evidence supporting the association between these viral infections and SLE disease. In addition, we did not find major pathophysiological effects of these viral infections. Further studies are warranted to confirm these findings and investigate other factors, such as IgM antibodies or viral loads, that may be more relevant for SLE disease pathogenesis.

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