Commentary

Exploring the Association between Epstein-Barr Virus and Systemic Lupus Erythematosus: Insights into Viral Triggers

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Abstract: Epstein-Barr virus (EBV) is ubiquitous in humans, which infects more than 90% of adults globally. Beyond its established association with malignancies, EBV infection is linked to several autoimmune diseases including systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis and Sjögren syndrome. SLE is characterized by systemic inflammation and multiorgan damage with unpredictable relapsing-remitting clinical course. Although significant evidence supports EBV infection as a contributing factor in SLE pathogenesis, the exact mechanisms linking EBV to SLE onset remain to be fully elucidated. Molecular mimicry is among the potential factors that may drive SLE development. Importantly, given this association, development of therapies targeting EBV is promising for novel SLE treatment.

Keywords: EBV; SLE; Molecular mimicry

1. Introduction

Epstein-Barr virus (EBV) belonging to the human gamma herpesvirus family is the first identified oncogenic virus, which causes several lymphoma, nasopharyngeal carcinoma, gastric cancer and post-transplant lymphoproliferative disease [1]. The ~172 kb genome of EBV encodes more than 80 proteins, including latent membrane proteins (LMPs), EBV nuclear antigens (EBNAs), structure proteins and proteins responsible for viral replication [2]. EBV is transmitted through saliva and primary infection mainly occurs in children [3]. After primary infection, EBV establishes lifelong latency in the host with limiting gene expression. According to the expression pattern, EBV latency states can be divided into four phases, which are well-studied in EBV-associated tumors instead of EBV-linked autoimmune diseases. EBV is reactivated to enter the lytic state by several stimuli including B cell receptor engagement, immunosuppressive drugs, inflammasome, hypoxia, DNA damage, Hippo pathway signaling and co-infection with cytomegalovirus or SARS-CoV-2 [4–9]. EBV infection and reactivation are also associated with autoimmune diseases including systemic lupus erythematosus (SLE), which occur long after the primary infection [10].

SLE is an uncurable autoimmune disease that primarily affects in women with the incidence of 6–35 new cases per 100,000 per year [11]. It is characterized by the presence of autoantibodies against nuclear antigens, immune complex deposition, and chronic inflammation in skin, joints, and kidneys. It is characterized by the presence of autoantibodies against nuclear antigens, immune complex deposition, and chronic inflammation in skin, joints, and kidneys [12].

The etiology of SLE is complicated and involves genetic and environmental factors. Infection is the major environmental risk factors. Since 1971, it was reported that antibody titers to EBV were increased in SLE patients [13]. EBV seroconversion rate of children and young adult SLE patients (99%) was much higher than that of young healthy controls (70%) [14]. Besides, SLE in adults is also associated with previous EBV exposure [15]. An epidemiological study in Taiwan showed that IgA antibody against EBV-VCA was significantly higher in SLE patients compared to healthy controls, which is associated with disease flare [16]. It was reported that both anit-EBV-VCA IgG and IgA titers elevated in patients with SLE in Hong Kong [17]. SLE patients had over a 15-fold increase in EBV copy numbers compared with controls in peripheral blood mononuclear cells [18,19].

Epidemiological studies have consistently demonstrated a strong association between EBV infection and SLE pathogenesis, suggesting that EBV may play a significant role in triggering SLE [10]. Given this connection,

developing EBV-specific prophylactic and therapeutic strategies holds promising potential for improving the treatment of SLE. By shedding light on the underlying biological mechanisms (Figure 1), these insights could pave the way for novel approaches to prevent and treat SLE.

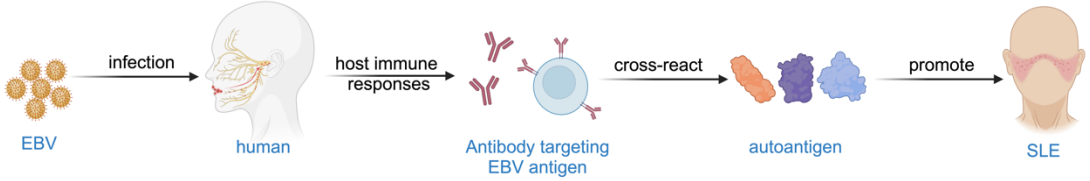

Figure 1. Molecular mimicry of EBV and SLE. The figure was created by Biorender.com.

1.1. Underlying Mechanism Induced by EBV-Molecular Mimicry

Molecular mimicry between EBV antigens and autoantigens may trigger SLE pathogenesis (Table 1). Molecular mimicry promotes the development of autoantibodies when viral or bacterial antigens share high sequence similarity with autoantigens. Immunization with peptides derived from EBV EA, gp350, LMP-1 and LMP-2A induced autoantibodies related to SLE pathogenesis in mice [20]. Antibodies targeting several peptides derived from EBNA-1 were reported to cross-react with autoantigens. Monoclonal antibody (mAb) 3D4, targeting 148 amino acid viral binding site of EBNA-1 carboxyl region, was cross-reacted with dsDNA while mAb 0211 recognizing both the amino and carboxyl regions of EBNA-1 cross-reacted with ribonucleoprotein Sm [21]. Besides, an IgM mAb 16D2 recognizing 148 amino acid viral binding site of EBNA-1 also cross-reacted with dsDNA [22]. Besides, autoantibody A08 isolated from SLE patients targeting complement C1q cross-reacted with peptide ^{348}GSGGRRGRGRERARGGS^{365} derived from EBNA-1 [23]. Additionally, peptide derived from EBNA-1 (^{58}GGSGSGPRHRDGVRR^{72}) cross-reacted with a peptide (^{169}TKYKQRNGWSHK^{180}) derived from 60 kD Ro protein [24]. Immunizing mice with ^{169}TKYKQRNGWSHK^{180} or ^{58}GGSGSGPRHRDGVRR^{72} leads to the gradual development of autoantibodies that recognize multiple epitopes on Ro [24]. Moreover, in sera from SLE patients, anti-SmD (^{95}RRPGGRGRGRGRGRGRGRGRGA^{119}) antibodies were also bound to EBNA-1 (^{35}GPAGPRGGGRGRGRGRGRGHNDGG^{58}) [25]. Mice immunized with ^{35}GPAGPRGGGRGRGRGRGRGHNDGG^{58} generated antibodies targeting SmD protein [25]. In addition, the octapeptides PPPGMRPP and PPPGIRGP, derived from Sm B/B' protein, serve as early targets of the autoimmune response in some lupus patients [26]. Antibody targeting peptide PPPGRRP derived from EBNA-1 cross-reacted with PPPGMRPP derived from Sm B/B' protein [27]. Mice immunized with plasmid encoding EBNA-1 induced IgG antibodies recognizing Sm and dsDNA[28].

Table 1. Molecular mimicry between EBV EBNA-1 and autoantigens.

Peptides of EBV EBNA-1	Autoantigens or Peptides of Autoantigens
GSGGRRGRGRERARGGS	C1q
GGSGSGPRHRDGVRR	TKYKQRNGWSHK (derived from Ro)
TKYKQRNGWSHK	Ro
GGSGSGPRHRDGVRR	Ro
GPAGPRGGGRGRGRGRGRGHNDGG	RRPGGRGRGRGRGRGRGRGRGA (derived from SmD)
GPAGPRGGGRGRGRGRGRGHNDGG	SmD
PPPGRRP	PPPGMRPP (derived from Sm B/B' protein)

1.2. Potential Treatment of SLE Targeting EBV

Given this association between EBV and SLE, development of therapies targeting EBV is promising for novel SLE treatment. Development of prophylactic vaccines to prevent primary EBV infection may inhibit SLE pathogenesis. Viral glycoproteins including gp350, gH, gL, gB and gp42 are the ideal antigen for the prophylactic vaccines against EBV. Moreover, the vaccines or mAbs targeting these glycoproteins may prevent the infection of progeny EBV to build new B cell repositories after EBV reactivation. However, whether the glycoproteins contribute to SLE pathogenesis remains to be determined. Antibodies targeting EBV glycoprotein may also cross-react with autoantigens. If so, the modification of antigens of EBV vaccines, such as deletion of the cross-reactive epitopes of glycoproteins, is needed.

B cell depletion by rituximab did not demonstrate efficacy in SLE patients while CD19-targeted CAR T cell therapy is feasible, tolerable and highly effective in SLE patients [29,30]. Targeted depletion of EBV-specific B cells from tissues and blood of SLE patients may be more effective. Meanwhile, allogeneic EBV-targeted T cell

therapy may be effective for SLE, although EBV-specific T cell therapy ATA188 failed in MS (NCT03283826). Nevertheless, the gene expression pattern of B cells in SLE patients remains to be determined, which is crucial for depletion of EBV-specific B cells. Besides, B cells with EBV in latent 0 states cannot be depleted. The efficiency of EBV targeted T cell therapy needs further evaluation.

Moreover, the small molecular inhibitors to block EBV reactivation and replication may also be effective for SLE treatment. VK-1727 is a small molecular inhibitor targeting EBNA-1 to block EBV replication, which suppresses the proliferation of spontaneous lymphoblastoid cell lines derived from MS patients [31]. VK-2019, another small molecular inhibitor targeting EBNA-1, is tested in Phase I/IIa clinical trial to treat EBV-positive nasopharyngeal carcinoma (NCT03682055).

1.3. Future Directions

Overall, accumulating evidence increasingly links EBV to SLE. A compelling paradox surrounds the potential role of EBV in autoimmune diseases. The virus infects more than 95% of the global adult population. However, the majority of infected individuals do not go on to develop autoimmune disorders. The specific mechanisms of how EBV infection induces SLE remains to be determined. Additionally, the low frequency of circulating EBV-positive B cells in patients with SLE complicates the identification and characterization of individual EBV-positive B cells within the context of autoimmunity. The latent states of EBV in SLE patients need to be further determined. Moreover, molecular mimicry mainly focused on EBNA-1. EBV encodes more than 80 proteins, whether antibodies or T cells targeting other EBV proteins cross-react with autoantigens remains unknown. Further studies should still focus on clarifying the role and underlying mechanisms of EBV in SLE pathogenesis and developing therapies targeted to EBV to prevent and treat SLE.

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