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Review

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Abstract

Epstein-Barr virus (EBV) infection is associated with a variety of the autoimmune diseases. There is apparently no unified model for the role of EBV in autoimmune diseases. In this article, the development of autoimmune diseases is proposed as a simple two-step process: specific autoimmune initiators may cause irreversible changes to genetic materials that increase autoimmune risks, and autoimmune promoters promote autoimmune disease formation once cells are susceptible to autoimmunity. EBV has several types of latencies including type III latency with higher proliferation potential. EBV could serve as autoimmune initiators for some autoimmune diseases. At the same time, EBV may play a promotional

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role in majority of the autoimmune diseases by repeated replenishment of EBV type III latency cells and inflammatory cytokine productions in persistent stage. The type III latency cells have enhanced capacity as antigen-presenting cells that would facilitate the development of both B and T cell-mediated autoimmunity. The repeated cytokine productions are achieved by the repeated infection of naive B-lymphocytes and proliferation of type III latency cells that produce inflammatory cytokines. Presentation of viral or self-antigens by EBV type III latency B lymphocytes may promote autoreactive B cell and T cell proliferation, which can be amplified by type III latency cells-mediated cytokines productions. Different autoimmune diseases may require different kinds of pathogenic immune cells and/or specific cytokines. Frequency of the replenishment of EBV type III latency cells may determine the specific effect of the promoter functions. A specific initiator plus EBV-mediated common promoter function may lead to development of a specific autoimmune disease and link EBV-infection to a variety of autoimmunity.

Keywords: autoimmune diseases, Epstein Barr virus, initiator, latency, lupus, multiple sclerosis, promoter

Epstein-Barr virus (EBV) is a human γ-herpesvirus that establishes a lifelong persistent and asymptomatic infection. Similar to other herpesviruses, EBV life cycle can switch between latent and lytic state. The lytic replication cycle results in the production of infectious virions. In addition, lytic replication takes place after reactivation from latency. In latency stages, EBV can express very limited gene from its genome without triggering a lytic replication process, and keep the viral genome in the cells (Figure 1A).

Autoimmune diseases are common diseases in which dysfunctional immune activation results in pathologic immune responses that target either cell or organ-specific self-antigens.[1] Autoimmune diseases are a significant clinical problem because of their chronic nature, the associated healthcare cost, and their prevalence in young populations during the prime of their working and peak reproductive years.[2] EBV infection has been linked to several autoimmune diseases such as multiple sclerosis (MS) and systemic lupus erythematosus (or lupus). The molecular mechanisms for the broader association between EBV and a variety of the autoimmune diseases are not very clear.

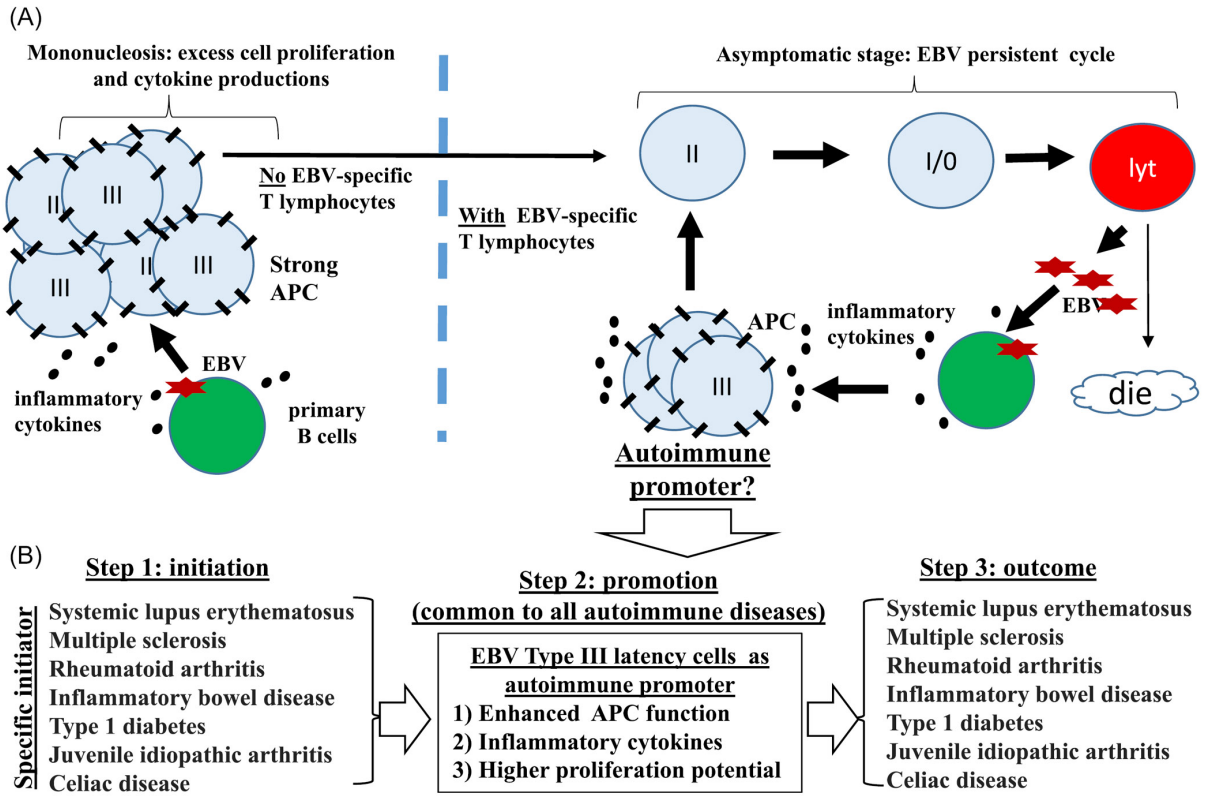

Figure 1 Schematic diagram of putative EBV-mediated autoimmune promoter function in vivo.

(A) EBV life cycle. The primary infections of EBV (red stars) may cause mononucleosis with huge proliferation of EBV type III latency cells. Both infection of B cells by EBV itself and type III latency cells would produce many inflammatory cytokines (black dots). Newly generated EBV-specific cytotoxic T lymphocytes (CTL) will keep mononucleosis under controls and EBV enters a persistent stage. Type II latency cells are located in germinal centers. EBV persists in memory B cells without viral protein expression (latency 0) or transient EBNA1 expression (latency I), during homeostatic proliferation. Lytic EBV replication occurs after plasma cell differentiation from memory B cells. In asymptomatic and healthy EBV-carriers, infectious EBV can be detected in saliva. The infectious virions, which might be from epithelial cells also, infects naïve B lymphocytes and establishes a type III latency. EBV-specific CTLs will quickly eliminate EBV-positive type III latency cells. The repeated production of inflammation cytokines may be from two major sources: (1) EBV infection of naive B cells; and (2) transient proliferation of type III latency cells. Type III latency cells are good APCs and have higher proliferation potential. The big open arrow indicates the type III latency cells are likely to be autoimmune promoter for majority of EBV-associated autoimmune diseases as shown below.

(B) Potential promotional role of EBV in autoimmune diseases. Each specific autoimmune disease may have a specific initiator. Presentation of viral or self-antigens by type III latency cells may promote autoreactive B cell and T cell proliferation, which can be amplified by type III latency cells-mediated cytokines productions. A specific initiator plus EBV-mediated common promoter function may lead to development of a specific autoimmune disease. Different autoimmune diseases may require different kinds of pathogenic immune cells and cytokines. Frequency of the replenishment of EBV type III latency cells may determine the specific effect of the promoter functions. The damage from the one cycle of EBV reactivation may be mild, but the cumulative damage from the repeated attacks may lead to the onset and/or relapse of an autoimmune disease. Other than promotional effect, EBV may serves as an autoimmune initiator by molecular mimicry mechanism. In addition, EBV-infection-mediated cell death and release of self-antigens may also contribute to the development of autoimmunity.

1 The development of an autoimmune disease may be a two-step process

It is well accepted in cancer research field that simplest model for a multistep cancer formation is a two-step model that includes initiation and promotion.[3–5] The development of autoimmune diseases is most likely a multistep process.[2,6] Although not all autoimmune diseases share exactly the same steps, some general features are shared in the development of many types of autoimmune diseases. For example, association with inflammatory cytokines seems to be a common feature for almost all autoimmune diseases. Therefore, it might be necessary to classify the factors involved in the development of autoimmunity into two categories: those factors that predispose cells to develop an autoimmune disease are classified as initiators, and those factors that stimulate autoimmune development are classified as promoters. Initiation is the first step in this two-step model of autoimmune development. Specific initiators may cause irreversible changes (mutations) to genetic materials such as DNA that increase autoimmune risk. Promotion is the second step, and once an initiator has mutated a cell, it is susceptible to the effects of promoters.

2 EBV may serve as an initiator for autoimmune diseases

Molecular mimicry is one of the leading mechanisms by which infectious agents may induce autoimmunity. It occurs when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by a foreign-derived antigen in a susceptible individual.[7] Molecular mimicry between viral Epstein-Barr nuclear antigen 1 (EBNA1) and host proteins may contribute to the development of MS and lupus.[8–11] In addition, EBV-infection-mediated cell death and release of self-antigens may also contribute to the development of autoimmunity (Figure 1A).[12–16]

3 EBV type III latency cells may function as an autoimmune promoter

In both primary and persistent EBV infections, type III latency cells are present and may serve as an autoimmune promoter.

(1) EBV type III latency cells produce inflammatory cytokines.

First, the type III latency cells itself are a good producer of inflammatory cytokines, such as interleukin 6 (IL6). Latent membrane protein 1 (LMP1) is one of the latent genes predominantly expressed in the type III latency cells, and LMP1 is expressed in healthy carriers transiently as well as in autoimmune disease patients, especially in lupus.[17–20] LMP1 functions as an inflammation-promoting factor, at least by inducing a panel of proinflammatory cytokines, some of which are clearly associated with autoimmunity.[19,21–23] Second, acute EBV infections in mononucleosis generate a wave of cytokines and chemokines including interleukin 1 beta (IL-1β), IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, IL-18, tumor necrosis factor-α, interferon alpha/beta (IFN-α/β), IFN-γ, monokine induced by IFN-γ (Mig), IFN-γ-inducible protein 10 (IP-10) and granulocyte macrophage colony-stimulating factor (GM-CSF) (reviewed in reference 24). During persistent phase, EBV infections of human naïve B-lymphocytes are predicted to produce the similar but less amounts of cytokines in vivo because EBV-specific CTLs will be present and functional (Figure 1A).

(2) EBV type III latency cells are good antigen presenting cells (APC)

EBV type III latency cells express high levels of human leukocyte antigens (HLA), and other antigen presentation-related molecules.[25–28] Functionally, EBV type III latency cells can induce a robust T-cell stimulation.[25,29,30] The strong APC function of type III latency cells may facilitate both viral and host antigen presentation, and furthermore both B and T cells mediated pathogenic autoimmunity[31–33] (Figure 1A). The importance of B cells as an APC in autoimmune diseases are well documented.[34–38]

4 Autoimmune promoter function might link EBV type III latency to many autoimmune diseases

Majority of the healthy individual have active EBV in their saliva,[39,40] and multiple reinfections of EBV in healthy individuals are common.[41–44] It is thus obvious that the replenishment of type III latency cells are frequent events in vivo. EBV type III latency cells are potent APCs, produce inflammation cytokines, and have higher proliferation potential (Figure 1B).

EBV is associated with many autoimmune diseases with different pathogenic mechanisms.[45,46] Does EBV play different roles in various autoimmune diseases? There is an interesting discovery that may offer a clue to the question. EBV EBNA2 protein occupies multiple loci associated with autoimmune genetic disorders including MS, lupus, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis and celiac disease.[45] EBNA2 is a hallmark for type III latency cells,[47–49] and the observation suggests that EBV type III latency cells might play a similar role in at least those six autoimmune diseases.[45] The list of EBV associated autoimmunity is also expanding and now includes chronic fatigue syndrome and Guillain-Barré syndrome.[50,51] In addition, the severe acute respiratory syndrome coronavirus 2-related long Coronavirus Disease 2019 might be considered as an autoimmune disease and associated with EBV reactivation.[52–55] Because different autoimmune diseases have different pathogenic mechanisms, it is tempting to speculate the following: presentation of viral or self-antigens by EBV type III latency B lymphocytes would promote autoreactive B cell and T cell proliferation, which can be amplified by type III latency cells-mediated cytokines productions. Different autoimmune diseases may require different kinds of pathogenic immune cells and cytokines. Frequency of the replenishment of EBV type III latency cells may determine the specific effect of the promoter functions. Without the specific initiator for an autoimmune disease, healthy individuals who are EBV positive with repeated type III latency cells replenishments and elevated inflammations do not develop to autoimmune disease. The promotional effects or damages from the one cycle of EBV persistent infection may be mild, but the cumulative promotional effects from the repeated attacks could lead to the onset and/or relapse

of an autoimmune disease (Figure 1B). A specific initiator plus EBV-mediated common promoter function may lead to a specific autoimmune disease.

5 The type III latency cells may have other properties related to autoimmune development

First, pathogenic antibodies against EBNA1 contribute to the development of MS and lupus.[8–11] Because EBNA1 expresses at higher levels in type III latency cells than others,[56] it is likely that the type III latency cells in vivo might be a major contributor to the pathogenic antibodies or immune cells against EBNA1. Second, EBV type III latency cells have antiviral activities and are primed for induction of type I IFNs via LMP1 expression.[57,58] This property might be related to the pathogenesis of lupus,[20] because IFNs are considered as a major contributor to lupus pathogenesis.[59,60]

6 EBV type III latency cells and MS

The autoimmune promoter effects of EBV persistent cycles may be operational in MS pathogenesis. First, mononucleosis is associated with MS but apparently not with lupus.[61–63] Therefore, higher EBV type III latency cells per se may provide an "initiator-like" factor to MS development, and support the recent assumption that EBV might be a causative agent in the development of MS.[61] Second, another big risk factor for MS maps to the class II region of the HLA gene cluster. HLA-DRB1*15:01 has the strongest effect with an average odds ratio of 3.08.[64,65] Interestingly, HLA-DRB1*15:01 is a coreceptor for EBV,[66] and associated with the attenuated immune control of EBV in humanized mouse model.[67] Third, decreased T cell reactivity to type III latency cells is observed in MS patients.[68] Fourth, type III latency cells could exacerbate experimental autoimmune encephalomyelitis in xenograft mice.[69] Finally and fifth, autologous EBV-specific T cell therapy, specifically against EBV latent antigens including LMP1, had some benefits for some MS patients.[70,71] It is likely that type III latency cells in vivo are a factor in the development or exacerbation of MS.

7 Biological roles of EBV type III latency in EBV life cycle

Because type III latency cells are efficiently targeted by EBV-specific CTLs in a healthy and asymptomatic individual, it is puzzling why EBV type III latency cells are challenging the host immune system. One possible explanation is that the type III latency cells might be required for the establishment of type I/0 latency in memory B cell phenotypes. Some type III latency cells are believed to convert into memory B cells and avoid the elimination, which might be a strategy for persistent infection of EBV (Figure 1A).

In vitro, after the initial virion attachment, EBV-infected cells have a period of rapid proliferation with minimally expression of LMP1 before establishment of a full-blown type III latency and avoid T cell recognitions and killings.[72–74] However, whether the rapid proliferation stage happens in persistent state in vivo need extensive experimental verifications. Nevertheless, the rapid proliferation stage provides a period for accumulation of type III latency cells before host cell-mediated killings (Figure 1A). In addition, some cytokines may help the establishment and proliferation of type III latency cells. For example, IL6 is induced by EBV infection of B-lymphocytes and produced by EBV type III latency cells, which in turn, promotes growth of type III latency cells.[75–82] Therefore, type III latency cells might present in a more abundant fashion in vivo.

In summary, the development of autoimmune diseases is proposed as a two-step process. EBV could serve as an initiator for some autoimmune diseases. In most cases, EBV may play a promotional role through its excellent APC functions and inflammation cytokine productions of EBV type III latency cells (Figure 1). The model may explain the role of EBV in many EBV-associated autoimmune diseases. A vaccine that targets type III latency cells might be a good candidate for therapeutic treatment for EBV-associated autoimmunity. A better understanding of the complex causes of autoimmunity and its association with EBV will lead to better treatment and prevention options.

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Conflict of interest The author declares no conflict of interest.

Data availability The data that support the findings of this study are available in PubMedCentral at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from resources available in the public domain.

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