A possible link between the Epstein-Barr virus infection and autoimmune thyroid disorders

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Abstract

The Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the Herpesviridae virus family. EBV infection can cause infectious mononucleosis (IM) in the lytic phase of EBV’s life cycle. Past EBV infection is associated with lymphomas, and may also result in certain allergic and autoimmune diseases. Although potential mechanisms of autoimmune diseases have not been clearly elucidated, both genetic and environmental factors, such as infectious agents, are considered to be responsible for their development. In addition, EBV modifies the host immune response. The worldwide prevalence of autoimmune diseases shows how common this pathogen is. Normally, the virus stays in the body and remains dormant throughout life. However, this is not always the case, and a serious EBV-related illness may develop later in life. This explains the chronic course of autoimmune diseases that is often accompanied by exacerbations of symptoms. Based on the present studies, EBV infection can cause autoimmune diseases, such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), Sjögren’s syndrome, and autoimmune hepatitis. The EBV has also been reported in patients with autoimmune thyroid disorders. Although EBV is not the only agent responsible for the development of autoimmune thyroid diseases, it can be considered a contributory factor.

Key words: autoimmunity, Epstein-Barr virus, autoimmune thyroid disorders.

Epstein-Barr virus: biology and disease

The Epstein-Barr virus (EBV) is a member of the Herpesviridae virus family. Human beings are the primary reservoir for EBV. Its main targets are B-lymphocytes and nasopharyngeal epithelial cells. It is estimated that the incidence of EBV infection among adults is between 90% and 95%. The EBV’s life cycle is divided into the lytic and latent phases [1]. Most infections are symptomless [2]. However, it is evident that EBV may cause infectious mononucleosis (IM) in the lytic phase of EBV’s life cycle. Past EBV infection is associated with Burkitt lymphoma, Hodgkin disease, and nasopharyngeal or stomach cancer [1]. In addition, there is a hypothesis that past EBV infection can also lead to certain allergic and autoimmune diseases [1]. Once a person has been infected with EBV, she or he will carry EBV latent infection of B-lymphocytes [3]. Viral load remains relatively constant over time in circulating B-cells with a non-activated phenotype [4]. However, during the latent phase, EBV reactivation is possible. It can be caused by either immunosuppression, certain cytokines, or steroid hormones [1].

Infectious agents and autoimmunity

Although potential mechanisms of autoimmune diseases have not been clearly elucidated, both genetic and environmental factors, such as infectious agents, are considered to be responsible for their development [5]. The microbial agents include viruses, bacteria, fungi, and parasites [6]. Also, five possible mechanisms for the pathogenesis of autoimmune diseases have been distinguished:

- molecular mimicry – activation of autoreactive T cells by microbial peptides with structural similarity to self-peptides;
- viral and bacterial superantigens – activation of autoreactive T cells that express particular Vβ segments;
- enhanced processing and presentation of auto-antigens by antigen-presenting cells recruited to an inflammatory site and followed by autoreactive lymphocyte priming.
• bystander activation – enhanced cytokine production that induces the expansion of autoreactive T cells;
• activation of lymphocytes by lymphotropic viruses – an infection of B cells resulting in B cell proliferation, excess antibody production, and formation of circulating immune complexes [6, 7].

**The role of the Epstein-Barr virus in autoimmunisation**

Epstein-Barr virus is considered to be an aetiopathological factor of autoimmune diseases because of the following:

• the virus is a common pathogen responsible for the worldwide prevalence of autoimmune diseases;
• EBV stays in the body throughout life, which explains the chronic course of autoimmune diseases that are often accompanied by exacerbations of symptoms;
• the virus modifies the host immune response [5].

Epstein-Barr virus shows immunomodulatory effects. It encodes a homolog of the bcl-2 oncogene that inhibits apoptosis and interferon γ (IFN-γ) signaling in B-cells. It is also responsible for changes in the production of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, and IL-6, as well as of viral cytokines that share immunosuppressive properties with IL-10 [8, 9]. Interleukin 10 intensifies B-cell expression and reduces IFN-γ production [10]. Interleukin 1, TNF-α, and IFN-γ can induce HLA class II expression and lead to auto-antigen presentation and auto-reactive T-cell activation [11]. The Epstein-Barr virus can also infect T lymphocytes [12].

In 1971, Evan demonstrated raised antibody titres to EBV in patients with systemic lupus erythematosus (SLE). This was the reason to suspect that the EBV might participate in the development of autoimmune diseases [13]. Moreover, there is now evidence that EBV infection can cause autoimmune diseases, for example SLE [13, 14], multiple sclerosis (MS) [15], rheumatoid arthritis (RA) [16], Sjögren's syndrome [17, 18], or autoimmune hepatitis [19]. Several mechanisms of autoimmunity have been shown to be involved in the pathogenesis of these diseases. As far as lupus erythematosus is concerned, these are: high EBV DNA viral loads, elevated EBV antibody concentrations, impaired EBV-specific T-cell responses, and the phenomenon of molecular mimicry [5, 20]. For rheumatoid arthritis, they include: high anti-EBV titres, cell-mediated control of EBV, cross-reactivity between EBV and human self-proteins (molecular mimicry), presence of the EBV genome in synovial membrane, and a cell-mediated response to the EBV within the joint [21]. For primary Sjögren's syndrome (pSS), they are: more frequent presence of EBV DNA in saliva and salivary tissue, as well as an elevated level of anti-EBV titres [22]. Patients with infectious mononucleosis have been reported with various antibodies in their serum. This can also suggest that there is a link between the EBV infection and autoimmune diseases [23].

**Aetiology of autoimmune thyroid disorders**

Autoimmune thyroid disorders (AITDs) are the most common organ-specific autoimmune diseases [24]. They affect up to 10% of the world’s population [25]. Autoimmune thyroid disorders develop upon activation of specific helper T cells directed against the thyroid antigens, the thyroid peroxidase (TPO), and the thyrotropin receptor (TSHR). Activated helper T cells induce B cells to secrete thyroid antibodies, such as the thyroid peroxidase antibodies (TPOAbs) and the thyrotropin receptor antibodies (TRAbs) [26].

Family clustering of these disorders may provide evidence for their genetic and environmental aetiology [27]. According to Hansen, between 60% and 70% of autoimmune thyroid disorders are genetic-related [28]. Environmental factors are also said to play a role in AITDs, accounting for 20–40% of cases with regard to monozygous twins [29]. Other factors that are also considered to be responsible for autoimmune thyroid disorders include: irradiation, treatment with radiiodine, iodine or iodine-rich amiodarone, selenium intake, hormones, oral contraceptives, drugs, antiretrovirals, pregnancy and/or parity, stress, direct trauma, seasonal variation, smoking, campath-1H anti-CD52, IFN-γ, IL-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), viral and/or bacterial infections, and lack of infections (the hygiene hypothesis) [27, 30].

The morbidity rate for Graves’ disease is increased in spring and summer. This confirms an infectious aetiology of the disorders [31]. To be specific, thyocytes express a functional toll-like receptor 3 (TLR3) which, when over-expressed, may cause Hashimoto’s thyroiditis (HT) that can be induced by a virus infection [32].

Penhale and Young have demonstrated that rats that have undergone both thymectomy and irradiation are less susceptible to AITDs if maintained under specific pathogen-free conditions [33]. In 1983, Carter and Smith infected chicken embryos with an avian leukemia virus, RAV-7. As a result, the chickens became hypothyroid [34]. Based on these results, infections may either induce or exacerbate autoimmune thyroid disorders [27]. Wolf found that infections with *Yersinia enterocolitica* could be linked to Graves’ disease [35]. Tzolli, in turn, has suggested that *Toxoplasma gondii* may participate in AITDs [26]. In a study by Wasserman, it was shown that prior infection with *Toxoplasma gondii* can be closely associated with elevated thyroid peroxidase antibodies [36].

In addition, researchers have shown that HTLV-1 may have an impact on the development of both Hashimoto’s thyroiditis [37, 38] and Graves’ disease [39]. Other studies have found that there is a possible link between HIV infection and autoimmune thyroid disorders [40, 41]. Also,
human foamy virus (HFV) proteins have been detected in the thyroid tissue of patients with Graves’ disease [42].

Serological data indicates that the influenza virus, hepatitis C virus, enterobacteriaceae, streptococci, staphylococci, *Yersinia*, and *Helicobacter* can have an influence on AITDs as well [26, 42]. Nevertheless, conflicting data has also been published with regard to the rubella virus, the parvovirus, as well as hepatitis B and C viruses [43].

**Epstein-Barr virus as an aetiological factor in autoimmune thyroid disorders**

In one study, thyroid tissue specimens obtained from AITD patients and patients with multinodular goitre have been investigated to detect Herpesviridae DNA. The group of AITD patients have been reported with Herpesviridae DNA more frequently than the other group. However, there was no statistical significance observed in AITD patients, nor in patients with any other viruses [44].

There is a hypothesis that in genetically susceptible patients, EBV-infected autoreactive B-cells seed the thyroid gland, produce autoantibodies, and send co-stimulatory signals to autoreactive T-cells [45]. Normally, the EBV infection is kept under control, especially by cytotoxic CD8+ T-cells that eliminate proliferating and lytically infected B-cells [46]. Impaired EBV control may result from a decreased number of EBV-specific CD8+ T-cells. An increased CD4/CD8 ratio is characteristic of autoimmune diseases [45].

In their study, Akahori et al. presented three cases of patients suffering from Graves’ disease comorbid with infectious mononucleosis due to primary EBV infection [47]. They suggested that inflammation from viral infection might be associated with the development of Graves’ disease [47].

Nagata has shown that *in vitro* reactivation of the EBV infection causes the production of thyrotropin receptor antibodies (TRAbs) in EBV-infected B-cells with TRAbs on their surface [48]. Moreover, Nagata has also reported increased TRAb titres in children with infectious mononucleosis due to EBV primary infection [23].

In a study by Janegova, subjects with Hashimoto’s thyroiditis were reported with latent membrane protein 1 (LMP1), which was not revealed in the case of Graves’ disease patients. Epstein-Barr virus-encoded small RNAs (EBERs) were detected in both Hashimoto’s thyroiditis and Graves’ disease patients, exclusive of negative control samples [25].

In addition, an elevated serum level of Epstein-Barr nuclear antigen (EBNA) was observed in patients with Hashimoto’s thyroiditis [49]. Also, it was found that antibodies against EBV viral capsid antigen (IgG-VCA) and against early antigen (IgG-EA-D/DR) were more common for patients with thyroiditis versus the controls [49]. The seroprevalence of EBV infection was reported to be higher in children with autoimmune thyroid disorders when compared to the controls [50]. However, Tozzi failed to observe elevated EBV-IgG levels in AITD patients when compared to the healthy controls [26].

It is said that thyroid autoantibodies occur more frequently in subjects with autoimmune diseases versus the general population [24]. Experts suggest that thyroid function screening should be conducted in patients with primary Sjögren’s syndrome, rheumatoid arthritis, and lupus erythematosus [24] because these diseases may be connected with EBV infection.

The EBV can lead to *in vitro* transformation of normal resting B lymphocytes to proliferating lymphoblasts [12]. Moreover, the virus can be found in many lymphomas [51]. Therefore, researchers suggest that EBV may participate in the malignant transformation of Hashimoto’s disease into malignant lymphoma of the thyroid [52] (Table 1). Over 90% of all primary thyroid lymphomas are diagnosed in individuals with a history of Hashimoto’s disease [53], and the majority of them are of B-cell origin [12].

| Table 1. A possible link between the Epstein-Barr virus (EBV) infection and autoimmune thyroid disorders (AITD) according to literature |
|---------------------------------------------------------------|
| AITD patients have been more frequently reported with Herpesviridae DNA |
| Graves’ disease coexisted with infectious mononucleosis due to primary EBV infection |
| Increased TRAb titres in children with infectious mononucleosis due to EBV primary infection were observed |
| *In vitro* reactivation of the Epstein-Barr virus infection caused the production of TRAbs in EBV-infected B-cells with TRAbs on their surface |
| Subjects with Hashimoto’s thyroiditis were reported with latent membrane protein 1 (LMP1) |
| EBERs were detected in Hashimoto’s thyroiditis and Graves’ disease patients |
| Elevated serum level of Epstein-Barr nuclear antigen (EBNA) was observed in patients with Hashimoto’s thyroiditis |
| IgG-VCA and IgG-EA-D/DR were more common for patients with thyroiditis |
Conclusions

Based on the study results, EBV is not the only agent responsible for the development of autoimmune thyroid diseases. However, it can be considered a contributory factor. Further investigations still need to be undertaken to explain the link between the EBV infection and autoimmune thyroid disorders.

The authors declare no conflict of interest.

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