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Review article

Epstein–Barr virus and multiple sclerosis. From evidence to therapeutic strategies

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ABSTRACT

Multiple sclerosis is caused by a complex interaction between genetic predisposition and environmental factors. Epstein–Barr virus (EBV) is an environmental risk factor that is strongly related to multiple sclerosis (MS), since EBV seropositivity is linked to a significant risk of developing MS. EBV may be involved in the pathogenesis of the disease and it is possibly a prerequisite for the development of MS. EBV infection persists in B-cells during the lifetime of the host and can modulate their function. In addition, MS patients might have a deficient capacity to eliminate latent EBV infection in the central nervous system and this would promote the accumulation of infected B cells. Several mechanisms of pathogenesis, including a direct and indirect function of infected B cells, have been postulated in inflammation and neurodegeneration. A relationship between EBV and human endogenous retroviruses in the pathogenesis of MS has also been reported. If EBV is important in the pathogenesis of MS, different therapeutic strategies seem possible for MS treatment.

Contents

1. Introduction

Multiple sclerosis (MS) is considered an inflammatory demyelinating disease affecting the central nervous system (CNS), leading to myelin and axonal loss and progressively increasing disability in the patient. MS is not a very common disease but it seems that there is a universal increase in prevalence and incidence of MS [36].

It is believed that MS might be caused by a complex interaction between genetic predisposition and environmental factors [27,38,57].

Abbreviations: BBB, blood–brain barrier; CIS, clinically isolated syndrome; CNS, central nervous system; CSF, Cerebrospinal Fluid; EBV, Epstein–Barr virus; HERVs, Human endogenous retroviruses; HERV-W, W family of human endogenous retroviruses; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSRV, multiple sclerosis associated retrovirus; NK, natural killer; OCB, oligoclonal bands; OR, odds ratio; RRMS, Relapsing remitting multiple sclerosis.

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Thus, several environmental risk factors have been proposed as triggers of MS, including Epstein–Barr virus (EBV). The present contribution is a narrative review of the literature on EBV and MS, including their relationship in MS pathogenesis and potential treatment strategies. In order to write this narrative review, a thorough search of medical literature (MEDLINE) to retrieve relevant studies have been done.

2. The biology of Epstein–Barr virus infection

At least 90% of the population worldwide is infected by EBV. EBV infection usually occurs in early childhood and most cases are asymptomatic, but it can cause the clinical syndrome of infectious mononucleosis [7], mostly when the infection occurs in adolescence or later. What makes EBV so interesting is the fact that its infection is linked not only to autoimmune diseases such as MS but also with the aetiology of a variety of human tumours [59,96]. This association might be explained by the capacity of EBV to cause a lifelong infection, hiding in a latent form in memory B cells whilst reducing its level of pathogenicity [54].

According to the Germinal centre model of EBV infection [85], the cycle of EBV infection (Fig. Fig. 1) starts with its transmission from an EBV-seropositive host to an EBV-naive person via saliva [95]. The replication of the virus is followed by the infection of naive B cells located in Waldeyer's ring. The virus activates its growth programme in the germinal centre, which leads the newly infected B cells to become activated B blasts and finally resting memory B cells that enter the peripheral circulation. The genome of the virus remains latent as an episome in the nucleus of infected memory B-cells, as part of the latent phase of the infection [56]. Sporadically, latently infected memory B cells return to the germinal centre in the tonsils where they reactivate into the lytic cycle.

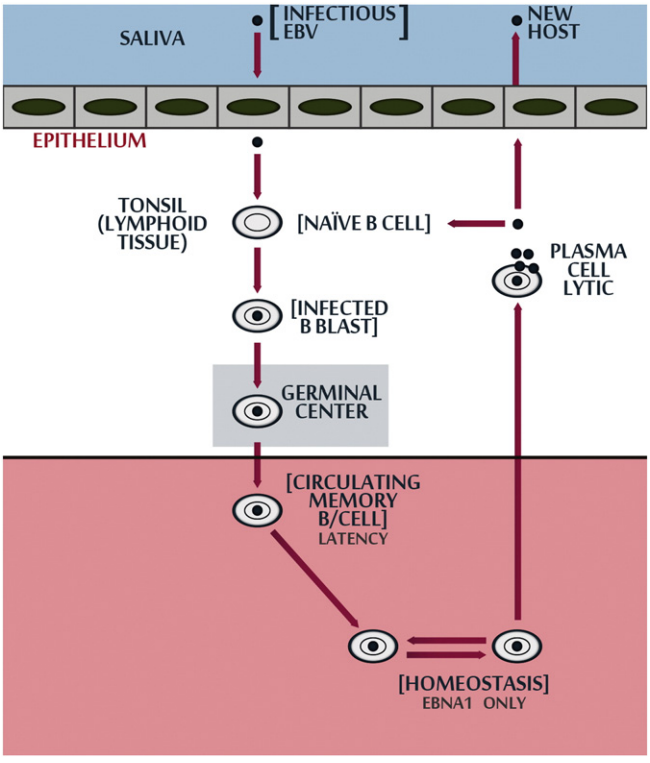

Fig. 1. Cycle of persistent infection of EBV according to the proposed Germinal Centre Model. During primary infection, EBV enters through the saliva and infects naïve B cells located in the tonsil. The cycle goes on with a first transformation to activated B blasts and then in the germinal centres a posterior proliferation and differentiation in latently infected memory B cells. These cells circulate in the blood without any expression of viral proteins except EBNA 1 during cell division due to cell homeostasis. The cycle finally ends in the tonsils again, where latently infected memory B cells return and differentiate into plasma cells. This transformation initiates the lytic phase of infection with production of new virions. A new cycle in the same or a different host starts again. The immune system, mainly the CD8+ cytotoxic cells and EBV antibodies, respond to and control EBV proliferation except in the latent phase of the infection.

In immunocompetent hosts, the immune system can detect, attack and control infections. In the latency phase, infected memory B cells do not express viral proteins since the growth-promoting genes of the virus are no longer expressed, and thus the immune system cannot detect them. However, EBV-infected memory B cells express EBNA-1 protein when they divide as part of their cell homeostasis and it occurs because the latent virus is reactivated in order to keep the viral genome in the new memory B cells. This way the infection can continue for a long time [84].

There are particular conditions that change the usual cycle of infection and lead to uncontrolled EBV replication as it occurs specifically in immunosuppressed or immunodeficient hosts, or in patients with a functional defect in their EBV-specific T cells or NK cells. So, the impairment seems to be a risk factor for malignant transformation and the development of autoimmune diseases [54,83].

3. 3. The relationship between EBV infection and multiple sclerosis

3.1. EBV serology in MS patients

Recently, an umbrella review of meta-analyses showed that smoking and previous infection with EBV, demonstrated by anti-EBNA IgG seropositivity or previous infectious mononucleosis, were the most strongly linked environmental risk factors for developing MS [9].

An association between EBV infection and MS has been hypothesised for 30 years, since a higher frequency of EBV seropositivity in MS patients in comparison with control patients had been reported [11,23,82].

Successive studies and systematic reviews showed that a history of infectious mononucleosis significantly increases the risk of multiple sclerosis [29], and that EBV seropositive subjects have an increased MS risk, especially in individuals with anti-EBNA-1 igG and anti-VCA IgG antibodies [1,72]. Interestingly, an odds ratio (OR) of 0,06 was found in a review that investigated EBV seronegativity and MS [6]. Paediatric onset MS patients do not seem to have the same high EBV infection rates seen in adult onset patients, and it has been calculated that 14% of the children diagnosed with MS were EBV seronegative [8], although another meta-analysis showed the same rate of seropositivity for both, child and adult onset MS patients [58].

The divergences found between studies carried out with adult and paediatric patients might be explained by the fact that it is more difficult to make a correct diagnosis of MS in children than in adults [17] and that there is no 100% sensitive and specific test for EBV antibodies [18].

Although most of the general adult population is infected by EBV, the vast majority do not develop MS. So, it seems that EBV infection is a prerequisite for the development of MS, but it is not sufficient to explain the cause of the disease. This leads to think that EBV infection must be part of the causal pathways leading to MS [26] and its interaction with other factors predispose each individual to developing MS, such as EBV genetic variants [52] or the controversial role of vitamin D deficiency [24,32,53,69] and genetic predisposition involving immune system function with MHC genes [68] and non-MHC genes ([13], Hadjixenofontos et al. [97]). In the same way there is a strong association between smoking and MS [9]. It has been reported a gene–environment interaction of smoking with genetic polymorphisms [12,30] and an interaction between smoking and EBV infection as a risk factor of MS [71].

3.2. EBV and MS pathology

MS pathology is characterized by the presence of tissue injury in the white and grey matter of the brain and spinal cord [41]. While focal demyelinating plaques associated with inflammation and blood–brain barrier (BBB) injury are predominantly seen in patients with Relapsing