Immunologic Research (2022) 70:546–549
https://doi.org/10.1007/s12026-022-09291-y

COMMENTARY

Involvement of age-associated B cells in EBV-triggered autoimmunity

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Received: 14 February 2022 / Accepted: 8 May 2022 / Published online: 16 May 2022

Abstract

EBV infection has long been suspected to play a role in the development of autoimmune diseases. Interestingly, a recently published study has provided the strongest evidence to date that EBV is truly a trigger for multiple sclerosis, a well known inflammatory and neurodegenerative autoimmune disorder. Taking into account the data derived from mice models of autoimmune diseases that were also infected with a murine analog of EBV, in this commentary, we highlight the involvement of age-associated B cells, a B cell population defined as $CD19^{+}CD11c^{+}CD21^{-}T\text{-}bet^{+}$, in the process of EBV-triggered autoimmunity. Of note, the aforementioned B cell subset expands continuously with age in healthy individuals, whereas displays a premature strong accumulation in cases of autoimmune diseases. These cells contribute to autoimmune disease pathogenesis via a variety of functions, such as the production of autoantibodies and/or the formation of spontaneous germinal centers. Latent form of EBV seems to modify these B cells, so as to function pathogenically in cases of autoimmunity. Targeting of ABCs, as well as the elimination of EBV, may both be potential treatments for autoimmunity.

Highlights

- Latent form of EBV potentially triggers autoimmune diseases
- ABCs expand in autoimmunity and contribute to disease pathogenesis
- EBV modifies ABCs, so as to function pathogenically in autoimmune diseases
- Apart from EBV elimination, targeting of ABCs may also bring therapeutic benefits to autoimmune patients

Keywords EBV · Autoimmunity · Age-associated B cells · ABCs · Double-negative B cells · DN

Abbreviations

ABCs	Age-associated B cells
DN	Double-negative B cells
EBV	Epstein-Barr virus
MS	Multiple Sclerosis
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus

Epstein-Barr virus (EBV) is a human herpesvirus that infects over 90% of the world's population by adulthood. Despite establishing — in nearly all adults — a lifelong persistent asymptomatic infection, the virus serves as the primary agent of infectious mononucleosis [1, 2]. EBV has also been associated with a variety of other illnesses, such as lymphoproliferative disorders and/or epithelial malignancies [3, 4], as it targets the host's B lymphocytes and epithelial cells, respectively. Interestingly, the virus is also associated with enhanced risks of developing certain autoimmune disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS) [5, 6]. Of note, according to recently published data, EBV infection causes a 32-fold increase in the risk of developing MS [7, 8], thus indicating that the aforementioned autoimmune disease is actually triggered by the virus. As expected, the elimination of EBV has been proposed as a potential treatment for MS [9].

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Apart from EBV elimination however, targeting of age-associated B cells (ABCs), a B cell population which is indissolubly linked to autoimmunity [10], may also serve as a therapeutic approach for MS and/or even other autoimmune diseases. More specifically, ABCs constitute a $CD19^{+}CD21^{-}CD11c^{+}$ B cell population that expands continuously with age in healthy individuals [11], whereas displays a premature accumulation in cases of autoimmune diseases [12, 13]. Taking into account the fact that EBV has a potential role in triggering autoimmune phenomena [7, 8], in conjunction with the fact that ABCs expand in autoimmune diseases [12], it is plausible to consider that this B cell subset may be somehow related to EBV-triggered autoimmunity.

It is important to mention that ABCs also expand in infectious diseases and thus contribute (probably) to the clearance of pathogens [14, 15]. However, as far as EBV infection is concerned, it is not clear whether anti-EBV ABCs are being produced. After all, EBV infection is in most cases asymptomatic [1], and ABC percentages seem to correlate with the severity of a disease (at least, in other infectious diseases such as COVID-19) [16]. Although the induction of anti-EBV ABCs can't be excluded, the relationship (if any) between anti-viral ABCs and autoimmunity ABCs remains until today incompletely understood [17]. A hypothesis suggests that EBV infection leads to ABC expansion and skews the population to a Th1 inflammatory phenotype, which may contribute to pathogenesis of autoimmunity [18].

As a result of a synergistic triggering of their BCR, TLR7 and IL-21 or IFNγ receptors [12, 19], ABCs highly express transcription factor T-bet. In the context of autoimmunity, T-bet seems to be the master regulator of processes such as the production of autoreactive IgG, the enhanced antigen presentation to T cells and the formation of spontaneous germinal centers [12, 20, 21]. However, despite the fact that the transcription factor is considered as essential for ABC biology [22], functional ABCs (in murine models) can also be generated in the absence of its expression [23].

In humans, the ABC subset is mainly composed of $IgD^{-}CD27^{-}$ double-negative (DN) B cells [24–26]. DN has further been divided in two discrete subgroups, based on the expression of CXCR5 chemokine, which serves as a follicular homing marker [26]. The $CXCR5^{+}$ subgroup (known as DN1) is expanded in elderly healthy individuals and lacks T-bet expression [24], while the $CXCR5^{-}$ subgroup (known as DN2) highly expresses T-bet and expands in autoimmune diseases, mostly SLE [26, 27]. Of note, DN2 cells are poised to generate autoreactive antibody-secreting plasmablasts [26], their exact role though in the development of autoimmunity is yet to be clarified.

Although DN2 cells are more marked in cases of SLE [26], DN B cells with proinflammatory characteristics are also expanded in a proportion of MS patients [28]. However, these DN cells in MS patients do not seem to correspond with DN2 [29]. Moreover, in RA patients, a subset of $IgD^{-}CD27^{+}$ ABCs has been characterized [12]. These facts make clear that ABC subpopulations, other than DN2, are present in autoimmune disorders and contribute to disease pathogenesis.

Due to some evidence, such as the elevated EBV load in the peripheral blood of SLE and RA patients [30–32], EBV infection has long been suspected as a potential etiologic factor in autoimmune diseases [33]. Notably, as mentioned above, a recent study has provided strong evidence about the role of EBV in the pathogenesis of MS [7], thus further strengthening the scenario of EBV being an initiating factor of autoimmune diseases. These data, in conjunction with the verified role of ABCs in the pathogenesis of autoimmunity, strongly indicate an ABC involvement in EBV-triggered autoimmunity.

Truly, data derived from murine models of RA and MS, both infected with a murine analog of EBV (known as gammaherpesvirus 68), suggest that EBV is actually capable of priming ABCs to contribute pathogenically during autoimmune diseases [18, 34, 35]. More specifically, as far as RA is concerned, latent gammaherpesvirus infection seems to exacerbate arthritis in murine models of the disease, in an ABC-dependent manner. The disease enhancement is not due to active virus stimulation of the immune system, but requires viral latency instead. Interestingly, the usage of ABC knockout mice revealed that ABCs are mechanistically required for viral enhancement of arthritis [34]. In addition to these results, the usage of mice with experimental autoimmune encephalomyelitis, which serve as in vivo models of MS, revealed that ABCs, following infection with gammaherpesvirus, secrete IFNγ and contribute to disease pathogenesis, whereas in the absence of the virus secrete IL-10, which has a protective role. Once again, knocking out ABCs resulted in an amelioration of encephalomyelitis in viral infected mice (but not in the case of non-infected mice), thus indicating that the virus modifies ABCs, so as to function pathogenically [18, 35].

Current therapies for autoimmune diseases are mostly based on immunosuppressive drugs [36], which globally affect the immune system and thus lead to increased risks of infection and/or cancer development [37]. In order to benefit the patients, targeted approaches need to be introduced to the clinical practice. More specifically, targeting of pathogenic B cell populations, such as ABCs which are also considered as drivers of autoimmunity [22], could probably bring the maximum benefits to the patients. It is important to mention that in mice models of autoimmunity, conditional T-bet targeting in B cells has led to general improvement of health status [22], a fact which further strengthens the opinion that ABCs may (and probably should) be targeted in clinical practice for therapeutic interventions [38]. We, ourselves, have proposed some ABC-based therapeutic approaches for SLE

treatment [38]. However, we can't guarantee yet that these approaches shall specifically deplete ABCs only. Moreover, pharmaceutical agents already used in clinical practice, such as belimumab for SLE treatment and/or tocilizumab for RA treatment, seem to significantly affect the ABC/DN percentages, but unfortunately are not limited only to these populations of B cells [39, 40]. Thus, it is obvious that therapeutic strategies to specifically deplete ABCs are needed.

To conclude, it seems that ABCs are (probably) a promising therapeutic target for EBV-mediated autoimmunity in humans [38]. From our point of view, targeting of ABCs is even more promising than EBV elimination, as EBV infects over 90% of the world's population [1], but not all these people develop an autoimmune disease (while autoimmune diseases coincide with ABC expansion, in all the cases [10, 12, 13, 22, 25, 26, 28]). The mechanisms underlying the modification of these cells by the virus, is an issue that requires thorough investigation and a research emphasis should be put on that. It is important to take into consideration the fact that EBV initiates infection of B lymphocytes by binding to CD21, a complement receptor known as CR2 [41]. Since ABCs lack expression of CD21 [11, 12, 26], it is probable that their modification by the virus, as observed in the gammaherpes virus infected murine models of RA and MS, happens in an indirect way.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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