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Perspective

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Coeliac disease as a model for understanding multiple sclerosis

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Abstract

The genetic architecture of multiple sclerosis (MS) is similar to that of coeliac disease, with human leukocyte antigen (HLA) being the greatest genetic determinant in both diseases. Furthermore, similar to the involvement of gluten in coeliac disease, Epstein–Barr virus (EBV) infection is now widely considered to be an important environmental factor in MS. The molecular basis for the HLA association in coeliac disease is well defined, and B cells have a clear role in antigen presentation to gluten-specific $CD4^+$ T cells. By contrast, the mechanisms underlying the HLA association of MS are unknown but accumulating evidence indicates a similar role of B cells acting as antigen-presenting cells. The growing parallels suggest that much could be learned about the mechanisms of MS by using coeliac disease as a model. In this Perspective article, we discuss the insights that could be gained from these parallels and consider the possibility of antiviral treatment against EBV as a therapy for MS that is analogous to the gluten-free diet in coeliac disease.

Sections

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Introduction

Autoimmune diseases have a strong genetic basis, and genome-wide association studies have yielded valuable insights into the genes involved without being influenced by preconceived notions about disease aetiology[1]. These studies have shown that human leukocyte antigen (HLA) is by far the most important genetic risk factor across autoimmune diseases and that many autoimmune diseases share predisposing non-HLA genes. Shared genetic architecture between diseases indicates that common biological pathways underlie the conditions, even when different organs are affected. Consequently, mechanistic insights into one autoimmune disease could help us to understand the underlying mechanisms of other diseases with similar genetic influences.

The pathogenic mechanisms of multiple sclerosis (MS) — a chronic autoimmune disease of the CNS — are unknown, but the disease has a high genetic correlation with coeliac disease[2], an autoimmune enteropathy with pathogenic mechanisms that are well understood. Furthermore, the development of coeliac disease clearly depends on an aetiological environmental factor — gluten — and strong evidence now suggests that Epstein–Barr virus (EBV) is an important environmental factor in the development of MS[3]. Importantly, in both coeliac disease and MS, these environmental factors are required for disease development, but only a fraction of those exposed to these factors develop disease. Given the shared genetic background of the two diseases and the involvement of a specific environmental factor in each, our understanding of the mechanisms of coeliac disease could serve as a valuable model to inform the investigation and elucidation of disease mechanisms in MS.

In this Perspective article, we consider the parallels between coeliac disease and MS, and how knowledge of coeliac disease can form the basis of testable hypotheses about the mechanisms involved in MS and the importance of EBV. We also consider how the management of coeliac disease could translate into a therapeutic strategy for MS by targeting EBV with antiviral drugs.

Coeliac disease as a model

In most autoimmune diseases, including MS, the reasons behind HLA associations remain unknown — but coeliac disease is the exception. In coeliac disease, the primary associations are with HLA-DQ2 (DQ2.5 and DQ2.2) and HLA-DQ8, which selectively present deamidated gluten peptides as antigens to $CD4^+$ T cells[4], leading to pathological inflammation. The three HLA allotypes associated with coeliac disease (DQ2.5, DQ2.2 and DQ8) differ in their peptide-binding specificity and therefore select different gluten T cell epitopes[5], yet they share a unique ability to bind to deamidated gluten peptides[4]. The post-translational deamidation of gluten peptides is mediated by the enzyme transglutaminase 2 (refs. 6,7), which is also the target of autoantibodies in coeliac disease[8]. Though these autoantibodies are highly disease-specific, to the degree that their presence enables the diagnosis to be made in children without examination of a gut biopsy sample[9], little evidence suggests that circulating autoantibodies are pathogenic in coeliac disease[4].

Given that coeliac disease is the only autoimmune disease in which the causal environmental factor, autoantigen and HLA association have all been defined, this disease can serve as a model to understand the role of environmental factors in other autoimmune conditions. EBV has long been proposed as an important environmental factor in MS, but evidence for its involvement has strengthened considerably in the past few years[10,11], thereby increasing the relevance of coeliac disease as a model for the mechanisms of MS.

An important consideration with respect to environmental factors involved in autoimmune diseases is whether they act as a trigger of disease (meaning that they initiate self-perpetuating autoimmune reactions that continue in their absence), a driver of disease (meaning that they fuel autoimmune reactions and their presence is required to maintain the disease process[12]) or both. Coeliac disease becomes quiescent if gluten is excluded from the diet and returns if gluten is reintroduced, strongly suggesting that gluten is a driver of the condition[12]. In principle, gluten could also be a trigger, though the evidence for this is minimal[12]. Whether EBV acts as a trigger or driver in MS remains unknown, and the pathogenesis of MS may be more complex than that of coeliac disease owing to the interplay between peripheral and intrathecal immune responses separated by the blood–brain barrier. Nevertheless, exploring mechanistic parallels between coeliac disease and MS under the assumption that EBV is a driver of MS, as gluten is of coeliac disease, could help us to determine the role of EBV and to discover which antigen or antigens drive the disease, with important implications for treatment.

Insight into HLA associations

Our understanding of coeliac disease has revealed that the association of the disease with specific HLA class II proteins is explained by the ability of these molecules to present deamidated gluten peptides to $CD4^+$ T cells[4]. The gluten proteome is exceptionally complex, including hundreds of proteins with similar sequences, and this extensive sequence microheterogeneity generates many distinct gluten T cell epitopes in coeliac disease[5]. Most other antigens do not display the same sequence microheterogeneity as gluten proteins; therefore, if the HLA association of a disease is explained by preferential binding and T cell presentation of epitopes, only one or a few peptides are likely to be involved in the pathogenesis of the disease. If many peptides and many HLA molecules were involved, a strong HLA association would be unlikely.

Using knowledge of the HLA association in coeliac disease as a model leads to the prediction that the HLA class II association in MS is dictated by the presentation of a few defined peptides. The HLA association is less uniform in MS than in coeliac disease. Though MS risk is often attributed to HLA-DR15, HLA-DR51 and HLA-DQ6 might also be involved, as they are encoded on the same conserved haplotype[13]. A few peptides, or possibly one, that are presented by one of the class II molecules of the DR15 haplotype are likely to explain the main HLA association of MS. However, some people with MS do not express the DR15–DR51–DQ6 haplotype; therefore, other HLA class II allotypes that are encoded on distinct HLA haplotypes could be involved through presentation of other pathogenic peptides. By analogy with coeliac disease, an attractive hypothesis for MS is that the HLA molecules involved in the disease present epitopes from the key environmental factor: EBV. Identifying such peptides would represent a major step forward in the understanding of the pathogenesis of MS.

Evidence from coeliac disease suggests that the selection and presentation of deamidated gluten epitopes that are presented by HLA-DQ2 or HLA-DQ8 involves B cell receptors specific for deamidated gluten or transglutaminase 2 (ref. 14) (Fig. 1). Transglutaminase 2-specific B cells can present deamidated gluten peptides to $CD4^+$ T cells because many gluten peptides are good substrates for transglutaminase 2, and B cells that are specific to transglutaminase 2 can bind to and internalize complexes of the enzyme and native gluten peptides, leading to the release of deamidated epitopes in endosomes[14]. B cells that are specific

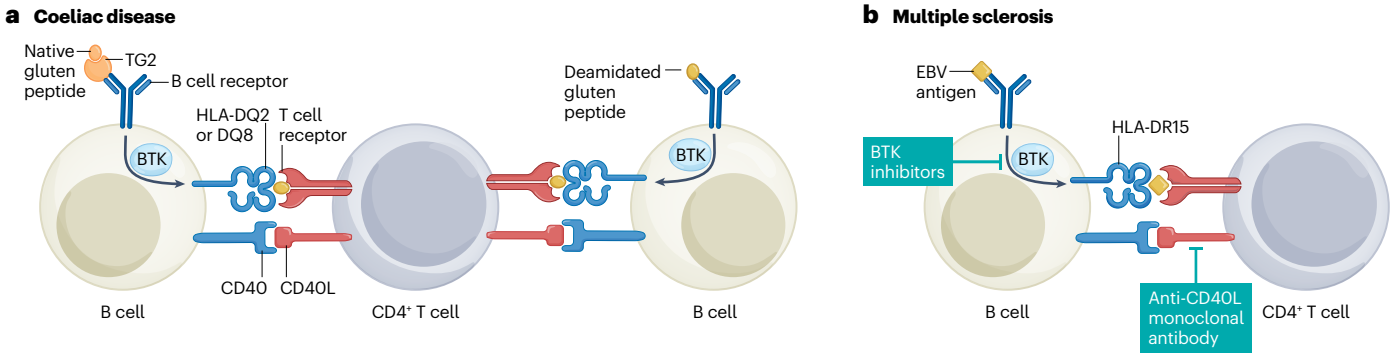

Fig. 1 | B cell and T cell crosstalk in coeliac disease as a framework for multiple sclerosis. a, Coeliac disease is driven by an immune response to dietary gluten that involves coordinated action of B cells and T cells. B cells that are specific for deamidated gluten peptides or for the autoantigen transglutaminase 2 (TG2) present these peptides to $CD4^+$ T cells via disease-associated HLA-DQ2 or HLA-DQ8. Bruton tyrosine kinase (BTK) is involved in the B cell receptor signalling that leads to antigen presentation. TG2 mediates deamidation of gluten peptides; therefore, upon internalization of the TG2–gluten peptide complex, deamidated gluten peptides will be formed in endosomes for antigen presentation. Pathogenic $CD4^+$ T cells recognize deaminated gluten peptides via T cell receptors, leading to their activation and subsequent inflammation and tissue destruction. **b**, We propose a similar model of B cell and T cell interactions in multiple sclerosis as in coeliac disease. In this model, B cells capture and present an Epstein–Barr virus (EBV) antigen (or antigens) via HLA-DR15 to EBV-specific pathogenic $CD4^+$ T cells, leading to activation of these T cells. BTK inhibitors and an anti-CD40L monoclonal antibody disrupt this process, and success with these therapeutic approaches in phase II trials in multiple sclerosis supports this model. CD40L, CD40 ligand.

for deamidated gluten peptides can also present deamidated gluten epitopes to T cells.

The strong association of antibodies against deamidated gluten and transglutaminase 2 with coeliac disease can be explained by such antibodies serving as B cell receptors, thereby facilitating effective presentation of deamidated gluten peptides to $CD4^+$ T cells. Most other autoimmune diseases with primary associations to class II allotypes are also characterized by the presence of autoantibodies, a feature that is not seen in diseases with primary HLA associations to class I allotypes such as ankylosing spondylitis and psoriasis[15]. Therefore, a role for B cells as key antigen-presenting cells (APCs) could be a common feature of such autoimmune diseases. Given the HLA class II allotype associations in MS, the possibility that B cell-mediated epitope selection occurs in MS should be considered and investigated.

B cell-mediated antigen presentation in MS

As discussed above, antigen presentation of deamidated gluten by B cells seems to drive coeliac disease, and clinical evidence now suggests that antigen presentation by B cells is also critical in MS. The involvement of B cells in MS has been established for many years, clearly demonstrated by the therapeutic benefits of anti-CD20 monoclonal antibodies, which deplete B cells and are widely used for the treatment of MS[16,17]. However, given that EBV resides in memory B cells, the question remained of whether the beneficial effects are due to depletion of the B cell reservoir of EBV or to elimination of the function of B cells as APCs.

Beneficial effects of Bruton tyrosine kinase (BTK) inhibitors in phase II trials in MS (NCT02975349, NCT03889639, NCT05119569)[18] indicate that elimination of the APC function of B cells underlies clinical benefits, as these drugs interfere with signalling downstream of the B cell receptor[18] that is required for B cells to function as APCs. However, these results are not conclusive because other reasons for the clinical effect of BTK inhibitors are feasible. Specifically, these drugs also affect the functions of macrophages and innate microglial cells, can act as EBV antivirals by reducing lytic reactivation (the mechanism by which an EBV-infected cell switches on production of viral progeny), and act downstream of the EBV protein LMP2A, which can mimic B cell receptor signalling[19,20].

Results of a phase II clinical trial that showed a reduction in lesions in the brains of people who were treated with the anti-CD40L monoclonal antibody frexalimab[21] provide further insight. The interaction between CD40, which is a membrane protein expressed by APCs, and CD40 ligand (CD40L), which is expressed on activated T cells, is essential in the communication between APCs and $CD4^+$ T cells[22]. The interaction is particularly important for T cells to instruct B cells to undergo immunoglobulin isotype switching and to differentiate into plasma cells that produce high-affinity antibodies. Treatment with frexalimab, in contrast to treatment with anti-CD20 antibodies, should not deplete B cells. Moreover, the therapeutic effect of frexalimab should not relate to the EBV-moderated mechanism of LMP1, which simulates activated CD40 receptors and causes proliferation of infected B cells[23]. Though anti-CD40 treatment could have pleiotropic effects, including restriction of leukocyte transmigration through the brain endothelium[24], the therapeutic effect of frexalimab in MS suggests that antigen presentation is key in the pathogenesis of the disease.

Taken together, the effects of anti-CD20 antibodies, BTK inhibitors and an anti-CD40L antibody indicate that the function of B cells as APCs has a key role in the pathogenesis of MS. Furthermore, the effects of these drugs suggest that an essential part of antigen presentation occurs in the periphery before lymphocytes migrate to the CNS, because monoclonal antibodies do not typically enter the CNS, and the irreversible BTK inhibitor evobrutinib does not reach its half-maximal inhibitory concentration intrathecally[18].

Potential for antigen identification in MS

Given the evidence that the APC function of B cells is important in MS, we suggest a model in which B cells play an important role in selecting the exogenous antigens that give rise to disease-predisposing HLA molecules, as in coeliac disease (Fig. 1). On the basis of this model, identifying intrathecal B cell receptors and antibodies that are shared

among people with MS could lead to identification of antigenic peptides that are responsible for the HLA association in MS.

People with MS do have elevated titres of antibodies against EBV latent antigen 1 (EBNA1), which is expressed when EBV is present in a host cell but not actively producing infectious progeny. Higher levels of EBNA1 antibodies are associated with a higher risk of MS[25], and some evidence suggests that specific HLA allotypes are associated with the production of such antibodies[26]. Given that enrichment of the EBV antibody repertoire in MS is primarily restricted to EBNA1 (ref. 27), though not to any particular region of EBNA1 (ref. 28), the model suggested above would indicate that EBNA1 is an immunogen that drives disease activity, a hypothesis that can be tested. EBNA1-reactive antibodies in people with MS cross-react with various CNS antigens, including anoctamin 2 (ref. 29), GlialCAM[30] and α-crystallin[31], and this cross-reactivity could explain how B cell reactivity to EBV results in autoimmunity. However, the target epitopes on the transmembrane antigens GlialCAM and anoctamin 2 map to their intracellular domains, meaning that the antibodies are unlikely to have a direct role in CNS damage via interactions with these proteins.

The proposed model also suggests that comparison of the B cell phenotypes that are present in the CNS of people with MS — especially those in tertiary lymphoid follicles, the presence of which is associated with disability[32] — with the phenotypes of gluten-specific B cells in coeliac disease could also be valuable. Similarities in B cell phenotypes between the diseases could help to identify strategies for selective targeting of B cell subsets.

An alternative model, albeit without a notable precedent, would involve the activation of $CD4^+$ T cells by an antigen that is presented by EBV-infected B cells in their capacity as APCs but which does not involve B cell receptor-mediated uptake of antigen. In this model, EBV antigens could be selected from those that are accessible to the intracellular pathways involved in HLA class II peptide loading. Given that some data indicate compartmentalized EBV lytic reactivation in the CNS[33], EBV antigens other than EBNA1 could be selected in this context. To address this hypothesis, broad approaches for identification of pathogenic EBV antigens in MS would be needed.

Identification of B cell receptors that might be responsible for selecting HLA ligands and determining the $CD4^+$ T cell repertoire in the CNS in MS could be instrumental in identifying the specific antigens that underlie the HLA association of the disease. If indeed EBV is a driver of MS, as gluten is a driver of coeliac disease, these antigens are likely to derive from EBV proteins and will be identifiable.

T cells in coeliac disease and MS

The specificity of coeliac disease to the gut is known to be due to the physical presence of the antigen (gluten) in the gut, which leads to local activation of $CD4^+$ T cells that drive a pathological immune response. The reasons for the specificity of MS to the brain are unknown but, if EBV antigens drive MS in a similar way to how gluten drives coeliac disease, the presence of EBV antigens would be expected in the CNS. Direct detection of EBV is challenging owing to the extreme rarity of EBV-infected B cells[34] and the robust immune response against the virus, and attempts to detect EBV in the CNS of people with MS have yielded contradictory results[35–37]. However, knowledge of the T cell response in coeliac disease could provide critical insights that help to resolve this challenge. In coeliac disease, an oral challenge with gluten during remission leads to expression of the activation marker CD38 on gluten-specific $CD4^+$ T cells a few days after gluten exposure[38]. By analogy, understanding the T cell activation kinetics in MS could help to clarify the role of EBV in the disease — the antigenic specificity and activation state of T cells in response to EBV can be used as a footprint to determine whether EBV antigens are present in the periphery or the CNS, even in the apparent absence of the virus.

Activation of tissue-resident, gluten-specific $CD4^+$ T cells in coeliac disease leads to local production of cytokines (particularly interferon-γ and IL-21) that instigate further immune reactions[4]. A similar role for interferon-γ is indicated in MS by an increase in the number of exacerbations after clinical administration of interferon-γ[39]. The cytokines produced by gluten-specific $CD4^+$ T cells in coeliac disease seem to have a particularly important effect on intra-epithelial $CD8^+$ T cells[4], which contribute to damage of enterocytes when activated[40–42]. Clonal expansion (albeit highly polyclonal) of $CD8^+$ T cells with αβ T cell receptors is also observed[42,43], although the role of the αβ T cell receptors in these T cells is unclear. The $CD8^+$ T cells kill epithelial cells upon recognition of stress-induced molecules on the epithelial cells via the natural killer cell receptors NKG2D and NKD2C; little evidence suggests that these T cells recognize the gluten antigen[41,44,45]. Similar NKG2D ligands are localized to oligodendrocytes in MS lesions and could be targets of cytotoxic $CD8^+$ T cells[46]. In MS, sequencing of αβ T cell receptors expressed by intrathecal T cells has revealed an altered repertoire in comparison with that in healthy people; this repertoire includes more sequences that are EBV-reactive and sequences that are reactive to a broader set of EBV epitopes. The presence of EBV-specific memory $CD8^+$ T cells in the cerebrospinal fluid suggests that antigenic stimulation is ongoing[33]. In addition, nearly all EBV-reactive $CD8^+$ T cells in the cerebrospinal fluid of people with MS expressed T cell receptors that were specific for EBV lytic antigens rather than EBV latent antigens[33]. These findings could be explained either by CNS-specific, localized EBV lytic reactivation or by trafficking of these T cells to the CNS after lytic activity in the periphery. Determining which of these processes occurs has important therapeutic implications as localized lytic reactivation in the CNS would mean that treatments would need to cross the blood–brain barrier to be effective. Further studies are needed to elucidate the contributions of latent and lytic EBV antigens and their associations with MS. Given the involvement of natural killer receptors in coeliac disease, investigation of these receptor types on intrathecal T cells in MS is also warranted.

Antiviral therapies in MS

If EBV antigens drive MS in the same way that gluten drives coeliac disease, then elimination of these antigens should alleviate the disease. By contrast, if EBV is a trigger and CNS autoimmunity develops as a result of epitope spreading (that is, diversification of the epitopes recognized), interventions that target EBV might not be effective once MS is established. However, the fact that coeliac disease resolves upon elimination of gluten combined with the possibility that similar mechanisms underlie MS suggests that targeting EBV with antiviral therapies in MS is worth exploring as a therapeutic strategy.

If MS is driven by the EBNA1 antigen, disrupting the binding of EBNA1 to episomal viral DNA to promote episome loss, which would eliminate the source of EBNA1 expression, could be an effective therapeutic strategy[47]. Alternatively, drugs that target the EBV DNA polymerase could be effective; these drugs strongly suppress the expression of a limited subset of viral antigens, referred to as late-lytic antigens[48], which primarily encode structural elements that couple DNA replication to packaging. These late-lytic EBV antigens are typically the targets of $CD4^+$ T cells (whereas the targets of $CD8^+$ T cells are typically immediate-early or early-lytic antigens that are not suppressed

by antivirals)[49,50]; therefore, if the pathogenic antigens presented to CD4$^+$ T cells in MS belong to this class, targeting the DNA polymerase would remove these antigens from immunosurveillance. Critically, any antiviral drug used to target EBV in MS should not depend on a viral enzyme for its metabolism, as expression of viral antigens would then be needed for the drug to accumulate in the cell, thereby defeating the purpose of the strategy.

Some evidence does indicate that antiviral therapy to target EBV is beneficial in MS. Though the findings are highly preliminary, treatment of several individuals with drugs that have anti-EBV activity in vitro seemed to suppress MS disease activity[48,51]. Similarly, in a study of spontaneous lymphoblastoid cell lines derived from people with active MS, EBV lytic reactivation was observed in these cells and activation of co-cultured autologous CD4$^+$ T cells was reduced upon treatment with the anti-EBV drug tenofovir, though only a limited number of lymphoblastoid cell lines were tested[52].

An important challenge in the use of antiviral therapy against EBV in MS is establishing biomarkers of antiviral efficacy in humans. EBV is latent in peripheral blood memory B cells, and its preservation in B cells could result from lymphoproliferation of cells that are already infected rather than from infection of additional B cells. Furthermore, salivary shedding of EBV seems to occur independently of the status of the B cell compartment, as this shedding is not affected by B cell depletion[53]. Again, knowledge of coeliac disease could provide a solution to this challenge of biomarkers. In coeliac disease, gluten-reactive CD4$^+$ T cells express a distinct and narrow phenotype that is likely to be a reflection of their role in providing B cell help[54]. In the presence of gluten in the diet, these CD4$^+$ T cells are activated and express the activation marker CD38, but this marker of activation is rapidly lost when gluten is eliminated from the diet[55]. Development of analogous EBV-specific CD4$^+$ T cell biomarkers that act as reporters of EBV presentation by APCs in MS could greatly facilitate the rational development of effective antiviral therapies.

Conclusions and future directions

EBV has been suggested as a trigger of MS, as the virus must be acquired before the onset of disease[11]. By contrast, drawing on coeliac disease as a model could help us to determine whether and how EBV is a driver of MS. Defining the pathogenic antigen or antigens in MS is essential for the development of novel therapeutic approaches. We propose that dissecting the crosstalk between T cells and B cells to explain the HLA association in MS, as has been done in coeliac disease, would help to identify those antigens. If EBV is indeed a driver of MS, the use of non-immunosuppressive antiviral therapeutics could be a novel treatment strategy for MS. To answer fundamental questions about the feasibility of this approach, a phase II study is needed to test an appropriately dosed EBV antiviral as a monotherapy with an end point of MRI disease activity. Investigating MS by using coeliac disease as a model in this way has the potential to answer questions that will further the scientific understanding and treatment of MS.

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Author contributions

The authors contributed to all aspects of the manuscript.

Competing interests

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