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Editorial

Nishizawa K*
Biomolecular Logic Research Laboratory, Takinogawa, Kita, Tokyo, Japan

Editorial

Important discoveries leading to a paradigm shift often give researchers excitement, encouraging further studies. In my view, remarkable developments in biomedical research in the recent two decades were witnessed in the field of autoimmune demyelinating diseases, that is, multiple sclerosis (MS) and other associated disorders. With the hope that such a success story will give insights to biomedical researchers, here I will briefly discuss several discoveries in this field. Firstly, I will focus on neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Studies of these diseases, which were once considered variants of MS, provided important insights into autoimmunity. I secondly discuss recent breakthroughs regarding the role of B cells in MS pathogenesis. Finally, I discuss some current studies on causative factors in MS mainly focusing on those on Epstein-Barr virus (EBV). As this editorial does not aim to cite many important papers, I will suggest readers excellent review articles cited below and papers cited therein.

Until 2000 or so, MS was a singular focus in demyelinating diseases, and neuromyelitis optica (NMO) (Devic's disease) has long been thought of as a variant of MS and with features overlapping with MS [1]. Historically, the term NMO or Devic's disease was used to represent a syndrome characterized by isolated optic neuritis with myelitis, which occur simultaneously or sequentially [1].

In 2004, autoantibodies that bind to murine tissue in a unique way were discovered in NMO and the antigen was identified as aquaporin-4 (AQP4) water channel afterwards. NMO diagnostic criterion was revised reflecting the clinical usefulness of anti-AQP4 antibody. The term NMOSD was introduced to allow for anatomically limited cases and was adopted as the name of the disease in 2015 [1]. The anti-AQP4 antibody is considered to be pathogenic, causing complement activation and primary astrocytopathy, leading to demyelination [1,2]. This was in accord with the finding that AQP4 orthogonal arrays of particles (OAPs), the target of pathogenic anti-AQP4 IgG in NMO, are expressed on astrocytes and the NMO lesion is localized to areas with high density OAPs [3].

Anti-myelin oligodendrocyte glycoprotein (MOG) antibody was found in MS patients since earlier than 1990 [4]. However, in 2006, anti-MOG antibodies were found from patients who suffered NMOSD-like optic neuritis and myelitis despite anti-AQP4 antibody negative. Later on, a seminal study elucidated that anti-MOG antibody causes disease that resembles NMOSD only when the antibody can bind to the antigen MOG with the native-type conformation [5]. In contrast, anti-MOG antibodies that only bind to unfolded MOG peptide were associated with experimental autoimmune encephalomyelitis (EAE), a well-studied model of MS [5]. This discovery led to the use of cell-based assays of anti-MOG IgG which helped discriminating MOGAD from conventional MS. (For methodologies for EAE model, Calvo et al is recommended, [6]).

Both MOGAD and NMOSD develop severe attacks of optic nerve and frequent involvement of spinal cord lesions and brain involvement, but their clinical features are different. While both diseases typically undergo more severe attacks than MS, recovery is generally better for MOGAD relative to NMOSD. MOGAD shows high frequency in young children compared to MS and NMOSD. MOGAD in pediatric population often causes acute disseminated encephalomyelitis (ADEM). Importantly, MOGAD shows more pronounced heterogeneity in location of lesion, age at disease and course compared to NMOSD. NMOSD is known to show high incidence rates in non-white populations. Of note, the MS criterion is basically 'a diagnosis of exclusion' [7] and MS diagnosis is made when there is no better explanation and there is no other diagnosis (including NMOSD and MOGAD) is possible. This is mainly because of the heterogeniety in pathogenesis of MS, which in turn can be influenced by genetic features of the patient and the relevant viruses.

MS has long been considered a prototypic T cell-mediated autoimmune disease. A number of studies with diverse approaches including genetic analyses, animal model studies, analyses using clinical samples pointed to the importance of T cell activation in MS [8]. Both Th1 and Th17 cells are considered important and, intriguingly, they use different mechanisms (e.g., anatomical entry sites) in the MS pathogenesis [8,9].

Studies of NMOSD and MOGAD have provided insights into roles of B cells. In general, antibodies recognizing AQP4 in NMOSD are pathogenic [2]. Although attempts to establish a mice model (based on immunization by AQP4) have been unsuccessful, the causative role of anti-AQP4 antibody is clear. AQP4 OAPs provide a platform for IgG clustering and subsequent complement deposition [10]. Rituximab, a monoclonal antibody that selectively targets and depletes $CD20^+$ B cells, showed significant clinical improvement in AQP4-positive NMOSD, in support of the pathogenic role of anti-AQP4 antibody [1,11].

In contrast to NMOSD, while anti-MOG 'antibodies' can exacerbate EAE and central nervous system (CNS) demyelination, those antibodies are neither necessary nor sufficient to cause EAE [3]. In MOGAD, the course of disease

(e.g., relapses) did not correlate well with the titers of anti-MOG antibody [3]. Importantly, anti-MOG antibody production may be a tip of iceberg and more complex but largely unknown processes are occurring both in the MOGAD and the MOG EAE model [3]. Such hidden interplays of immune cells, genetic factors and effects from EBV are likely to increase the heterogeneity across patients with MOGAD as well as MS. Studies with EAE models gave profound insights into such 'antibody-independent' pathogenic roles of immune cells [3]. Thus, MOGAD is now considered a disease not caused by anti-MOG antibody as the primary cause. Of note, MOG-EAE model has been repurposed to a model better mimic early onset MOGAD. Combination of the transgenic mice expressing H–chain of the anti-MOG antibody and immunization (with a MOG peptide) was shown to mimic pediatric MOGAD [12].

MS and EAE have longer research histories compared to MOGAD. To name just a few findings implying B cells' role, Serafini et al showed ectopic follicles-like aggregates containing B cells in the meninges of post-mortem patients with MS [13], which were later shown to be associated with severe tissue change such as pronounced subpial demyelination, microglia activation and disease severity [9]. In 2006, the use of anti-CD20 monoclonal antibody (rituximab), which results in nearly complete depletion of B cells, showed clinical success in MS, supporting the idea that B cells and EBV, which infects B cells, play important roles in MS. Notably, several findings led to focusing on the antigen-presenting cells (APC) function of and cytokine secretion from B cells. Using mice selectively MHC II-deficient on B cells, Molnarfi et al. showed that MHC II expression in B cells was required for EAE induction by recombinant human MOG [14]. In their study, the mice containing B cells that expressed cell surface MOG-specific B cell receptor (BCR) but could not secrete antibodies are susceptible to MOG protein EAE. Cytokine production by B cells is also of importance. Using mice with a B-cell specific IL-6 deficiency, Barr et al found that B cell depletion therapy effect in EAE was clear only with B cells producing sufficient IL-6. Moreover, the B cell-specific IL-6 deficiency caused reduced IL-17 response [15].

In MS, interaction between B and T cells is dysregulated [16]. Specifically, peripheral tolerance checkpoints (that normally removes autoreactive B cells in periphery) are defective in MS, that is, increased frequencies of naive polyreactive populations in the blood. This phenomenon may be attributable to impaired Treg function [16]. Suppressive effect of $FoxP3^+$ Treg on B cells is impaired in MS [17]. One current issue is how such a basic scheme should be updated considering recent findings on EBV. EBV infection can cause continuous antigen presentation by B cells, giving rise to exhausted T cells [16]. The question of 'where' B cells uptake myelin antigens and exert APC function was addressed by Kim et al. Upon viral infections, B cells can infiltrate into the brain and that myelin-reactive B cells can capture antigen directly from parenchyma (see below) [18]. Such a mechanism could be more important than considered previously.

EBV infection is likely to be a prerequisite for developing MS. Memory B cell is a reservoir for latent EBV virus [19]. Intermittent replication or latent-lytic cycling of EBV is likely to enable intermittent exposure of immune system to EBV antigens, causing expansion of myelin-reactive T cells (via molecular mimicry and epitope spreading), immune dysregulation and ongoing inflammation as discussed in excellent review articles [19,20,21]. Patients with MS show higher titers of EBV-specific antibody (e.g., against EBV nuclear antigen 1 (EBNA-1)) before the disease onset compared to healthy controls. Patients with MS also show more EBV-specific T cells, some of which are cross-reactive to myelin epitopes [22]. People with MS have expanded T cells in the cerebrospinal fluid that are specific to LCLs (, that is, EBV-associated lymphoblastoid cell lines) [23].

Why does MS occur only in a small fraction of EBV-infected individuals [21]? Analyzing a high-throughput experiments-based dataset, Mechelli et al showed that the genes encoding proteins interacting EBV proteins are associated with MS-predisposing genes but not with genes predisposing other diseases including rheumatoid arthritis, Crohn's disease and Type 1 diabetes [24]. They showed that the CD40 pathway is likely to be affected by the EBV interactome-MS associated gene interaction. They further showed that 1.2 EBNA-2 allele downregulates the expression of the CD40 molecule on EBV-infected B cells [24]. This may cause dysregulation in tolerance induction as CD40 pathway is likely to play multiple roles in autoimmunity. Afzali et al showed that AQP4 is expressed in B cells in a CD40-dependent manner and presented to AQP4-specific thymocytes, leading to negative selection of the thymocytes. They suggested that thymic B cells tolerize against a group of germinal center-associated antigens, including disease-relevant autoantigens such as AQP4 [25], highlighting the importance of CD40 in tolerance induction. CD40 is of interest also because of its viral mimic, late membrane protein 1 (LMP1). LMP1 can grant survival permission to B cells in the CNS, thereby increasing the chance for APC function of B cells important in MS pathogenesis (see below) [18].

Molecular mimicry resulting in cross-reactive responses is believed to occur between EBNA-1-derived antigen and glial cell adhesion molecule (GlialCAM). In an extensive analysis comparing MS patients, $EBNA^{high}$ healthy donor and $EBNA^{low}$ healthy donor (, where high/low stratification was based on $EBNA_{386–405}$-specific IgG antibody level), Vietzen et al found that $NKG2C^+$ and $NKG2D^+$ natural killer (NK) cells repress autoreactive $GlialCAM_{370-389}$ specific cells, which normally exist in EBV-infected healthy individuals [26]. That is, in patients with MS, the NK cell-dependent removal of the autoreactive cells is ineffective. This inefficacy becomes clear with deficiency of *KLRC2*, the gene encoding NKG2C molecule [26]. They also showed that the NK-cell mediated removal of autoreactive cells is modified negatively by HLA-E expression and positively by cytomegalovirus (CMV) infection (via UL40 peptide) in a genetic variant-specific manner. This was an influential study that evaluated many relevant cells/molecules including NK

cells, CMV, HLA-E, LMP-1, IL-27 and EBV reactivation [26].

Due to the narrow tropism of EBV, the animal models used for MS studies cannot be used for EBV infection directly [22]. Several studies nonetheless developed new animal models. Using mice harboring human *HLA-DRB1*15:01*, a risk factor for MS, Läderach et al showed that EBV promotes differentiation of neuroinvasive B cells; specifically, T-bet$^+$CXCR3$^+$ B cells expand and migrate into CNS and organize perivascular aggregates of T cells [27]. In another study, the immuno-compromised mice (NOD-scid-gamma mice) engrafted with human donor peripheral blood mononuclear cells (PBMCs) and immunized with myelin antigen were susceptible to EAE symptoms and demyelination similar to classical EAE mice [22]. As the donor of PBMCs, the authors compared relapsing-remitting MS (RRMS) patients, EBV-positive healthy donors and HBV-negative healthy donors. In this model, EBV serostatus of donor defined the time of EAE symptoms and severity of disease. This model appears to recapitulate the features of MS better compared to classical EAE model; EAE mice are known for CD4$^+$ T cell-biased infiltration, but the CNS of symptomatic mice of the authors' model was enriched for hCD8$^+$ T cells, similar to postmortem MS brain lesions [22]. Kim et al addressed a question *where*, after the EBV infection, B cells capture the antigens. Strikingly, naive myelin-reactive B cells can enter the CNS during infections and capture antigen directly from myelin. Normally, without help from T cell via CD40L, such B cells rapidly die. However, EBV LMP1, which mimics CD40, rescues them from normal tolerance mechanism and allowing them to cause MS-like demyelination [18]. Although a mouse model in combination with influenza and VSV infection was used in [18], which differs from the EBV–human system in many points, the proposed process appears important in MS pathogenesis. The scheme that migration of B cells into the CNS occurs first and local inflammation comes next is suggested by several authors [18,27].

In conclusion, these discoveries have provided the image of a continuum to autoimmune diseases. NMOSD forms its extreme end, where autoantibodies play a direct causative role. This is different from most inflammatory autoimmune diseases, where the impact of antibody is diverse across diseases. In terms of NMOSD etiology, AQP4 antibody-positive NMOSD showed association with reduced complement C4, which is reminiscent of the 'lupus paradox' [28]; C4a is necessary for B cell tolerance induction and C4a deficiency is known to associate with systemic lupus erythematosus and other autoimmune diseases [28]. The latter study also showed importance of a few HLA alleles, which may explain unique features of NMOSD and help further studies. From immunological perspectives, future studies may focus on the dysregulation of survival permission to B cells and the role for CD40 and LMP1 in this regard. It is notable that the APC function of B cells plays a role in T cell negative selection to prevent NMOSD [25]. In further support to the B cells' role in autoimmunity, in addition to the anti-CD20 therapy, Bruton's tyrosine kinase inhibitors are likely to widen therapeutic approaches in MS [29]. On the other hand, etiology of MOGAD remains largely unclear; while EBV is important in MS, EBV serology does not show clear association with MOGAD [30]. For MOGAD, animal models may become important approaches. From technical perspectives, pathogenesis in autoimmune diseases is often inferred first by epidemiologic approaches employing genetics and bioinformatics analyses. Some of such associations are uncovered using human samples as in Wang et al that showed that EBV infection alters the immunopeptidome presented on HLA-DR15 of B cells and drive MS [31]. On the other hand, it is of encouragement to the biomedical field that many of such associations can be investigated with animal models including humanized models and tissue-specific knockout mice, which often help deep understanding and translation to therapeutics. Cooperation between clinical research teams and biological laboratories is now even more important than two decades ago.

Conflict of Interest

The author declares no competing interests.

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***Corresponding author:** Kazuhisa Nishizawa, Biomolecular Logic Research Laboratory, Takinogawa, Kita, Tokyo, 114-0023 Japan; Email: kazu.nishizawa.nik@gmail.com

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