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REVIEW ARTICLE

B cells in multiple sclerosis

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Abstract

B lymphocytes have essential roles in the autoimmune pathogenesis of multiple sclerosis (MS). They regulate the autoimmune response and participate in the development of the CNS lesions. This review discusses nature and functions of B cells in MS, and retraces the recruitment of brain-autoimmune B cells from the B cell repertoire. Multiple sclerosis is commonly considered as an autoimmune demyelinating disease, where myelin-reactive T cells enter the CNS from outside, and drive the inflammatory changes that ultimately create the degenerative MS plaque. Most therapeutic strategies focus on eliminating or mitigating these pathogenic T cells. Less consideration has been devoted to the role of autoimmune B cells in the autoimmune pathogenesis. Indeed, this role is now supported by a number of convergent lines of evidence, which are briefly outlined in a first part of this overview. A second part describes experimental studies in transgenic mouse models of brain autoimmunity, EAE, which relate to possible functions of autoimmune B cells and to their recruitment from the regular B cell repertoire.

Keywords

Multiple sclerosis, autoimmunity, B cell, central nervous system, experimental autoimmune encephalomyelitis

History

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B cells in MS lesions

B cells are regular components of immune infiltrates in the early active MS lesion. They are a minor subset in brain and spinal cord, mostly located in perivascular cuffs but also disseminating into the surrounding parenchyma [1]. Alternatively, B cells form packed aggregates in the leptomeningeal space covering the cortical surface. Some of these aggregates seem to be organized, reminiscent of germinal centers [2]. Leptomeningeal B cell accumulations are common features of progressive MS, but have also been noted in early relapsing-remitting MS [3]. The multifarious pathogenic functions of autoimmune B cells are listed in Box 1.

Oligoclonal bands in cerebrospinal fluid

The CNS tissues are permanently perfused by interstitial fluid that drains into the cerebrospinal fluid (CSF). The healthy CSF transports spent CNS structures and metabolites, but is devoid of immunoglobulins and other plasma proteins. However, importantly, in MS the fluid typically contains immunoglobulins distributed as individual bands, not as continua like in plasma. For their predictable appearance, oligoclonal bands (OCBs) have been used as a valuable biomarker in diagnosis of MS. But neither their cellular origin nor their target antigens have been identified until recently. Combining transcriptomics to characterize the immunoglobulin gene repertoire of individual CSF B cells with proteomics sequencing isolated oligoclonal immunoglobulin bands, Dornmair et al. proved that most, if not all OCBs were the product of local, CSF or parenchyma resident B cells [4]. Several groups were able to clone the paired genes of CSF immunoglobulins and to produce recombinant antibodies. Screenings for target antigens yielded divergent results. One group identified ubiquitous intracellular proteins as binders [5], while other investigators found binding to lipid determinants [6]. However, the search for autoantibodies responsive to major myelin structures has failed in all studies so far.

The CNS a B cell niche?

OCBs form highly characteristic pattern in each MS patient, and, quite surprising, the patterns may persist over years [7]. This stability is surprising, as the CNS parenchyma has been considered as a microenvironment insufficient to support long-term survival of immune cells [8]. Instead, persistence of OCBs implies that the immunoglobulin forming B cells, or their clonal progeny, can survive in this tissue over extended periods of time, characterizing the CNS milieu as a fairly friendly B cell biotope. Indeed, Meinl and colleagues showed that astrocytes, a major plurifunctional CNS glia lineage, produce B cell growth factors including BAFF, CXCL10 and CXCL13, which may contribute to support B cell survival, and that inflammatory activation enhances their production [9]. Yet, CNS resident B cells do not form a completely

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Box 1. B cell functions in autoimmune disease.

- Secretion of pathogenic autoantibodies
  - Mechanisms:
    - Complement-dependent destruction of target cells
    - Blockade of surface structures (e.g. direct blindfolding or internalization of receptors)
    - Autoantigen complex binding to antigen presenting cells
  - Evidence:
    - Neuromyelitis optica (NMO, alias Devic's disease); anti-aquaporin-4 autoantibodies)
    - Autoimmune encephalitis variants: anti-neuronal receptor autoantibodies (N-methyl-D-aspartic acid [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], gamma-aminobutyric acid [GABA], etc.)
  - MS: no pathogenic autoantibodies as yet
- Antigen presentation
  - Mechanism: soluble autoantigens bound to B cell surface immunoglobulin (specific autoantibody), concentrated and processed for presentation to autoimmune T cells
  - Evidence: spontaneous EAE model (OSE mouse), *in vitro* antigen presentation
  - MS: CD40/IL-4 activated B-APC present antigen to $CD4^+$ T cells (no preferential preference shown)
- Cytokine release
  - Mechanisms: B-cell derived cytokines/chemokines imprint the local immune milieu
    - B-regs: release anti-inflammatory cytokines (IL-10, TGF-b);
    - Pro-inflammatory B cells: release cytokines like GM-CSF to fuel inflammatory (auto-)immune responses
  - Evidence: isolation from recovering EAE mice, transfer of protection;
  - MS: isolation of $CD4^+$ memory subsets from peripheral blood lymphocytes
- Autoantigen transport
  - Mechanism: antigen specific B cells capture antigen via surface antigen receptors and transport them to splenic and/or lymph node follicles
  - Evidence: experimental systems;
  - MS: not known

secluded community, but seem to be in some exchange with peripheral B cell populations, as evidenced by recent deep-sequencing analysis identifying similar gene pedigrees in CSF as well as in the periphery [10].

B cell target autoantigens?

There is circumstantial evidence that, at least in some patients, humoral autoantibodies contribute to tissue injury by binding to brain cells and by destroying them dependent on complement factors. First, Lucchinetti et al. showed in a major class of MS plaques decoration of lesional tissue structures by activated complement C'9neo, indicating an antibody/antigen reaction going on [11]. Second, in a limited cohort of patients with this response pattern documented in biopsies, plasmapheresis improved neurological deficiencies [12]. Third, cortical areas beneath leptomeningeal B cell aggregates show demyelination and neuronal degeneration possibly due to humoral factors (antibodies) diffusing into the tissue [13]. Finally, B cell depleting anti-CD20 antibodies (rituximab) have become a powerful therapy of early MS substantially reducing relapse frequency, radiologically determined lesional load and improving neurological deficiencies [14].

The target antigens of MS involving B cells have remained matter of debate. While studies of recombinant antibodies representing CSF OCB immunoglobulins reacted with a set of intracellular structures, they did not note binding to any known myelin or other glia autoantigens, thus hardly qualifying as classic demyelinating antibody candidates [5].

On the other hand, there were reports pointing to antibodies to ion channels and synaptic structures. In a detailed trial, Hemmer and collaborators found in a substantial proportion of patients with relapsing-remitting MS autoantibodies against the glial potassium channel KIR4.1 [15], although this was not seen in other cohorts [16]. Then, some few patients produce antibodies against determinants located around axonal paranodes [17]. A most intriguing target is myelin oligodendrocyte glycoprotein (MOG), a major encephalitogen in rodent EAE, which, located on the surface of myelin, is directly accessible to humoral antibodies. Anti-MOG autoantibodies are a hallmark of childhood MS and acute disseminated encephalomyelitis (ADEM) [18]. Further they have been discovered in aquaporin-4 negative neuromyelitis optica (NMO), and most recently in a newly recognized spectrum of demyelinating diseases sharing features of both MS and NMO [19]. Interestingly, human anti-MOG antibodies are species-specific, recognizing conformational epitopes on human, not on rodent MOG [20].

Experimental models of B cells in brain autoimmunity

Important questions arise with regard of the mechanisms that lead to the recruitment of autoimmune B cells in a spontaneously developing brain autoimmune disease, and their function in this pathogenesis. B cells can contribute to autoimmune development by secreting injuring autoantibodies, by transporting autoantigen from tissue to secondary immune organs, by presenting autoantigen to T cells, and by secreting cytokines that condition the lesional tissue milieus [21].

Clinical investigations may be difficult to resolve these problems, and also classical EAE models are of limited value owing to their artificial methods of induction (adjuvant immunization, immune cell transfers). As an alternative, we have developed two transgenic mouse models, which feature spontaneously developing EAE, and which are based on the cooperation of autoimmune T and B cells.

The OSE mouse is double transgenic C57BL/6 mouse with MOG specific T cells exposing a MOG specific T cell receptor along with a knocked-in MOG specific H chain in its B cells [22,23]. EAE incidence is about 60% and involves lesions restricted to optic nerve and spinal cord, sparing most of the brain.

In contrast to the OSE mouse, a second mouse model of spontaneous EAE, the RR mouse, is a single-transgenic SJL/J mouse with a MOG reactive transgenic TCR expressed on >70% of CD4 T cells [24]. RR mice come down with a relapsing-remitting EAE in close to 100%. Both in OSE and RR mice, disease development critically depend on the presence of an intact intestinal microbiota [25]. Germfree animals fail to develop EAE, but when colonized with fecal samples, disease appears promptly.

B cell has distinct roles in both EAE models. In OSE mice, they capture soluble MOG antigen present even in very high dilutions, concentrate it process and present it to cognate T cells, thus amplifying the autoimmune response process [22].

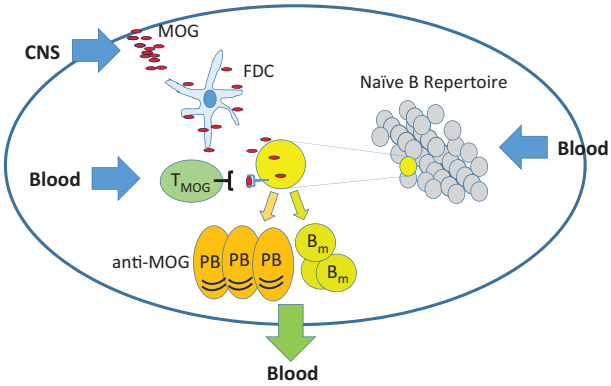

Figure 1. Recruitment of MOG autoimmune B cells in the CNS draining cervical lymph nodes. B cell recruitment depends on activated MOG specific helper T cells entering via blood or lymphatic vessels, as well as on MOG containing material transported from the brain via lymph vessels (soluble, particulate or by phagocytes).

In contrast, in RR mice, the role of B cells is focused to the production of demyelinating autoantibodies [24]. This is remarkable, as these single-transgenic TCR mice has a unmanipulated, non-transgenic B cell repertoire, and yet, from about 4 weeks of age, anti-MOG autoantibodies appear in the plasma, which recognize conformational MOG epitopes on myelin surfaces and, when transferred to recipient mice with mild, non-demyelinating lesions, produce large confluent lesions, with severe ongoing myelin destruction, creating pathological patterns strongly reminiscent of human MS plaques. The B cells are crucial for the pathogenesis, since B cell depleted RR mice fail to develop relapsing EAE. Recruitment of MOG reactive B cells depends on the availability of MOG: MOG-deficient knockout mice with full expression of the RR T cell receptor will not form anti-MOG antibodies. Second antibody formation depends on microbiota: germfree RR mice will neither form anti-MOG autoantibodies, nor develop EAE [25].

Both EAE models offer unique opportunities to study recruitment, expansion and activation of autoimmune B cells (Figure 1). In particular, with their spontaneous development, the models allow investigations into the initial stages of autoimmune disease, as they may take place in spontaneous human disorders. These involve interactions of intestinal microbiota with dormant autoimmune T and B cell clones, and the genetic factors that regulate these processes. Obviously, the models are of use to develop and test diagnostic and therapeutic strategies [26].

B cell therapies

Ideal therapies of B cell mediated autoimmune diseases target either the pathogenic B cell directly, or its effector molecule, the autoantibodies. Both strategies have been tried out. Although to date no MS specific autoantibodies have been identified, there is indirect evidence pointing to humoral mechanisms involved in the pathogenesis of the disease. In particular, a subset of MS patients has lesions with activated complement indicating binding and destructive action of anti-myelin autoantibodies, termed lesional pattern II (vide supra). This has been corroborated by a limited study with patients whose pattern II lesions had been proven by brain biopsies. Plasmapheresis, which removed plasma antibodies that included suspected autoantibodies from blood circulation, alleviated fulminant attacks [27].

B-cell target therapies have a much broader application. The most successful anti-B cell therapy uses monoclonal antibodies (Mab) against the B cell marker CD20. CD20 is expressed on a broad range of B cell differentiation, from pre-B cells to mature B cell subsets, but not in plasma cells [28]. A landmark study infused the chimeric Mab rituximab and found a profound reduction of inflammatory CNS lesion [14]. The efficacy of anti-CD20 Mab therapies was confirmed by numerous subsequent trial, which in addition documented a relatively low rate of the dreaded opportunistic virus encephalitis progressive multifocal leukoencephalopathy (PML), which has been noted in other immunomodulatory therapies [29]. The mechanism of rituximab's therapeutic action is not definitely illuminated. However, it now appears that the Mab affects mostly B cells, but not plasma cells, it interferes with antibody-independent B cell functions, such as antigen presentation and cytokine release (Box 1) [30].

A third approach to contain autoimmune B cells, namely by neutralizing B cell growth factors, were less gratifying. Neutralization of B cell activating factor of the TNF family (BAFF), an essential B cell survival factor, not only was inefficient in mitigating the disease, but, paradoxically, led to exacerbations [31]. This failure came as a surprise, considering the beneficial effect of BAFF/TACI neutralization in other B cell autoimmune diseases, like systemic lupus erythematosus (SLE) [32].

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Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this article.

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