

The idiotype connection: linking infection and multiple sclerosis

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B cells present idiotopes (Id) from their B cell receptor to Id-specific CD4⁺ T cells. Chronic Id-driven T-B cell collaboration can cause autoimmune disease in mice. We propose that Id-driven T-B cell collaboration mediates the development of multiple sclerosis by perpetuating immune responses initiated against infectious agents. During germinal centre reactions, B cells express a multitude of mutated Ids. While most mutations lead to decreased affinity and deletion of the B cell, some B cells could be rescued by Id-specific T cells. Such Id-connected T-B cell pairs might initiate inflammatory foci in the central nervous system. This model may explain the intrathecal synthesis of low-avidity IgG against viruses, and the synthesis of oligoclonal IgG with unknown specificity in multiple sclerosis.

Multiple sclerosis: genes and environment

Genetic predisposition explains the clustering of multiple sclerosis (MS) within families, but it does not fully explain the geographical distribution of MS, the effect on MS risk imposed by migration and month of birth, or the increase in sex ratio over time [1]. Therefore, environmental factors are probably involved, and an infectious etiology of MS was suggested as early as the 19th century, and is still supported by strong epidemiological evidence [2].

It has been assumed that MS is mediated by T cells targeting a central nervous system (CNS) antigen, similar to the animal model experimental autoimmune encephalomyelitis (EAE). Accordingly, prevailing hypotheses suggest that microbes in some way break the self-tolerance against CNS antigens. Although the structural requirements for T cell receptor (TCR) cross-reactivity between CNS antigens and viral antigens have been demonstrated, it is not clear if, or how, self-tolerance against CNS antigens is broken in MS [3]. Moreover, this concept does not explain an immunological hallmark of MS, namely the persistent intrathecal (i.e. within the CNS, including the meninges) synthesis of oligoclonal IgG. By emphasizing T-B cell collaboration as a link between an infectious trigger and the persisting synthesis of oligoclonal IgG, we suggest an alternative model for elicitation of MS.

Idiotype-driven T- B collaboration

The variable (V) regions of immunoglobulin (Ig) molecules contain immunogenic determinants referred to as idiotopes (Id), which can be recognized by Id-specific T cells [4]. T cells are generally tolerant to germline-encoded Ig sequences, and the somatic hypermutation occurring during Ig affinity maturation seems to be a cornerstone in the creation of immunogenic Ids [5–9]. Such mutations may enhance the binding of Id-derived peptides to MHC class II or TCR, and allow mutant Id-peptides to be perceived as immunological “non-self” by Id-specific T cells [5,10,11].

Two pathways have been identified for MHC-restricted presentation of Id-peptides to CD4⁺ T cells: i) extracellular Ig can be endocytosed by antigen presenting cells (APC), followed by classical peptide processing in the class II pathway [8,12,13], or ii) B cells constitutively present their own B cell receptor (BCR)-derived Id-peptides on their MHC class II molecules [13–15]. These observations led to the hypothesis that Id-specific T cells that recognize Id-peptide/MHC class II complexes on B cells can sustain the activation, proliferation and differentiation of Id⁺ B cells into plasma cells producing Id⁺ Ig with a wide variety of specificities [16]. This concept is supported by experimental evidence in transgenic mice models [17,18]. Since such Id-driven T-B cell collaboration does not require that T cell epitopes and B cell epitopes reside on the same molecule or molecular complex, it has been denoted as non-linked T-B cell collaboration [17] (Figure 1).

Given that B cells can present their own BCR-derived Id-peptides to Id-specific T cells, it has been proposed that such peptides may contribute to the development of immunological memory and autoimmune diseases [16,19]. This concept has been supported in a transgenic mouse model that allows direct study of Id⁺ B cells and Id-specific T cells (Figure 2), and is also underpinned by the detection of Id-specific T cells in humans with autoimmune diseases (Box 1).

Glossary

Idiotope (Id): a unique antigenic determinant (epitope) in Ig V regions.

Idiotype: the collection of idiotopes in Ig V regions.

Id-peptide: a short V region sequence presented on MHC molecules.

Id⁺ B cell: a B cell that expresses an Id or Id-peptide.

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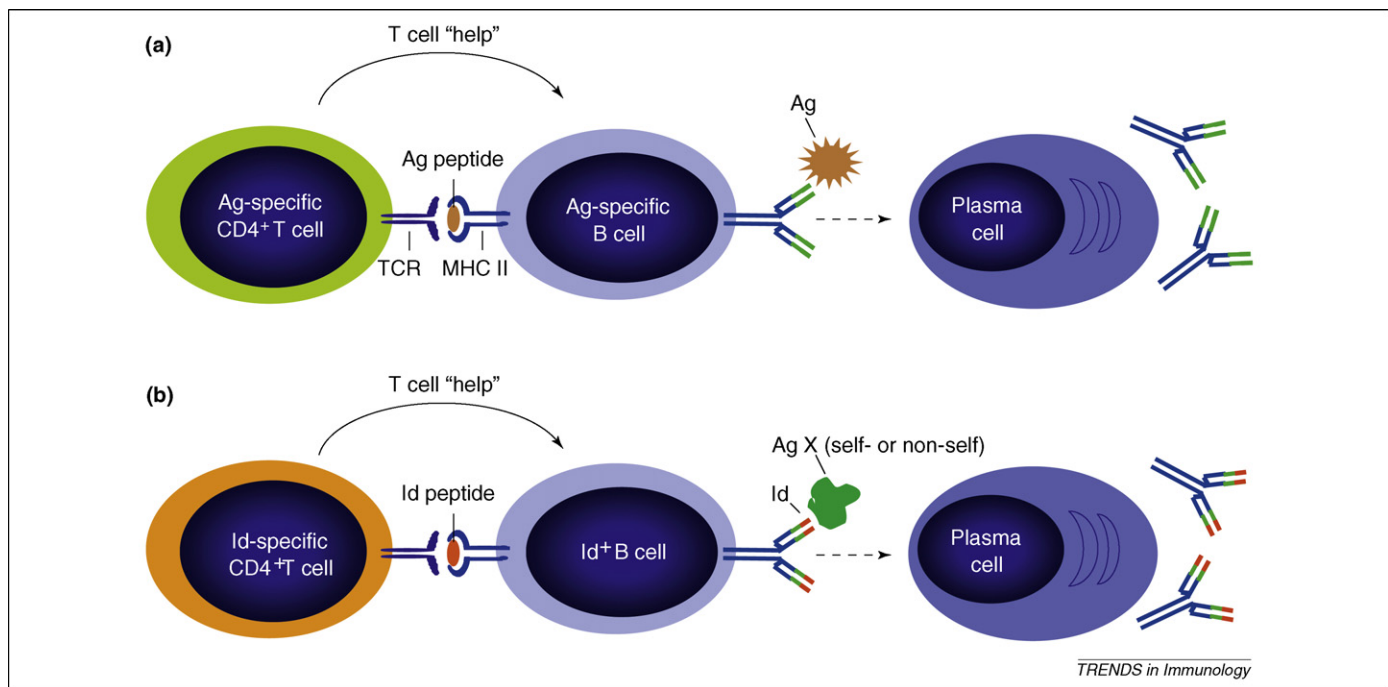


Figure 1. Conventional (linked) and Id-driven (non-linked) T-B cell collaboration. **(a)** In conventional T-B collaboration B cells recognize antigens via their membrane-bound B cell receptor (BCR). The antigen is internalized and processed, and antigenic peptides are loaded onto MHC class II molecules for presentation to antigen-specific CD4⁺ T cells. Because the T cell receptor (TCR) and BCR recognize parts of the same molecular complex, this is referred to as 'linked recognition'. **(b)** In Id-driven T-B cell collaboration, B cells process their own BCR V region and present Id-peptides to Id-specific CD4⁺ T cells. The Id-peptide may originate from membrane-bound BCR or from nascent BCR in the secretory compartment. The BCR may either lack specificity or be specific for any antigen (Ag X), including self antigens and infectious agents. Because the TCR and BCR in this case recognize different molecules, i.e. Id-peptide and antigen X, such Id-driven T-B collaboration is referred to as 'non-linked'. In both **(a)** and **(b)**, reciprocal stimulation of the B cell by the T cell results in differentiation of the B cell into an immunoglobulin (Ig)-producing plasma cell. Ligation of the BCR by antigen may be required for isotype switching in non-linked Id-driven T-B collaboration [17].

The B cell response in MS

Intrathecal synthesis of oligoclonal Ig in MS was described 50 years ago, but the specificity of the main IgG fractions remains unknown. Compatible with an antigen-driven immune response involving T cell help, transcribed BCR genes from clonally expanded B cells in the cerebrospinal fluid (CSF) and brain of MS patients use a restricted repertoire of VH (variable-heavy) families and carry a high number of replacement mutations in the antigen-binding complementarity determining regions (CDRs) [20]. A similar mutation pattern has been observed in isolated optic neuritis which often precedes MS, showing that somatic hypermutation is an early event in MS development [21].

In addition to the main IgG fractions of unknown specificity appearing as oligoclonal bands on isoelectric focusing gels, intrathecal synthesis of oligoclonal IgG against one or several microbes, most commonly measles and varicella zoster virus, occurs in most patients with MS and isolated optic neuritis [22,23]. This phenomenon is not observed in patients with other demyelinating CNS diseases such as neuromyelitis optica [24], and therefore seems to be an early and specific feature of MS. Virus-specific IgG constitutes a minor fraction of the total CSF IgG in MS, it has low binding avidity compared to virus-specific IgG produced during CNS infections [25], and may have a dynamic clonal pattern during early stages of the disease [26].

Sustaining the B cell response in MS: a case for T cells?

The mechanisms sustaining the intrathecal synthesis of IgG in MS is a question of controversy. In addition to T

cells, astrocytes and microglia can also provide survival factors for the maintenance of memory B cells and plasma cells, including brain derived nerve growth factor (BDNF), the chemokine CXCL12, B cell activator of the tumor necrosis family, and vascular adhesion molecule 1. MS brains have therefore been suggested to be a "B cell friendly environment", where plasma cells can survive for many years [27]. Another possibility is that the intrathecal IgG is produced by Epstein-Barr virus (EBV)-infected B cells that can survive independently of T cell help [28]. This hypothesis has been supported by the demonstration of EBV-infected B cells in the brain of MS patients in one study [29]. The presence of EBV-infected B cells in MS brains is, however, controversial [30].

Several observations suggest that T cells drive the B cell response in MS. First, the strong correlation between intrathecal IgG synthesis and the proportion of CD138⁺ plasmablasts in the CSF from MS patients suggest that short lived plasmablasts are the dominating intrathecal IgG-producing cell type in MS [31]. Second, recapitulation of the major stages of B cell development in secondary lymphoid organs, including CD19⁺, CD38^{high}, CD77⁺, Ki67⁺, Bcl-2⁺ centroblasts that are otherwise exclusively found in germinal centres, have been detected in the CSF from MS patients [32], further supporting the contention that T cell-dependent differentiation of B cells into plasmablasts takes place within the CNS. This process has been attributed to the tertiary B cell follicles found in the meninges of some MS patients [33]. Such B cell follicles have, however, not been identified so far at early stages of MS, and they may therefore not be the primary foci for the

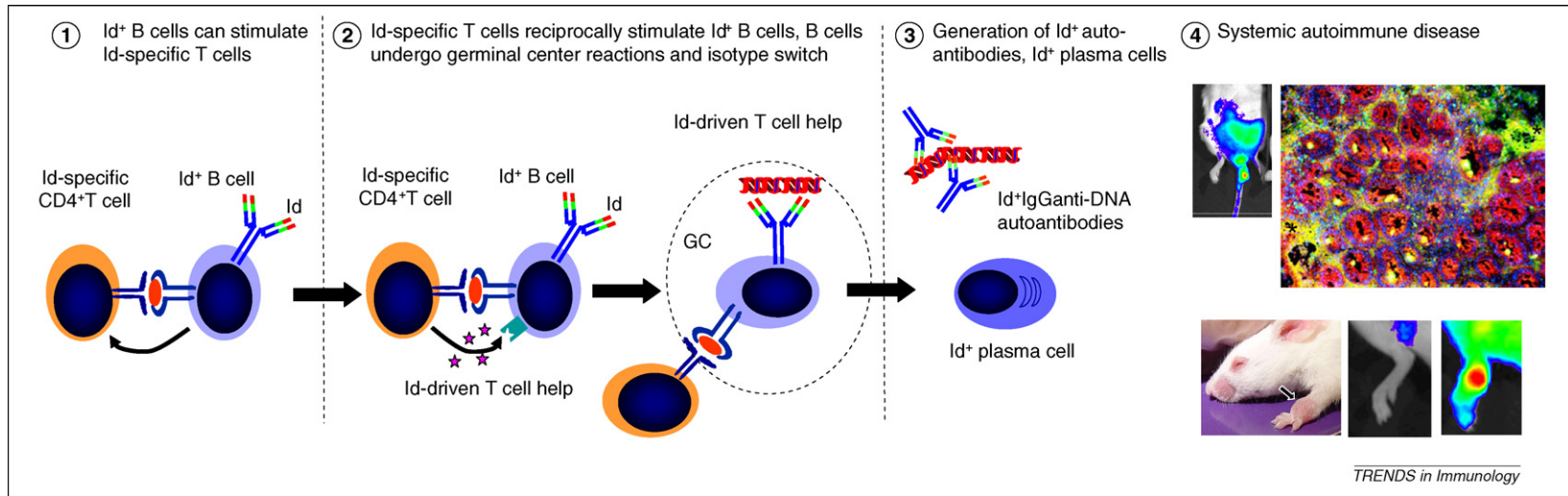


Figure 2. Id-driven T-B cell collaboration causes autoimmune disease in a paired Id⁺ Ig transgenic and Id-specific T cell receptor (TCR) transgenic mouse model. 1) Id-specific T cells can be stimulated directly by resting B cells that present Id-peptide on MHC class II [5,64]. 2) Id⁺ B cells can be activated by Id-specific T cells to proliferate and differentiate. In the presence of B cell receptor (BCR) ligands, the B cell can undergo a germinal center (GC) reaction and receive Id-dependent T cell help, and generate Id⁺ Ig secreting plasma cells [17,68]. 3) Id-driven T-B cell collaboration has the propensity to cause secretion of antibodies towards ubiquitous autoantigens, including anti-dsDNA [17,68]. B cells that receive autoantigen-BCR stimulation may undergo the GC reaction and receive Id-specific T cell help, as shown in 2). 4) Prolonged Id-driven T-B cell collaboration in double transgenic mice (Id⁺ BCR x Id-specific TCR) results in systemic autoimmune disease with systemic lupus erythematosus (SLE)-like features, massive colitis, and, in some mice, arthritis [68,69]. Some of these mice also develop symptoms compatible with CNS inflammation (L. Munthe, unpublished results). In triple transgenic mice (Id⁺ BCR x Id-specific TCR x NF-κB-luciferase reporter) autoimmune disease can be followed in mice that transcribe luciferase upon activation of the transcription factor NF-κB [69], which acts as an indicator of inflammation. Top left panel: An abdominal light signal (left) from a mouse with severe inflammatory bowel disease. Top right panel: Massive colitis stained by anti-luciferase (secondary to activated NF-κB, red) and anti-C3 (complement activation, secondary to Id⁺ Ig autoantibody deposition, green) [69]. The colon architecture is effaced by cellular infiltrates and erosions. Magnification: x100. Bottom left panel: Arthritis (photo), with swelling indicated on the forepaw (arrow) [68] (reprinted with permission of The American Association of Immunologists, Inc). Bottom middle: control luciferase reporter mouse. Bottom right: An arthritic paw, with intense light emission indicating joint inflammation. All panels except bottom left are reprinted with permission from the American Society for Investigative Pathology.

Box 1. Id-driven T-B cell collaboration and autoimmune disease

Syngeneic immune responses towards Id was recognized in the early 1970's, laying the basis for the idiotype network theory [57]. The theory was initially restricted to Ig and B cells. However, thymectomized and nude mice failed to produce anti-Id antibodies upon immunization with Id⁺ Ig [58,59], demonstrating that Ig molecules are T-cell dependent antigens. Thus, extracellular Ig is endocytosed and processed by APC, and Id-peptides are presented on MHC class II molecules to Id-specific CD4⁺ T cells [9,13,7,60]. Id-specific T cells have been found in lupus-prone mouse strains [19,61]. In humans, Id-specific CD4⁺ T cells have been identified in the blood of patients with systemic lupus erythematosus (SLE) and Wegener's granulomatosis [52–55], in the synovial fluid from patients with rheumatoid arthritis (RA) [56], and in the blood and CSF from patients with MS [46,47]. Furthermore, modulating Id-specific T cell responses by injecting inhibitory Id-peptide analogues can perturb the development of SLE in mice and humans [62,63].

The finding that B cells process their own BCR and present endogenous Id-peptides to T cells introduces another level of immune regulation [13,15,16,18,38,64], where Id⁺ B cells and Id-specific T cells may cooperate in an Id-driven manner (see Figure 1). Such Id-driven T-B cell collaboration can cause systemic autoimmune disease, autoantibody production, secretion of inflammatory cytokines and tissue destruction in experimental settings (see Figure 2).

Given their potential pathogenicity, it is likely that Id networks are regulated at multiple levels: 1) Frequency issues. Paired Id-specific T cells and Id⁺ B cells or Id-specific T cells and anti-Id-specific B cells are rare, and therefore unlikely to interact. 2) Restricted T cell repertoire. Id-specific T cells probably only exist towards CDR3 N-region diversity sequences and somatically mutated Id [6,9]. 3) Id-network regulation. Pathogenic Id⁺ Ig can be regulated by anti-Id B cells and T cells collaborating to secrete anti-Id antibodies; loss of such regulation may cause disease [65]. 4) T cell effector functions. Id-specific T cells (e.g. Th1 or CTL) can kill Id⁺ B cells. Further, Id-specific regulatory T cells can suppress Id-driven immune responses [66,67].

B cell response. This view agrees with the seminal observation that IgG eluted from individual MS lesions display distinct clonal patterns [34], suggesting that they contain partly different B cell clones. Taken together, the evidence favors that T-B cell collaboration takes place within the CNS during the early stages of the disease and persists throughout the disease course.

A unifying concept

To explain the perpetuating synthesis of oligoclonal IgG in MS, we propose that the initial triggering event is an infection or a series of infections outside the CNS that induce the generation of B cells carrying rare immunogenic Ids, and that these B cells later engage in Id-driven T-B cell collaboration in the CNS (Figure 3). This idea is consistent with the high number of CDR-targeted replacement mutations in BCR V genes of CNS B cells from patients with MS and optic neuritis, showing that potentially immunogenic Ids appear early and persist throughout the disease course.

During somatic hypermutation, B cells are selected for their antigen affinity, either through BCR signalling or through competition for T cell help. Most BCR V genes will undergo mutations leading to inferior or lost affinity for the target antigen, and B cells carrying such mutations will die from apoptosis. Such mutations may, however, create immunogenic Id, either through enhanced binding affinity

of the Id-peptide for MHC class II molecules or through enhanced affinity for the TCR [10,35]. Given the immense number of mutating BCRs, it is conceivable that some B cells which would otherwise die from lack of affinity for their original antigen are rescued by Id-specific T cells [8–10,16,36]. Initial activation of Id-specific T cells could be mediated by dendritic cells that have taken up secreted Id⁺ IgG [37], or directly by Id⁺ B cells themselves [14]. The process could lead to reciprocal activation of the Id⁺ B cell and the Id-specific T cell, inducing the expression of adhesion molecules and chemokine receptors required for migration into the CNS. In some individuals, such Id-connected T-B cell pairs may haphazardly re-encounter in the CNS or in other organs, leading to foci of Id-driven T-B cell collaboration. The B cell clones participating in this process could have either low or completely lost affinity for their original antigen. We suggest that these B cells produce the low-avidity virus-specific IgG and the main IgG fractions with undetermined specificity, respectively.

This hypothesis is consistent with the genetic association between MS and human leucocyte antigen (HLA) class II, because some HLA class II molecules bind viral peptides and Id-peptides more efficiently than others. It also fits with the observations that deletion of CD20⁺ B cells with Rituximab significantly reduces the number of MS relapses and the number of T and B cells in the CSF, but not the synthesis of antibodies against myelin proteins [38,39]. The hypothesis does not exclude that some Id-specific T cells or Id⁺ B cells, either by chance or selection, recognize CNS antigens, or that some T cells and B cells are recruited to the CNS by other mechanisms. Indeed, T cells and B cells specific for myelin proteins have been shown to accumulate in the CSF from MS patients [40,41], but it is not clear whether this occurs as a cause or a consequence of the disease.

One candidate initiator of the proposed mechanism is EBV, which seems to be almost a prerequisite for the development of MS [2]. EBV causes infectious mononucleosis, which is associated with massive activation of T- and B cells and a 2–3 fold increase in MS risk, and exploits germinal centres to establish latent infection of memory B cells [42]. The hypothesis is, however, not restricted to EBV, because Id-driven T-B cell collaboration could be triggered by any infection or vaccination. This is in agreement with the epidemiology of MS, as environmental factors are likely to operate on a population level rather than affecting selectively MS patients [1].

An important question is whether Id-driven T-B cell collaboration not only drives synthesis of oligoclonal IgG but also explains the killing of oligodendrocytes and neurons characteristic of MS. Theoretically, Id-specific T cells may either kill neural cells through Fas-Fas ligand or other cell-cell interactions [43], or through cytokines that kill neural cells directly or indirectly. Id-specific CD4⁺ T cells have been demonstrated to kill lymphomas through interferon- γ -mediated activation of macrophages [44], which are important effector cells in MS [45]. The ability to recruit and activate sufficient numbers of macrophages and other effector cells is probably crucial for the outcome of Id-driven T-B cell collaboration, and could be influenced both by the phenotype and number of the cells involved.

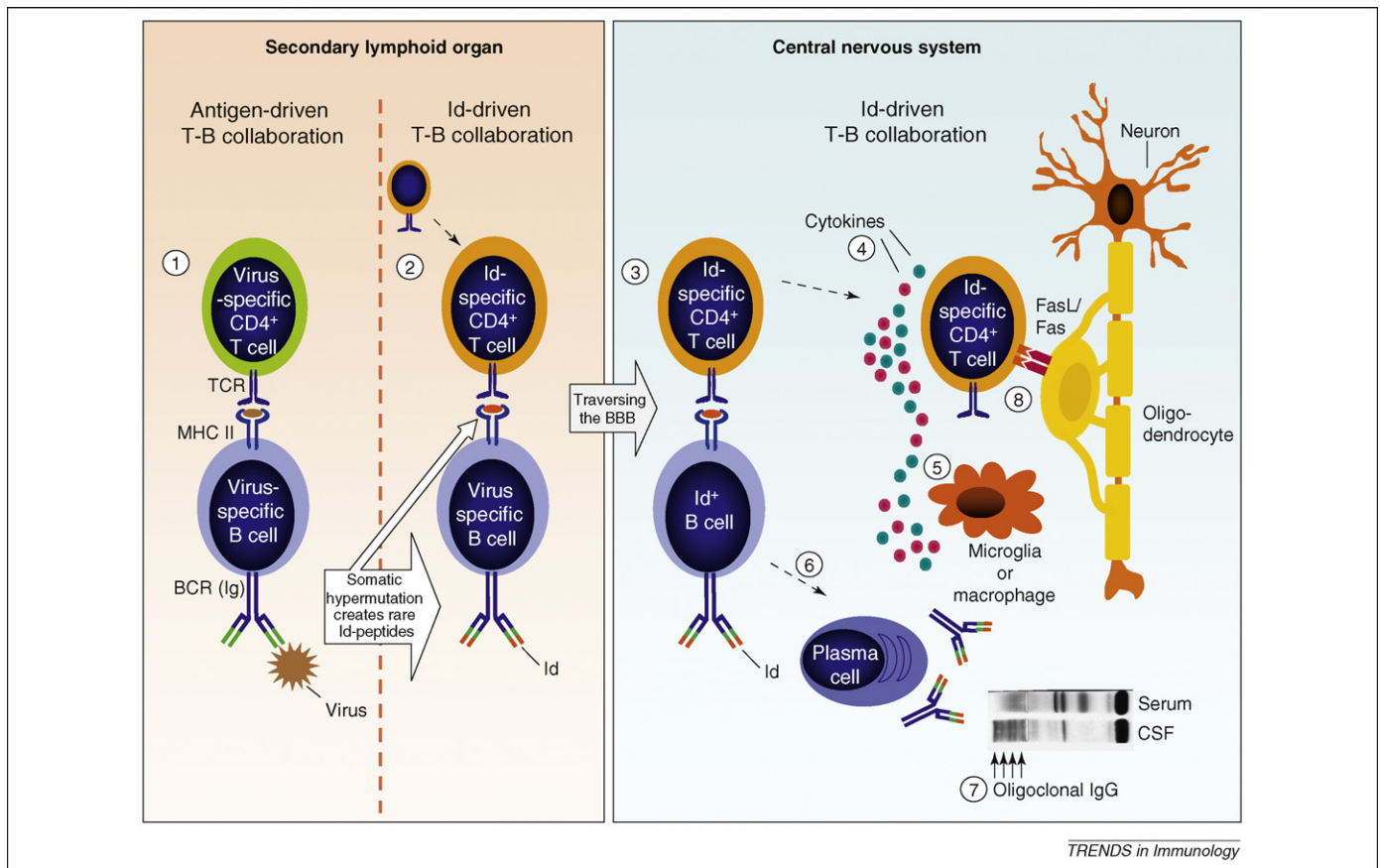


Figure 3. Can Id-driven T-B collaboration induced by infection in the periphery cause MS? Virus-specific B cells that present viral antigen to T cells in secondary lymphoid organs (1) undergo class shift and somatic hypermutation (indicated by color change of V-regions). In most cases these mutations lead to loss of affinity and T cell help. However, mutations also generate rare Id-peptides, which are constitutively presented via MHC class II to Id-specific CD4⁺ T cells that enter the scene (2). Such Id-connected B and T cells may traverse the blood-brain barrier (BBB) and haphazardly reencounter in the CNS (3), where their reciprocal stimulation leads to cytokine production (4). Id-specific T cells may recruit microglia, macrophages, and other accessory cells through secretion of interferon- γ and other cytokines (5), and mediate differentiation of the B cell into plasma cells (6) producing oligoclonal IgG as visualized by electrophoresis of CSF and serum (7). The activated Id-specific T cell may induce apoptosis of nearby oligodendrocytes through Fas/Fas ligand interactions (8), or via accessory cells such as microglia and macrophages.

Our studies suggest that Id-specific CSF T cells have a predominant Th1 phenotype, that they kill oligodendrocytes *in vitro*, and that they are quite prevalent in the CSF of MS patients [43,46,47]. Their pathogenicity *in vivo* is, however, difficult to establish in humans. To resolve this issue, studies of CNS-directed Id-driven T-B cell collaboration in transgenic mice have been initiated.

Experimental support of the hypothesis

In agreement with the proposed hypothesis, most MS patients display proliferative T cell responses against autologous CSF IgG [46]. Further, Id⁺ B cells and Id-specific CD4⁺ T cells have been cloned from the CSF of MS patients, and EBV transformed CSF B cells were shown to activate CSF CD4⁺ T cells in an Id-specific manner [47,48]. CD4⁺ T cell clones from one MS patient were also shown to recognize several mutant Id-peptides from the BCR of a single CSF derived B cell clone [48], suggesting that a single B cell clone may engage in Id-driven T-B cell collaboration with several distinct T cells. Co-culture of these Id-matched T-B cell pairs activates the T cells, and enables them to kill oligodendrocytes *in vitro* through Fas-Fas ligand interactions [43].

Neither recombinant IgG derived from clonally expanded CSF B cells [49] nor the IgG secreted by Id⁺

CSF B cells [47] of MS patients react with CNS antigens, suggesting that B cells may not be selected to the CSF for their antigen specificity. Their ability to engage in Id-driven T-B cell collaboration may possibly explain why these B cells were maintained intrathecally. In line with this idea, an Id-specific CSF T cell clone recognized a mutated framework region on the BCR [47]. Replacement mutations in the framework regions will usually not increase the antigen affinity of the BCR and are therefore usually not selected for during affinity maturation. They could, however, create T cell epitopes. Accordingly, tracking the genealogical tree of a large B cell clone spontaneously arising in lupus-prone mice showed that the oldest BCR mutation did not increase the affinity for chromatin, but rather created an immunodominant T cell epitope [19]. In our own model system, transfer of Id⁺ B cells and Id-specific CD4⁺ T cells to normal mice has shown that B cell presentation of an Id-peptide to Id-specific T cells leads to formation of germinal centres, class shift, and maturation of B cells into antibody secreting plasma cells [17], indicating that Id-driven T-B cell collaboration may indeed occur during germinal centre reactions.

It should be stressed that Id-specific CD4⁺ T cells, depending on their phenotype, may either kill or help Id⁺ B cells [17,50]. Id-specific CSF T cells from MS patients

were predominantly Th1-type, but also secreted substantial amounts of Th2 cytokines [47]. The co-occurrence of Id-matched T-B cell pairs in the CSF argues that at least some Id-specific T cells sustain rather than kill Id⁺ B cells.

Why MS?

Any hypothesis answers some questions and raises others, and does not necessarily apply to all subtypes of a heterogeneous and complex disease like MS. As a case in point, intrathecal synthesis of oligoclonal IgG is less frequent in the minority of patients with primary progressive MS, and the hypothesis outlined here may therefore be less relevant in this subtype. An important question is why Id-driven T-B cell collaboration elicited by infection, which might occur in most individuals, leads to MS only in a few. This may reflect the low number of activated lymphocytes patrolling the healthy CNS and possibly also the lack of preferential homing mechanisms for Id-matched T-B cell pairs, making their re-encounter in the CNS (or elsewhere) a stochastically rare event. On the other hand, the vulnerability and the relative immune privilege of the CNS may allow Id-matched T-B cell pairs lodged there to escape regulatory mechanisms and cause more damage than elsewhere.

Another question is whether the mechanism proposed here is involved in other immune mediated diseases. Given the epidemiological and immunological similarities between MS and other immune mediated diseases [51], and the presence of Id-specific T cells in the blood from patients with several autoimmune diseases [52–56], this is possible and perhaps even likely. We have, however, focused our human studies on MS, because the blood-brain barrier makes it likely that Id-matched T-B cell pairs, which would be outnumbered by other lymphocytes in the blood, could be more easily identified in the CSF.

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