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Review

The role of the adaptive immune system in the initiation and persistence of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS) in which complex networks of interacting immune cells initiate and sustain the disease. The pathogenesis of relapsing MS is driven by adaptive immune cells that become activated outside the CNS compartment and then migrate into the CNS to initiate a presumably autoimmune inflammatory process. Recent technological advances, particularly single-cell analyses, have revealed substantial heterogeneity in T and B cells involved in this stage of the disease. Disease progression involves different mechanisms, with compartmentalized inflammation and chronic activation of CNS-resident cells becoming predominant features. The contribution of tissue-resident adaptive immune cells to the pathology of progressive MS, including tissue-resident $CD8^+$ T cells and B cells in the meningeal compart, is increasingly debated. Here, we will discuss concepts of how adaptive immune cells might initiate and maintain autoimmune inflammation in the CNS, while the responses to autoimmune inflammation of CNS intrinsic cells, including astrocytes, oligodendrocytes, and neurons, are described elsewhere [1–5] and will not be a particular focus of this overview. Finally, it is the aim of this review to conceptualize the grounds for efficient therapeutic interventions targeting players of the adaptive immune system in relapsing but also in progressive MS.

1. Introduction

Multiple sclerosis (MS) is the most prevalent inflammatory disease of the central nervous system (CNS), affecting over 2.5 million individuals worldwide [6,7]. The disease typically manifests between the ages of 20 and 40 and affects women about twice as often as men. Approximately 85–90 % of patients initially develop relapsing-remitting MS (RRMS), characterized by episodes of acute worsening followed by recovery. Many RRMS patients eventually transition to secondary progressive MS (SPMS), while 10–15 % experience primary progressive MS (PPMS) from the onset [8].

MS is considered an immune-mediated disease triggered by environmental factors in genetically susceptible individuals. Genome-wide association studies have identified over 200 risk variants, particularly affecting T and B cell responses, with HLA-DRB1 * 15:01 conferring the strongest risk [9,10]. However, genetic factors account for only approximately 30 % of the disease risk, highlighting the crucial role of environmental factors such as vitamin D deficiency, obesity, smoking, and Epstein-Barr virus (EBV) infection in triggering MS [11–13].

Recent years have witnessed significant developments in the field of MS immunology, with researchers moving beyond the limitations of conventional paradigms to recognize the intricacies of cellular interactions. The advent of novel technologies enabling deep immune profiling has revealed substantial heterogeneity in immune cell populations and their functions [14–17]. Conceptually, single-cell-based analytic approaches are being applied to identify subsets of patients due to common endophenotypes comprised within the "syndrome" of MS. On the other hand, a number of key features have recently emerged to be surprisingly common to all MS cases: First, the susceptibility loci for the development of MS are essentially the same irrespective of the clinical presentation as relapsing-remitting or primary progressive MS [10]. Second, the clinical worsening of disability independent of

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relapses is an early phenomenon also in relapsing-remitting disease. The term PIRA ("progression independent of relapse activity") was coined to describe this observation [18]. Third, the depletion of circulating B cells, which is a recently broadly applied therapeutic intervention in MS, is efficient early in the disease course of all putative subsets of MS, indicating that adaptive immune responses, driven by the interaction of $CD4^+$ T cells and B cells as antigen-presenting cells (APCs), are highly relevant for the induction of immunopathology in the CNS of MS patients.

In this review, we will focus on how adaptive immune cells, including T and B cells, orchestrate MS pathogenesis through complex cellular networks. We will emphasize how recent technological advances are reshaping our understanding of these cellular interactions and how this understanding might drive the development of more targeted therapeutic approaches.

2. MS: A T cell-centric pathogenic concept

Manipulation of the $CD4^+$ T cell compartment has clear effects on the inflammatory disease activity in MS patients, supporting a role of $CD4^+$ T cells in the pathogenesis of MS. First, T cell depletion – attempted through anti-CD4 antibodies and a monoclonal antibody targeting CD52, which also depletes B cells and monocytes – prevented relapses in MS, provided that adequate depths of T cell depletion were achieved [19–24]. However, due to the essential role of T helper (TH) cells in orchestrating immune responses for host defense and tumor immunity, and because the $CD4^+$ T cell population includes $FOXP3^+$ Treg cells, achieving a deep depletion of the polyclonal $CD4^+$ T cell repertoire is not a reasonable approach. Second, the unintentional activation of TH cells that respond to myelin basic protein can lead to inflammatory episodes in MS patients that mimic clinical relapses, both in symptoms and imaging [25]. Third, preventing effector TH cells from entering the CNS effectively reduces MS relapses [26,27]. These points are consistent with the idea that TH cells, activated in the systemic immune compartment followed by recruitment to the CNS, are key initiators of inflammatory demyelination in MS. Even the success of anti-CD20-antibody-mediated depletion of circulating B cells in preventing MS relapses is in line with T cells as drivers of MS relapses since B cells act as antigen-presenting cells (APCs) to $CD4^+$ T cells [28].

Yet, to a large extent, our understanding of a potentially pathogenic role of $CD4^+$ T cells in MS is based on an animal model (experimental autoimmune encephalomyelitis, EAE), which is dependent on autoreactive $CD4^+$ T cells and which has been instrumental in investigating the antigen drainage from the CNS [29–31], the activation of CNS-reactive $CD4^+$ T cells in the systemic immune compartment [32], the trafficking of T cells across the blood-brain-barrier (BBB) [33], and the immunogenic or tolerogenic re-activation of antigen-specific T cells in the CNS compartment [34,35]. A key argument for the pathogenic role of neuroantigen-specific T cells in EAE is the fact that these cells are the only cells that can transfer the disease to naive (unimmunized) experimental animals. While molecular details of the behavior of neuroantigen-specific T cells in EAE are compatible with the observed mode of action of therapies that are efficient in human MS, the putative role of $CD4^+$ T cells in human MS has been debated for a number of reasons. First, while they dominate the lymphocyte infiltrate in acute demyelinating encephalomyelitis (ADEM) – very similar to what is observed in EAE –, $CD4^+$ T cells are just not abundant in human MS lesions. Second, no public HLA class II-restricted autoantigen is known in human MS. For decades, the quest for a public autoantigen in MS has failed, which makes it very difficult to prove that MS is truly an autoimmune disease of the CNS like myelin oligodendrocyte glycoprotein (MOG)-associated disease (MOGAD) or neuromyelitis optica spectrum disorder (NMOSD) where MOG and aquaporin-4 (AQP4) were unambiguously identified as disease-relevant autoantigens, respectively. Nevertheless, the beneficial effect of immunomodulatory interventions in MS support the idea that immunopathology is a key driver of the disease process in MS.

2.1. $CD4^+$ T cells: beyond the TH1/TH17 paradigm

The role of $CD4^+$ T cells in the pathogenesis of MS is supported by genetic evidence. In particular, HLA class II alleles, most notably HLA-DRB1 * 15:01 (DR15), represent the strongest genetic risk factor for MS [10]. Moreover, several prominent MS risk haplotypes influence genes that directly affect the functional characteristics of T cells, particularly $CD4^+$ TH cells [36]. While early studies focused on myelin proteins as potential T cell targets, more recent work has identified additional antigens [37–39]. Analysis of T cell receptor (TCR) repertoires demonstrated that HLA-$DR15^+$ memory B cells can activate $CD4^+$ T cells through the presentation of both CNS-derived and non-CNS antigens, including EBV antigens, indicating that EBV infection might be connected to MS through the initiation of adaptive anti-myelin responses [40,41]. However, a clear link of $CD4^+$ T cell responses to EBV epitopes with enhanced anti-myelin-responses of $CD4^+$ T cells has still not been shown experimentally. Moreover, a recent approach has focused on the emergence of class-switched, TH cell-dependent autoantibodies in populations with incipient MS. About 10 % of MS patients have developed a "stable" autoantibody signature years before the onset of clinical MS symptoms. Although the targets of these autoantibodies and, thus, the specificity of the involved TH cells are not clear, commonly recognized antigenic peptide motifs were defined [42].

Myelin-reactive T cells have been identified in the TCR repertoire of both healthy donors and MS patients [43–46]. However, the functional profiles of disease-relevant T cells in MS patients differ from those of healthy controls, suggesting that factors beyond antigen specificity may play a role in determining pathogenicity [25,47]. $CD4^+$ T cells in MS comprise a number of functionally distinct subsets. TH1 cells, which express T-bet and produce IFN-γ, promote macrophage activation and tissue inflammation [32,48]. TH17 cells, defined by ROR-γt expression and IL-17 production, have been demonstrated to be particularly effective at disrupting the integrity of the BBB [32,48–50]. Recent studies employing single-cell technologies have revealed that the TH1/TH17 binary paradigm is oversimplified. Effector $CD4^+$ T cells exhibit considerable functional heterogeneity and plasticity both in animal models and in human MS [51,52]. Rather than representing distinct lineages, pathogenic T cells often co-express multiple cytokines and manifest context-dependent functional states. T cells might even be able to transition between states, acquiring or losing pathogenic features contingent on the local environment [53]. Although the plasticity of TH cell subsets is remarkable, it is not arbitrary. For example, in the CNS, TH17 cells acquire TH1-like features while maintaining core TH17 programs [54,55]. This observation has been made in animal models of MS and has been validated in the $CD4^+$ T cell compartment in the CSF of MS patients [56]. The functional adaptation of neuroantigen-specific T cells appears to enhance their pathogenic potential in the MS disease context and may explain why targeting individual cytokines has had limited therapeutic success. Yet, some cytokines, including GM-CSF, which is expressed by activated TH cells (irrespective of their lineage commitment), are particularly pro-inflammatory. GM-CSF-producing T cells express high levels of CXCR4 and are increased in MS patients compared to healthy controls [57].

Follicular T helper (TFH) cells, which express CXCR5 and PD-1 and the lineage determining transcription factor BCL-6, are specialized for the purpose of assisting B cell responses in lymphoid tissues. They support B cell survival, proliferation, and differentiation into either memory B cells or antibody-secreting plasma cells through the provision of CD40L and the secretion of IL-21 [58,59]. TFH cells have initially been described to be restricted to the light zone of germinal centers. However, T cells with a similar signature as TFH cells have been identified in the circulation [60]. In experimental models of MS, TFH cells have regained attention due to their unique potential to interact with B cells in CNS draining lymph nodes but also in tertiary lymphoid tissue in

the meningeal compartment [61]. TFH cells are increased in the CSF and blood of MS patients and likely contribute to creating a local B cell-fostering environment [62–66]. Interestingly, the increased TFH cell fraction and an increased ratio of TFH cells vs. regulatory subset of TFH (TFR) cells are associated with increased fractions of intrathecal immunoglobulin [65,67]. Circulating TFH cells from MS patients have been observed to produce abnormally high levels of IL-21, particularly during relapses [64,68]. TFH cells have the capacity to facilitate both TH17 and B cell responses [61]. Therefore, TFH cells likely have an active part in driving inflammation in MS. Conversely, B cells from MS patients appear to fail to control the fraction of circulating TFH cells via the TIGIT/CD155 pathway [69]. B cell-depleting therapies but also a series of non-B cell-depleting therapies, including Fingolimod and Dimethylfumarat, correct the increased fractions of TFH cells in the blood of MS patients [65,70,71].

Taken together, recent advances have fundamentally reshaped our understanding of $CD4^+$ T cells in MS pathogenesis. Moving beyond the traditional TH1/TH17 paradigm, single-cell analyses have revealed remarkable functional plasticity and heterogeneity within the $CD4^+$ T cell compartment. Rather than representing fixed lineages, pathogenic T cells exhibit context-dependent functional states and can transition – according to specific rules – between different phenotypes, particularly within the CNS microenvironment. The TFH-B cell axis appears to be central not only in peripheral lymphoid organs but also in maintaining inflammatory responses within the CNS through meningeal follicle-like structures [64]. Understanding these complex cellular interactions and their tissue-specific regulation will be crucial for developing more targeted therapeutic approaches that can address both relapsing and progressive forms of MS.

2.2. Regulatory T cells: gatekeepers in steady state and auditors in inflammation

$CD4^+$ T cells expressing the transcription factor FOXP3 are essential regulators of immune responses and maintainers of self-tolerance [72]. These Treg cells suppress inflammatory responses through multiple mechanisms, including inhibitory cytokine production (IL-10, TGF-β), metabolic disruption via CD39/CD73, and direct cell contact-dependent suppression through CTLA-4 [73]. Given that the frequencies of CNS-reactive T cells in the systemic immune systems of healthy individuals and those with MS are largely similar, it was early on proposed that a dysfunctional or deficient $FOXP3^+$ Treg cell population, rather than an aberrant autoreactive T cell repertoire, might account for the breakdown of immune tolerance to CNS autoantigens. Supporting this idea, Treg cells in the peripheral blood of MS patients exhibit reduced suppressive abilities [74,75]. In experimental mice, depleting $FOXP3^+$ Treg cells leads to multi-organ autoimmunity [76]. Furthermore, when the TCR repertoire favors CNS antigen reactivity, the depletion of $FOXP3^+$ Treg cells promptly triggers EAE [77], underscoring the role of Treg cells in regulating the activation threshold of autoreactive T cells in the systemic immune compartment.

In addition to thymus-derived $FOXP3^+$ Treg (tTreg) cells, conventional T cells can also acquire FOXP3 in specific tissue niches, such as mucosal-associated lymphoid tissue (pTreg cells). However, highly inflammatory environments, particularly those with elevated IL-6 levels, hinder the induction of pTreg cells [78,79]. Consequently, CNS inflammation is thought to be predominantly managed by tTreg cells, which proliferate in the CNS and adopt suppressive effector functions in a TCR-dependent manner [80] rather than by pTreg cells. A model has been suggested stating that, similar to conventional T cells, CNS autoantigen-dependent Treg cells must expand in the peripheral immune system, then migrate into the CNS, receive re-stimulation, further proliferate, and develop suppressive capabilities [79]. Consistent with the crucial role of the TCR in $FOXP3^+$ Treg cell function [81], loss of TCR signaling prevents their activation, rendering them non-functional while maintaining their cellular identity [82]. Upon reaching inflammatory sites, Treg cells adopt tissue-resident transcriptional programs [83] and exhibit an "effector" Treg cell signature (including the transcriptional regulator Blimp1) that allows them to remain functional and preserve their identity despite a highly inflammatory environment [84]. Nevertheless, excessive pro-inflammatory factors (such as IL-6 and TNF) can inhibit Treg cells from effectively controlling autoimmune responses locally due to the increased resilience of effector T cells to regulation [79].

These findings from experimental models of autoimmune CNS inflammation align with clinical observations in MS, which suggest that once immune tolerance is compromised, MS relapses are strongly autoregulated. While this is undoubtedly a multifactorial phenomenon, genuine $FOXP3^+$ Treg cells likely play a crucial role in this regulation. Indirect evidence supporting this notion comes from the harmful side effects associated with a blocking antibody targeting the high-affinity IL-2 receptor (IL-2Rα, CD25). IL-2 is an essential (and likely non-redundant) growth factor for Treg cells both in the systemic immune system and in non-lymphoid tissues [85,86], and a lack of IL-2 signaling leads to insufficient Treg cell responses. The use of a blocking monoclonal antibody against IL-2Rα (daclizumab) in MS patients was linked to a reduction in Treg cell number and function [87] and, in some instances, resulted in severe inflammatory syndromes in the liver and skin, including encephalitis [88], leading to the discontinuation of this treatment [89].

In summary, CNS antigen-specific $FOXP3^+$ Treg cells are crucial for both maintaining T cell tolerance to CNS autoantigens and, once tolerance is disrupted, for managing the inflammatory response locally. Current research is focused on understanding the specific characteristics of Treg cells in the CNS, such as whether they are formed through local imprinting or the selective recruitment of Treg cells that already possess a "CNS-specific" signature in the systemic immune compartment [90]. Moreover, at least in animal models of MS, autoantigen-specific $FOXP3^+$ Treg cells appear to persist in the post-inflammatory CNS for extended periods of time, and little is known about their immune surveillance function in this situation. Therefore, gaining more insight into the traits of CNS-resident Treg cells may present opportunities to utilize them not only for sustaining organ-specific immune tolerance but also for promoting regenerative processes.

2.3. $CD8^+$ T cells: mostly tissue-resident memory (TRM) cells in the CNS

$CD8^+$ T cells represent the predominant T cell population in MS lesions, largely outnumbering $CD4^+$ T cells [91,92]. Specific HLA class I haplotypes are significantly associated with MS and constitute either risk factors or are protective as to the development of MS [93].

Recent studies have revealed that $CD8^+$ T cells in MS lesions express elevated levels of cytotoxic molecules, including granzyme B [92]. The number of $CD8^+$ T cells correlates with axonal injury in lesions, thereby suggesting direct involvement in tissue damage. Beyond direct cytotoxicity, these cells produce inflammatory cytokines, including IFN-γ and TNF, which can activate local glial cells and promote inflammation. Tissue-resident $CD8^+$ T (TRM) cells can be detected in both white and grey matter lesions and may contribute to ongoing tissue damage through local reactivation. In postmortem brain tissues, $CD8^+$ T cells express canonical markers of tissue residency, including CD69 and CD103, suggesting adaptation to the local CNS environment [92,94]. Similar to $CD4^+$ T cells, it is unclear whether CNS-residing $CD8^+$ T cells recognize CNS antigens rather than common neurotropic virus epitopes. As has been shown in experimental models, TRM cells may reside in the CNS and expand due to the inflammatory environment, independent of their primary antigen specificity [95]. Analyses of CNS autopsy specimens of MS patients indicate that MS lesion-associated $CD8^+$ T cells proliferate and exhibit signs of cytotoxicity [96,97]. Since MS lesion-derived $CD8^+$ T cells respond to autologous EBV-infected lymphoblastoid cell lines (B-LCL), they likely recognize antigens (including autoantigens) that are presented by B-LCLs [96]. Interestingly, broader

HLA class I-restricted EBV-specific TCR repertoires are also found in the systemic compartment of MS patients as compared to controls [98].

In summary, the cumulative evidence points to the idea that CNS-located $CD8^+$ TRM cells likely reflect an individual's past history of exposure to infectious (neurotropic) agents. Should no re-infection with those agents occur, CNS TRM cells are likely inert. However, it remains to be determined which signals (apart from their cognate antigen) can trigger TRM cells to participate in inducing immunopathology in the CNS. In experimental systems, $CD8^+$ TRM cells have been shown to lower the threshold for autoimmune responses in the CNS [99,100]. Also, even in the absence of an independent autoimmune attack, for which TRM cells might provide a fertile field, TRM cells can maintain persistent low-grade inflammation and initiate cellular programs in neighboring neurons that accelerate their demise. This chronic, non-resolving inflammatory process – often referred to as smoldering inflammation – involves continuous, subclinical activation of immune pathways that gradually compromise neuronal function. At the molecular level, IFN-γ released by TRM cells activates STAT1-dependent pathways in neurons, leading to altered mitochondrial function, increased oxidative stress, and impaired cellular metabolism [101]. Similarly, TRM cell-derived factors can activate the STING pathway in neurons, resulting in dysregulated calcium homeostasis and excitotoxicity [102]. These processes have been associated with the aging of the brain, and they may be prematurely initiated in patients with MS. Some evidence suggests that TRM cell-associated pathways are the biological basis for a continuous loss of neurons and axons and, thus, perhaps part of the biological basis of progressive disease in MS [103].

In the future, a key challenge will be to disentangle whether clonally expanded $CD8^+$ T cells in MS lesions are bystander TRM cells or autoreactive $CD8^+$ T cells that are direct drivers of immunopathology. Notably, if those MS-lesion-associated $CD8^+$ T cells were truly autoreactive, they would constantly see their antigen and should adopt an exhausted phenotype. In experimental models of $CD8^+$ T cell-dependent CNS autoimmunity, an exhausted phenotype has indeed been observed in CNS-residing $CD8^+$ T cells, characterized by upregulation of the transcription factor TOX, which drives a program in $CD8^+$ T cells that preserves them from death under conditions of persistent antigenic stimulation [104]. From the perspective of the target tissue, an exhausted phenotype of tissue-residing $CD8^+$ T cells restrains further immunopathology and can be considered as an autoregulatory principle. Indeed, the exhausted state appears to be unstable in MS, which could potentially contribute to ongoing disease activity and increased immunopathology [105].

In summary, $CD8^+$ T cells represent a complex player in MS pathology, being the predominant T cell population in lesions while exhibiting features of tissue residency. Their contribution likely extends beyond classical cytotoxic functions, as chronic CNS inflammation drives these cells toward an exhausted phenotype. The instability of this exhausted state in MS, combined with the TRM phenotype of lesion-associated and also extra-lesional $CD8^+$ T cells, may contribute to ongoing diffuse tissue damage even in the absence of new inflammatory waves from the periphery.

3. B cells: T-B interactions in hot spots of MS pathogenesis

The importance of B cells in MS pathogenesis has been highlighted by the therapeutic success of B cell-depleting therapies, which reduce disease activity without affecting antibody levels [106,107]. This suggests that antibody-independent B cell functions, particularly their interaction with T cells, might be crucial for disease activity.

T-B cell interactions occur in distinct anatomical compartments during MS pathogenesis. In peripheral lymphoid organs, memory B cells serve as highly efficient APCs, activating myelin-reactive T cells through both CNS-derived and non-CNS antigens, including EBV-derived peptides [28,40]. Within the CNS, B and T cells establish complex networks in both acute lesions and chronic inflammatory sites. Of particular interest are meningeal follicle-like structures, where B cells interact with TFH cells to maintain local inflammatory responses [108]. These structures may serve as sites of ongoing B cell activation and differentiation. While intrathecal antibody production and oligoclonal bands are hallmarks of MS, their pathogenic relevance remains debated, and the quest for identifying potential autoantigens is unresolved [109–112].

Beyond antibody production, B cells secrete pro-inflammatory cytokines, including TNF, lymphotoxin-α, and IL-6, that can promote T cell responses [113–116]. Single-cell analyses have revealed distinct B cell subsets with pro- or anti-inflammatory functions in MS. Memory B cells, particularly those expressing CD11c and T-bet, exhibit enhanced pro-inflammatory properties and are enriched in MS patients [117]. A population of GM-CSF-producing B cells with enhanced capacity to activate myeloid cells is abnormally increased in MS patients [118]. Since subpial cortical pathology in MS has been found in close spatial relationship with meningeal B cell aggregates, the idea that B cells in this anatomical niche might secrete toxic mediators to lead to a "surface-in" pathological process has been proposed particularly in chronic MS [119]. In contrast, regulatory B cells producing IL-10 show numerical and functional deficits in MS, and very recent work has identified a circulating, gut-derived IgA^+ B cell population with anti-inflammatory properties [120,121].

The interaction between B and T cells is bidirectional - while B cells present antigens and provide costimulation to T cells, T cells shape B cell responses through cytokines and surface molecules, including CD40L, which promotes class switch recombination in B cells and is a major communication pathway between TFH cells and B cells in germinal centers [122]. Understanding these complex cellular interactions in different anatomical compartments may provide new therapeutic opportunities in MS beyond current B cell-depleting approaches. Notably, anti-CD40L antibodies have recently been successfully tried in relapsing MS patients [123].

Finally, B cells are the cellular target of EBV. Although there has been a long debate about whether EBV would persist in B cells residing in the CNS compartment and maintaining adaptive immune responses in situ [97,124], the persistence of EBV in the CNS of MS patients has not been confirmed [125]. Rather, the immune response against EBV is primed in deep cervical lymph nodes where antibodies and T cell responses against specific EBV epitopes have been discovered to cross-react with CNS antigens. For instance, antibodies to EBNA1 may cross-react with GlialCAMs [126]. However, EBV infection of deep cervical lymph nodes also alters the entire B cell landscape, decreasing germinal center B cells and increasing a population of so-called double negative (DN, $IgM^-IgD^-CD27^-CD38^-$) memory B cells [127] that have received some attention in the pathogenesis of systemic lupus erythematosus and rheumatoid arthritis as well [128–130]. In addition, DN B cells carry features of lytically EBV-infected B cells but do not contain viral DNA [127]. Mechanistically, DN B cells in deep cervical lymph nodes may be very efficient in presenting CNS autoantigens to T cells outside the germinal center niche. Together, these findings support the idea that the EBV-mediated perturbation of the B cell compartment of deep cervical lymph nodes may be associated with the initiation of autoimmunity against CNS antigens.

4. Contribution of the adaptive immune system to relapsing MS

The pathogenesis of relapsing MS involves spatially and temporally distinct immunological events that occur both in the peripheral immune compartment and within the CNS (Fig. 1). These processes include peripheral immune activation, BBB disruption, and a complex sequence of tissue damage followed by partial resolution [131].

Initial immune activation in MS likely occurs in peripheral lymphoid tissues, potentially triggered by molecular mimicry or bystander activation in response to environmental factors. According to a broadly accepted hypothesis, dendritic cells sample antigens in tissues such as the lung, skin, or gut and migrate to draining lymph nodes where they

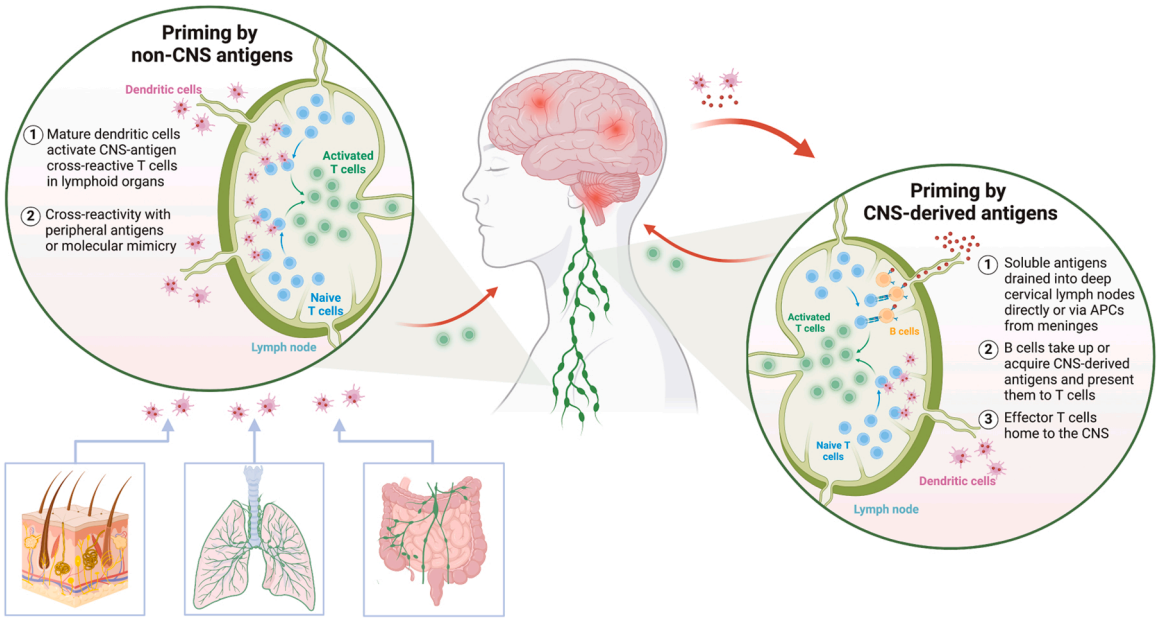

Fig. 1. Contribution of the adaptive immune system to relapsing MS. The pathogenesis of relapsing MS involves distinct immunological events in the peripheral and CNS compartments. In an initial episode, T cells that are cross-reactive for CNS antigens are primed by mimic antigens in the systemic immune compartment. Antigen-presenting cells (APC), such as dendritic cells (DCs), present non-CNS antigens from peripheral sites. Activated T cells travel to the CNS where they are reactivated by CNS-antigens to get licensed for infiltration into the CNS parenchyma. Self-antigens expressed in the CNS are drained into the deep cervical lymph node either in a soluble form or perhaps via APC-mediated delivery after uptake in the meningeal linings. After priming of antigen-specific T cells in the CNS-draining LN, these T cells home back to the CNS in order to cause autoimmune inflammation. This cascade might be particularly relevant for relapses. The figure was created with Biorender.

present these antigens to T cells [132]. Similarly, prior to relapse, CNS-antigen-specific T cells may be activated and expanded in the systemic immune compartment before they migrate to the CNS [25]. It is an appealing hypothesis that an altered B cell compartment in deep cervical lymph nodes that are exposed to drained CNS antigens might provide significant APC capacity to reactivate antigen-specific T cells with real CNS autoantigens (Fig. 1).

Following their activation, immune cells express specific adhesion molecules and chemokine receptors that facilitate CNS entry. This process involves sequential interactions between activated lymphocytes and the cerebrovascular endothelium, with key molecular pairs including VLA-4/VCAM-1 and LFA-1/ICAM-1 [133]. Within the CNS, the reactivation of infiltrating T cells by local APCs triggers an inflammatory cascade [34,134]. Single-cell analyses have revealed distinct cellular states associated with different stages of lesion evolution [14,135]. Initial phases of lesion development are dominated by pro-inflammatory myeloid cells and activation of glial cells [136].

Following acute inflammation, several mechanisms contribute to lesion resolution. Regulatory T cells, including both $FOXP3^+$ Treg cells and $FOXP3^-$ IL-10-producing type 1 regulatory (Tr1) cells, increase during remission and suppress inflammatory responses [137].

5. Contribution of the adaptive immune system to progressive MS

Progressive MS is characterized by a continuous accumulation of neurological disability that occurs largely independently of relapses. While relapsing MS is driven primarily by waves of peripheral immune cell infiltration into the CNS, progressive MS involves compartmentalized inflammation within the CNS and chronic activation of tissue-resident immune cells [138,139]. The inability of current immunotherapies to effectively treat progressive MS underscores that distinct pathological processes are operational in progressive disease and, perhaps most of all, the differential significance of the systemic vs. the CNS compartment as the center stage for disease activity.

Progressive MS is characterized by compartmentalized inflammation within the CNS, where tissue-resident innate immune cells, particularly microglia and astrocytes, maintain a chronic inflammatory environment largely independent of peripheral immune responses [14,140]. These CNS-resident cells interact dynamically with tissue-resident lymphocytes and meningeal immune cell aggregates, creating complex networks that drive chronic tissue injury [141,142]. While the role of innate immune cells in progressive MS has been extensively reviewed elsewhere [103,143,144], we would like to highlight a few key aspects of the adaptive immune response that characterize progressive disease (Fig. 2).

A key feature of progressive MS is the persistence of TRM-like cells in the CNS parenchyma. $CD8^+$ TRM cells, characterized by unique molecular markers like CD69 and transcription factors Hobbit and Runx3, may contribute to chronic tissue damage even in the absence of their cognate antigens [94,145,146]. Through constitutive production of inflammatory chemokines like CCL5 and IFN-γ, TRM cells create a 'smoldering' inflammatory environment that facilitates recruitment of additional autoreactive T cells. However, recent studies also demonstrate the ability of CNS-residing $CD8^+$ T cells to directly target neural cells, particularly when supported by $CD4^+$ T cell help, triggering microglia activation and synaptic pruning, which eventually leads to neuronal dysfunction. Gene polymorphisms associated with MS susceptibility, e.g., for Runx3, further underscore a putative role of TRM or TRM-like cells in disease pathogenesis}[10]. EBV-specific TRM cell clones in distinct CNS compartments may link the EBV hypothesis of MS pathogenesis with chronic inflammatory conditioning of CNS tissue [147].

The failure of local Treg cells to control inflammation may represent a more critical aspect of progressive MS pathogenesis than previously anticipated. Treg cells are rare in naive CNS tissue but accumulate in the inflammation-experienced CNS [148]. Treg cells are particularly concentrated in distinct CNS compartments, including meningeal sites, perivascular spaces, and active demyelinating lesions [149]. In animal models, CNS Treg cells have been proposed to promote tissue repair.

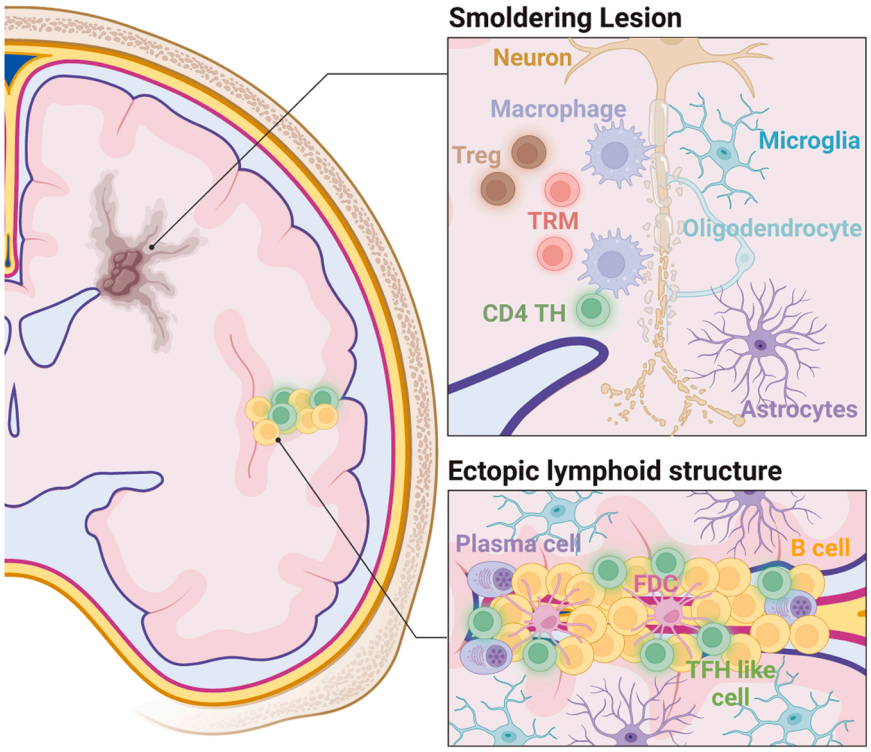

Fig. 2. Contribution of the adaptive immune system to progressive MS. Disease progression in MS involves different mechanisms, with compartmentalized inflammation and chronic activation of central nervous system (CNS)-resident cells becoming predominant features. The tissue response extends beyond classical inflammatory mechanisms. Complex interactions between CNS-resident cells (microglia, astrocytes) and adaptive immune cells ($CD8^+$ TRM cells, $CD4^+$ TH cells, and Treg cells) create an environment promoting chronic tissue injury. In meningeal linings, organized lymphoid-like structures containing follicular dendritic cells (FDC), B cells, T cells, and plasma cells maintain local inflammation through both pro-inflammatory and potentially regulatory mechanisms. These structures may contribute to subpial demyelination and cortical pathology in the underlying tissue. The figure was created with Biorender.

However, their fundamental capacity to maintain immune homeostasis in the chronically inflamed CNS has emerged only recently. In experimental systems, a major problem has been to locally deplete Treg cells in the CNS without touching the systemic Treg cell compartment. However, a gain-of-function approach built on locally providing IL-2, the major growth factor for $FOXP3^+$ Treg cells, succeeded in expanding CNS Treg cells with beneficial effects for immune homeostasis and reparative functions of CNS Treg cells in models of inflammation, traumatic tissue damage, and even neurodegeneration [150].

While chronic inflammation in the CNS is a major trigger for the accumulation of Treg cells in the CNS, it may, at the same time, contribute to dismantling the protective functional phenotype of CNS Treg cells over time. $FOXP3^+$ Treg cells show a marked inability to suppress local inflammation, with reduced proliferation and diminished suppressive capacity within these critical neuroinflammatory niches. Recent investigations suggest that the CNS microenvironment creates a hostile inflammatory landscape that progressively impairs Treg cell suppressive mechanisms. Aberrant epigenetic and metabolic alterations within Treg cells may contribute to their dysfunction and provide a conceptual framework for investigating the loss of resilience of Treg cells that reside in an inflammatory environment [90]. These concepts are mostly being developed in experimental models due to the difficulty of directly investigating CNS Treg cells from human CNS tissue.

The inflammatory environment is further shaped by ectopic lymphoid-like structures in the meninges containing organized aggregates of B cells, plasma cells, and T cells [108]. The interactions between T and B cells within these structures reveal a nuanced pathophysiological mechanism with potentially dual inflammatory roles [115]. Some studies indicate that meningeal lymphocyte aggregates could function as either inflammatory amplifiers or potential regulatory sites, challenging the simplistic view of uniform pathogenicity [151–154]. Meningeal lymphocyte aggregates appear to sustain local inflammation through the production of inflammatory mediators that can promote subpial demyelination and cortical pathology in the underlying tissue [119,155]. The severity of meningeal inflammation correlated with the rate of clinical progression in a cohort of MS patients from whom autopsy material was available, suggesting an important role in disease advancement [156, 157]. Critically, the question remains whether these lymphoid-like structures in the meninges represent a primary pathogenic mechanism or a reactive epiphenomenon of ongoing neuroinflammation. The persistence of meningeal tertiary lymphoid tissues, maintained by complex T and B cell interactions, continues to intrigue researchers seeking to unravel their precise role in MS progression [158]. Since B cell depletion by systemic administration of anti-CD20 antibodies fails to efficiently deplete B cells in meningeal aggregates, newer therapeutic approaches, including anti-CD19 CAR-T cells [159], are being tried in MS with the aim to explicitly target B cell accumulations also in the CNS compartment. It remains to be seen whether this will be a means to prevent progressive disease in MS.

6. Conclusion and perspective

Recent advances in our understanding of MS immunology have revealed remarkable complexity in both cellular interactions and tissue responses. These insights are reshaping therapeutic approaches, particularly regarding the distinct mechanisms driving relapsing versus progressive disease.

The tissue response in MS extends beyond classical inflammatory mechanisms and involves complex interactions between immune cells and CNS-resident cells. Astrocytes emerge as key players in both relapsing and progressive MS through multiple mechanisms, including regulation of BBB integrity, immune cell recruitment, and metabolic

support of neurons. Recent studies have identified distinct reactive astrocyte states that can either promote neurodegeneration or support tissue repair [140,141,160,161]. Eventually, neurons respond through cellular programs that impair their resilience to inflammatory environments and may herald their premature demise.

While it is important to understand the molecular underpinning of tissue response programs in MS (also in distinction to other chronic diseases of the CNS), decades of evidence in MS research point to the idea that these response programs in cells of the CNS parenchyma are not intrinsically initiated but are triggered by the immune system. Microglial cells and perhaps other CNS-resident myeloid cell populations are prime players in inflammatory processes compartmentalized in the CNS [162,163]. In addition, unconventional lymphocytes at the intersection of the innate and adaptive immune systems, including MAIT cells or γδ T cells, participate in key positions in tissue immunity (outside secondary lymphoid organs). γδ T cells and MAIT were also identified in the CNS tissue of MS patients [164–167].

However, over the last decade, it has been an emerging topic that cells of the classical adaptive immune system are important orchestrators not only of the relapsing phase of MS, where they convey inflammation from the systemic compartment into the CNS, but also in progressive disease. Here, TRM cells, CNS-resident FOXP3$^+$ Treg cells, and meningeal B cells interacting with local TFH cells set the scene for an inflammatory environment that appears to be very specific for multiple sclerosis. The relative contribution of these adaptive players to immunopathology in progressive MS needs to be determined. Although the definition of their effector functions might provide fundamentally new targets for therapeutic interventions, any therapeutic approach directed at CNS-resident adaptive immune cells needs to be brought into the CNS compartment. Modern drug application strategies, including "brain shuttle" principles (e.g. [168], are being developed to tackle this issue.

CRediT authorship contribution statement

Korn Thomas: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Afzali Ali Maisam:** Writing – original draft.

Declaration of Competing Interest

The authors declare that there are no competing interests.

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Author contributions

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Data availability

No data was used for the research described in the article.

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