The Enigmatic Role of Viruses in Multiple Sclerosis: Molecular Mimicry or Disturbed Immune Surveillance?

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Multiple sclerosis (MS) is a T cell driven autoimmune disease of the central nervous system (CNS). Despite its association with Epstein-Barr Virus (EBV), how viral infections promote MS remains unclear. However, there is increasing evidence that the CNS is continuously surveyed by virus-specific T cells, which protect against reactivating neurotropic viruses. Here, we discuss how viral infections could lead to the breakdown of self-tolerance in genetically predisposed individuals, and how the reactivations of viruses in the CNS could induce the recruitment of both autoaggressive and virus-specific T cell subsets, causing relapses and progressive disability. A disturbed immune surveillance in MS would explain several experimental findings, and has important implications for prognosis and therapy.

Genetic and Environmental Factors Contribute to the Risk of MS

MS is the most common inflammatory autoimmune disorder of the CNS [1,2]. It is characterized by the destruction of the protective myelin sheath of neurons, resulting in macroscopic lesions in the brain and causing progressive disability. MS can be subdivided into relapsing–remitting (RR), primary progressive (PP) or secondary progressive (SP; i.e., the RR subtype worsening over time to SP-MS) forms. RR-MS is the dominant form at disease onset, and is characterized by acute clinical attacks followed by apparent disease stability. Symptoms can be alleviated with several therapies, but, in some patients, there is no beneficial effect and the disease may evolve to a SP form. PP-MS and SP-MS remain difficult to treat and are also mechanistically poorly understood [3].

The etiology of MS is still unknown, but both genetic and environmental factors contribute to the risk of developing MS [1,2]. The major genetic risk factor maps to the human leukocyte antigen (HLA) gene cluster, and the strongest risk is conferred by HLA-DRB1*15:01 in the class II region [4,5]. The principal function of MHC class II proteins is to present peptide ligands to CD4+ lymphocytes and these T cells are consequently believed to have a key pathogenic role in MS. However, the MHC class I cluster, which regulates cytotoxic lymphocyte responses, contains polymorphic regions that are associated with protection against MS [4]. Several other gene
polymorphisms associated with MS are involved in immune responses, in particular in the activation and homeostasis of T cells [6], consistent with the concept that MS is a T cell-driven autoimmune disease.

The importance of the environment in determining whether a genetically susceptible individual develops MS has been underlined by studies of monozygotic twins and of genetically susceptible individuals migrating from low- to high-risk areas. The strongest environmental risk factors are Vitamin D deficiency, smoking, and viral infections [7]. Interestingly, infections with helminths have been shown to have a protective effect [7,8]. Among viral infections, EBV shows the strongest association, and it was estimated that EBV-induced infectious mononucleosis increases the risk of MS to a similar degree as the strongest genetic risk factor (HLA-DRB1*15:01) [4,9–11]. In addition to EBV, several other viruses have been implicated in MS [12], in particular neurotropic viruses, including human herpes virus-6 (HHV-6) [13], herpes zoster virus [14] and John Cunningham virus (JCV) [15], but also endogenous retroviruses [16]. Based on this evidence, a possible viral etiology of MS has been proposed [9,13,15,17] and continues to stimulate intense research in the field (see Outstanding Questions).

The risk of life-threatening JCV-induced progressive multifocal leukoencephalopathy (PML) in patients with MS undergoing therapy with natalizumab [18], a therapeutic antibody that binds to the α4-integrin adhesion receptor and blocks lymphocyte migration to the CNS, has highlighted the importance of antiviral immune surveillance of the CNS. Indeed, the presence of a lymphatic system in the CNS has challenged the view of the CNS being an immune-privileged site [19,20], and it is now widely accepted that the CNS is surveyed and protected by antiviral T cells [21] (Box 1).

Given this updated view of immune responses in the CNS, here we discuss different models of how viral infections could promote MS, and illustrate how a defective antiviral immune surveillance could be a driving force in its pathogenesis.

The Most Widely Studied Animal Models of MS Induce CNS Inflammation in the Absence of Viral Infections

Although the epidemiological data clearly indicate that viral infections are a critical risk factor for MS, the underlying mechanisms are poorly understood [12]. Animal models that induce experimental autoimmune encephalomyelitis (EAE) in the absence of viral infections by priming pathogenic CD4+ T cells with myelin antigens are widely used to study neuroinflammation and MS [22]. Self-tolerance has to be broken in these models by adjuvants such as CFA, which contain killed mycobacteria, intracellular pathogens that potently activate the innate immune system. Alternative models of MS, in which demyelination is induced by neurotropic viruses, such as mouse hepatitis virus or Theiler’s murine encephalomyelitis virus (TMEV), are less studied, but enable researchers to address how viral infections could promote MS [23]. TMEV induces chronic inflammation and demyelination in the brain and, importantly, both virus-specific and myelin-reactive effector T cells are generated in this MS model [23]. Thus, antiviral immune responses in the CNS can result in the breakdown of self-tolerance to myelin antigens,
which is normally prevented by regulatory T cells (Tregs) [24]. In addition, viruses and antiviral T cells can also lead directly to damage and demyelination in the CNS [23,25–28]. Thus, viral MS models are highly relevant, but less studied than are those of EAE, and this is one reason why the role of viruses in MS is still poorly understood.

**The Antigen Specificity of Encephalitogenic T Cells Is Incompletely Defined**

The use of myelin antigens to induce EAE is consistent with demyelination in the brain of patients with MS and with the presence of autoreactive CD4+ T cells recognizing myelin-derived antigens that are restricted by the major MS risk allele, HLA-DRB1*15:01 [29,30]. However, myelin-reactive CD4+ T cells are rare and were found at similar frequencies in the peripheral blood of healthy individuals and of patients with MS [30]. However, myelin-reactive T cells have more proinflammatory properties in patients with MS than in healthy donors [31,32], and are enriched in the CSF of patients with MS shortly after an attack [32,33]. Nevertheless, myelin-derived antigens are probably not the only relevant self-antigens in MS. In particular, pathogenic T cells in MS may have a degenerate T cell receptor (TCR) that cross-reacts with several structurally related self-peptides, or potentially even directly with the backbone of some MHC molecules [34–37]. These autoreactive T cells have a high pathogenic potential because they could be activated by any antigen-presenting cell (APC) that expresses MHC class II and costimulatory molecules. Finally, virus-specific CD4+ and CD8+ T cells could also cause collateral damage in the CNS following an antiviral immune response, in particular those that cross-react with relevant self-antigens due to a phenomenon known as ‘molecular mimicry’ [38,39].

**Molecular Mimicry Is unlikely to be the only Virus-Related Pathogenic Mechanism in MS**

Molecular mimicry is the most frequently discussed mechanism for how viruses could induce autoimmunity and MS (Box 2), and excellent reviews have been published on this topic [34,39,40]. Some TCRs recognize several similar peptides, and this cross-reactivity is relevant for autoimmunity [41] and might be exploited by pathogens, such as viruses, to avoid recognition by the adaptive immune system [42]. Indeed, autoreactive T cells are either deleted in the thymus, rendered unresponsive in the periphery, or even redirected to the Treg lineage that induces dominant immune suppression [43,44]. Some viral proteins contain peptide sequences that are similar to the self-proteins of their hosts [39]. In the case of MS, molecular mimicry between myelin basic protein (MBP) and the EBV latency antigen EBNA-1 is well documented, since CD8+ T cell clones isolated from patients with MS could be activated by both MBP- and EBNA-1-derived peptides [38]. In addition, CD4+ T cells that cross-reacted with both EBNA-1 and MBP were identified [45], and molecular mimicry might also be exploited by HHV-6 [13]. Interestingly, commensal bacteria are known to be essential for autoimmune demyelination [46], and T cells expressing a TCR that cross-reacted with MBP and a common bacterial peptide was able to induce MS-like disease in humanized mice [37]. However, while molecular mimicry is largely accepted as the driving force in some autoimmune diseases, such as *Streptococcus*-driven rheumatic fever, its relevance in MS is still debated [39,40]. Moreover,

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**Box 2. Molecular Mimicry**

Mimicry is an evolutionary process whereby one organism acquires a similarity to another organism to obtain a survival advantage. Molecular mimicry is a phenomenon whereby molecules of a pathogen, in particular peptides, are similar to peptides of its host. T cells mount an immune response when they are activated by foreign peptides, but do not normally react against self-peptides. The latter is ensured by a combination of central and peripheral tolerance mechanisms, which lead to the deletion of highly autoreactive T cells in the thymus and ensures that T cells with an intermediate autoreactivity are not aberrantly activated in the periphery. The molecular mimicry hypothesis of autoimmunity proposes that T cells cause autoimmune disease following an antipathogen immune response when they cross-react with self-peptides from healthy, unaffected tissues. Molecular mimicry is thought to be a driving force in, for example, *Streptococcus*-driven rheumatic fever and has also been documented for the EBNA-1 protein of EBV and myelin basic protein in MS.

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**Glossary**

**Blood-brain barrier (BBB):** comprises two physical barriers of endothelial cells and the parenchymal base membrane that strongly limit the access of macromolecules and cells to the CNS parenchyma. The endothelial and parenchymal basement membranes define the inner and outer limits of the perivascular space, which is filled by cerebrospinal fluid (CSF), which drains macromolecules and immune cells into deep cervical lymph nodes.

**Central memory (TCM) and effector memory T (T<sub>EM</sub>) cells:** distinguished by CCR7 expression in humans and by CD62L expression in mice; these cells home preferentially to lymphoid and nonlymphoid tissues, respectively. T<sub>EM</sub> produce higher levels of proinflammatory cytokines than do T<sub>CM</sub>, but both T<sub>CM</sub> and T<sub>EM</sub> contain Th1, Th17, and Th1/17 cells. Moreover, T<sub>CM</sub> express adhesion and chemokine receptors, enabling them to home to the CNS.

**Clinically isolated syndrome (CIS):** a first attack is classified as CIS unless MS is diagnosed following the demonstration of lesion dissemination in space over time at MRI or the occurrence of a second clinical attack.

**Experimental autoimmune encephalomyelitis (EAE):** the most-studied animal model of MS. CNS inflammation and disability is induced by immunization with myelin antigens and adjuvants, or by the adoptive transfer of activated, myelin-specific Th cells.

**Progressive multifocal leukoencephalopathy (PML):** an often fatal demyelinating CNS disease caused by uncontrolled JCV replication. It is largely limited to individuals where CD4+ T cell responses are impaired, such as patients with AIDS or MS, where CNS immune surveillance is inhibited by natalizumab.

**T helper 1 (Th1) and T helper 17 (Th17) cells:** uncommitted naïve CD4+ T cells can differentiate upon antigenic activation under the influence of different cytokines to IFN-γ-producing Th1- or IL-17-producing Th17 cells. Th1 cells are induced by IL-12 and mediate protection against intracellular pathogens, such as viruses, while Th17 cells are induced by TGF-β, IL-
it was found T cell responses to antigens derived from EBV, JCV, and myelin were largely confined to **T helper type 1 (Th1) and Th1/17 cell** subsets in patients with MS [32]. Therefore, CD4+ T cell responses in MS against these viruses and myelin antigens are predominantly mediated by distinct Th cell subsets rather than by virus-specific T cell clones that cross-react with self-antigens. Nevertheless, Th1/17 cells isolated from the CSF reacted with autologous APC in the absence of exogenous antigens, and they might cross-react with peptides from other viruses or bacteria. Thus, although molecular mimicry is likely to contribute to the MS risk conferred by infections, other mechanisms are also likely to be important.

**The Complex Relationship between MS and Antiviral Immune Responses**

In addition to CD4+ T cells, B cells and CD8+ T cells are also involved in human MS, as evidenced by their presence in the cerebrospinal fluid (CSF) and in demyelinated brain lesions in patients [47]. In particular, the production of oligoclonal antibodies in the CSF is highly characteristic for MS and, therefore, has been used as a supportive criterion for diagnosis [48,49]. Moreover, B cell depletion with rituximab reduces relapses in patients with RR-MS [50,51]. This therapeutic effect could reflect the capacity of B cells to present antigens to pathogenic T cells [52], since rituximab does not deplete plasma cells and antibody levels are poorly affected [51]. However, rituximab could also inhibit viral delivery to the brain, because B cells represent a cellular reservoir of both EBV and JCV [53] and, therefore, are a likely vehicle for these viruses to pass across the **blood-brain barrier** (BBB). Interestingly, secondary progressive MS is characterized by tertiary meningeal lymphoid structures, which might contain infected B cells as a constant local source of EBV [54]. Oligoclonal antibodies in the CSF were first thought to represent non-sense IgG [55], and their physiological relevance is a matter of debate. However, several groups found that they could react with neurotropic viruses [56,57]. Conflicting results have been published on EBV-specific antibodies in the CSF [9,58], but several groups reported that antibodies against measles, Rubella, and herpes zoster viruses, known as the ‘MRZ reaction’, are present in 80–100% of patients with MS [57], and might predict whether patients with a **clinically isolated syndrome** (CIS) will go on to develop MS [49]. The presence of virus-specific antibodies in the CSF suggests that demyelination in MS is accompanied by antiviral immune responses. Consistent with this notion, EBV-specific CD8+ T cells are specifically expanded in the CSF of patients with MS [59], and CD8+ T cells interacting with lytically infected B cells have been identified in MS brain lesions [60,61]. However, whether the presence of EBV in brain lesions is characteristic for MS is debated [62]. Of note, several viruses persist in a latent stage, are neurotropic and, thus, might be present in the brain. Moreover, herpes simplex virus (HSV) was shown to trigger the generation of autoantibodies in the brain [63], and the neurotropic viruses HHV-6, JCV, and herpes zoster were proposed to have a role in MS [13,15,18]. Direct detection of viral nucleic acids is limited to a minority of patients [64], but localized viral reactivation in the parenchyma might not be necessarily detectable in the CSF by standard techniques [65]. Of note, many viruses, including EBV and JCV, are efficiently controlled in healthy individuals, but can cause life-threatening infections in immuno-compromised individuals [66,67]. These findings raise the question whether patients with MS mount a somehow altered immune response against viruses, in particular in the tolerogenic environment of the CNS. The association of MHC class I polymorphisms with protection is consistent with an inefficient antiviral cytotoxic immune response in patients with MS. However, so far, antiviral immune responses in patients with MS were found to be either normal or even increased, in the case of EBV [60], and patients with MS treated with strong immune suppressants, with the notable exception of natalizumab, do not experience increased viral reactivations. Nevertheless, more qualitative approaches might be required to monitor antiviral immune responses in patients with MS [54,68]. For example, antiviral T cell responses are normally measured by IFN-γ production; however, **central memory T cells** (T<sub>CM</sub>), which could perform antiviral immune surveillance of the CNS (see below), produce only limited amounts of IFN-γ, but can be efficiently expanded with viral antigens [69]. In summary, the role
of different viral infections in MS is debated, and more research is needed to understand the regulation of antiviral immune responses in patients with MS and how they might impact pathogenesis and disease progression.

T Cell Migration from Lymph Nodes to the CNS Is Required for Antiviral Immune Surveillance and Relapse

A required feature of T cells to not only induce relapse, but also perform antiviral immune surveillance is their capacity to migrate from lymph nodes to the CNS. Access to the CNS by immune cells is tightly controlled, and the brain is separated from the blood by the BBB [70]. Nevertheless, autoreactive effector T cells induced in the EAE model can spontaneously home to the CNS upon adoptive transfer and cause disease.

The migration of leukocytes into different tissues is controlled by specific adhesion molecules and chemokine receptors. The α4/β1-integrin is known to be a key adhesion molecule for CNS entry [70], although Th17 cells can home to the CNS independently of the α4/β1-integrin [71,72]. Nevertheless, natalizumab inhibits relapses and promotes JCV reactivation and PML in patients with MS, indicating that the α4/β1-integrin has a critical role for CNS homing of both pathogenic and protective, antiviral T cells. Integrins have to be activated by inside-out signaling and, in human Th1 cells, different chemokine receptors can induce α4/β1-driven adhesion [73]. However, the relevant chemokine receptors in CNS homing and MS are debated. One candidate is CCR6, which is induced by TGF-β and proinflammatory cytokines [74] and is stably expressed on human IL-17-producing Th17 cells [75–77]. CCR6 was proposed to allow access of T cells to the CNS via the lumbar spinal cord upon EAE induction [78] or at steady state via the choroid plexus [79], paving the way for the consecutive recruitment of additional T cells upon ensuing inflammation. Inflammatory chemokine receptors implicated in CNS homing and MS are CXCR3 and CCR5 [80]. These two chemokine receptors are selectively expressed on IFN-γ-producing Th1 and Th17 cells, which fight viruses [81]; the CXCR3 ligand, CXCL10/IP-10, is induced upon viral infections in the canonical response to interferons [82]. Finally, CCR7 is also implicated in T cell migration in the CNS and MS [83]. This is somewhat surprising, since a key function of CCR7 on T cells is to mediate homing of naïve and CCR7-expressing TCM to lymph nodes, while homing of CCR7+ effector memory T cells (TEM) to nonlymphoid tissues is predominantly mediated by inflammatory chemokine receptors, such as CCR5 [84]. However, relevant fractions of TCM express the α4/β1-integrin [84], CXCR3 [69], and CCR6 [77], suggesting that some TCM shuttle between lymph nodes and the CNS. Indeed, CCR7+ T cells are highly abundant in the CSF of patients with MS [85] and CCR7 ligands are expressed in the CNS, including in MS lesions [86]. The expression of CCR7 and of other chemokine receptors is dynamic in antigen-activated T cells [87] and, therefore, it is uncertain whether CCR7 expression reliably identifies TCM and TEM in the CNS of patients with active MS [85]. Nevertheless, an encephalitogenic role for TCM in MS is suggested by the therapeutic efficiency of fingolimod (FTY20), which sequesters naïve and TCM in lymph nodes, but spares TEM [88]. Furthermore, in the CSF of patients with natalizumab-treated MS, CCR7+VLA-4+ T cells were depleted, while CCR7−VLA-4− T cells were strongly enriched [72]. Since these patients had stable disease, these findings are consistent with the view that TCM-derived cells drive pathogenic CNS inflammation in MS. CCR7 ligands are also crucial for protective antiviral T cell responses in the CNS in mice [27], further suggesting that the CNS migrations of antiviral and pathogenic T cells rely on similar mechanisms. In summary, different migratory routes for T cells to reach the CNS have been described, but the α4/β1-integrin appears to be critical for both antiviral immune surveillance and relapse, while the identities of the relevant chemokine receptors are uncertain.
Different Cytokine Requirements of Pathogenic T Cells in MS and its Animal Models

The EAE model was instrumental for the identification of proinflammatory cytokines that can drive pathogenic CNS inflammation. A seminal finding in autoimmunity was that IL-23, but not the closely related cytokine IL-12, has a nonredundant pathogenic role [89–91]. IL-12 potently induces Th1 cells, whereas IL-23 induces the maturation of Th17 cells, suggesting that Th17 but not Th1 cells are the key pathogenic cells. This concept was rapidly expanded to human organ-specific immune-mediated diseases, because single nucleotide polymorphisms (SNPs) in IL-23R, which reduces IL-23-mediated signaling [92], were shown to have a strong protective effect in psoriasis [93] and Crohn’s disease [94]. However, a similar protective effect of SNPs in IL-23R was not found for MS [95]; instead, polymorphisms in the gene locus encoding the IL-12-specific subunit p35 showed a strong association [4–6,95]. Interestingly, in viral encephalitis induced by neurotropic coronavirus in mice, IL-12, but not IL-23, enhanced morbidity, and this was associated with enhanced T cell IFN-γ production [25]. Thus, while IL-23 has a nonredundant pathogenic role in EAE, IL-12 appears to be relevant in viral MS mouse models and possibly also in human MS [95].

In the EAE model, different T cell subsets, including both Th1 and Th17 cells, could induce pathogenic neuroinflammation, although with different characteristics [89]. Th1/17 cells that co-produce IFN-γ and IL-17 have high pathogenic potential and are also enriched in brain lesions of patients with MS [96]. In humans, they can be induced from not only naïve T cells with IL-18 and IL-23 [97,98], but also from conventional Th17 cells with IL-1β and/or IL-12 [32,76,99]. IL-17 can enhance BBB permeability [100] and has neurotoxic potential [101]; in addition, promising results were obtained in a clinical trial with a neutralizing anti-IL-17 antibody in RR-MS [102]. However, deficiency for neither IL-17 [103,104] nor IFN-γ [105] completely prevents EAE induction, while GM-CSF is absolutely required [106,107].

The proposed pathogenic mechanism in EAE is that dendritic cell (DC)-derived IL-23 induces Th17 cells to produce GM-CSF, which in turn leads to the recruitment and activation of additional myeloid cells [89]. GM-CSF-producing T cells are also abundant in the CSF of patients with MS, but GM-CSF appears to be regulated differently in humans compared with mice [98,108], and is produced not only by Th17 cells, but also by Th1 cells [32,108]. In summary, relevant differences exist in the regulation and pathogenicity of key proinflammatory cytokines, including IL-12, IL-23, and GM-CSF, in EAE, viral MS models, and patients with MS.

MS Could Be Initiated by Virus-Induced Bystander Activation of Autoreactive CCR6+ T Cells: The Original Sin?

An alternative mechanism that could explain a pathogenic role of viral infections in MS is bystander activation (Box 3). Viruses potently induce the maturation of DCs that consequently upregulate MHC and co-stimulatory molecules [109], thus favoring the activation of not only virus-specific, but also potentially autoreactive T cells. In addition, lytic viruses, such as JCV, can induce the death of myelin-producing oligodendrocytes [28], inducing the release and

Box 3. Bystander Activation

Bystander activation is a process whereby an adaptive immune response against a specific pathogen leads to the activation not only of pathogen-specific T cells, but also of ‘bystander’ T cells that are not specific for the pathogen. Two different mechanisms have been described: bystander T cell activation can occur in a TCR-independent fashion via homeostatic cytokines, such as IL-7 or IL-15. The latter allows established CD8 memory T cells and antiviral CD4+ T cells to survive despite the high number of new effector and memory T cells that are generated to protect against a new invading pathogen. This has been well documented in the case of viral infections in mice, and TCR-independent proliferation induced by cytokines has been documented in humans. Second, bystander T cells can be activated via the TCR, because pathogens induce DC maturation and, thus, upregulate MHC and co-stimulatory molecules. This TCR-driven bystander activation is particularly important for autoreactive T cell responses, and can be further modulated by cytokines.
presentation of myelin-derived self-antigens in deep cervical lymph nodes by DCs [19] (Figure 1). The inhibition of bystander activation of autoreactive T cells is the task of Tregs [24], but several Treg subsets appear to be defective in patients with MS [110]. Moreover, the MS-associated polymorphisms in genes regulating T cell activation suggest that Th cells are more resistant to suppression [6]. However, naïve T cells have a high activation threshold and, therefore, it appears more likely that autoreactive memory T cells are aberrantly activated. Importantly, healthy individuals harbor a population of autoreactive memory T cells that secrete IL-10 in response to low-level TCR stimulation, such as self-MHC, to inhibit their own proliferation [74]. These autoreactive T cells express CCR6, possibly as a consequence of exposure to TGF-β at steady state and, thus, appear to be closely related to Th17 cells [74,77]. They are distinct from autoreactive CD25+ Tregs because they do not express Foxp3, and can also be distinguished from Foxp3+ IL-10-producing regulatory “TTr1” cells [111–113]. Interestingly, some of these autoreactive CCR6+ memory T cells are specific for recall antigens, such as tetanus toxoid [74], suggesting that they have a degenerate TCR specificity. In response to optimal TCR stimulation or to recall antigens, they behave in a similar way to conventional memory T cells, suggesting that they contribute to protective recall responses in healthy individuals [74]. Intriguingly, patients with RR-MS have an expanded population of autoreactive CCR6+ T cells, which express CXCR3 and co-produce IL-17 and IFN-γ [32]. IL-10 production is reduced in CXCR3+CCR6+ T cells [32], suggesting that these autoreactive Th1/17 cells are more pathogenic [114] and have a reduced capacity to inhibit their own activation in response to low-level TCR stimulation [74]. Notably, Th1/17 cells can be induced from CCR6+ T cell precursors in response to IL-1β and/or IL-12 [32,76,99,115], proinflammatory cytokines that are produced by DCs in response to viruses [109,116]. A conversion of Th17 cells to
IFN-γ-producing Th1/17 cells also occur in inflamed tissues in mice in vivo [117–119]. In addition, the expanded Th1/17 cells in patients with MS proliferated with myelin antigens, produced high levels of GM-CSF and expressed the α4/β1-integrin and CCR7 [32], indicating that these cells are potentially encephalitogenic. Consistent with this hypothesis, these Th1/17CM cells are selectively expanded in patients with RR-MS with a high disease severity score, and might represent a cellular ‘Sword of Damokles’. Following their generation, which could be a key pathogenic event in MS, these Th1/17CM cells probably no longer require IL-12, consistent with the unexpected failure of anti-IL-12/23p40 antibodies to inhibit relapse in established RR-MS [120]. In summary, virus-induced DC maturation and cytokine production could lead to the generation of potentially pathogenic Th1/17CM cells from autoreactive, IL-10-producing CXCR3+CCR6+ memory T cells, which are constitutively present in healthy individuals [32,74] (Figure 1).

**Competition between Autoreactive and Antiviral T Cells Could Favor Relapses and PML**

Genome-wide association studies have identified SNPs in the loci of IL-2Rα and IL-7Rα as MS-associated risk factors [6,121]. These cytokine receptors not only control the homeostasis of CD4+ regulatory and Th cells, respectively [81,122], but are also essential for protective CD8+ T cell responses [123,124]. Notably, the risk-conferring SNP of the IL-7R reduces IL-7R expression [6,121], suggesting that IL-15, which controls memory T cell homeostasis together with IL-7 [69,125–128], is particularly important in patients with MS. Based on T cell repopulation studies following therapeutic lymphocyte depletion with anti-CD52 antibodies, it was previously proposed that IL-15-dependent T cell homeostasis might be disturbed in MS [129]. It was found that, while Th1/17CM cells were expanded in patients with MS with a high disease score, conventional Th1 cells were selectively decreased, in particular Th1CM cells in patients treated with natalizumab [32]. The latter was unexpected, since natalizumab leads to the accumulation of proinflammatory T cells in the circulation [130]. Notably, in healthy individuals, both Th1 and Th1/17 cells respond to viruses [77,99], including JCV [32]. Conversely, in patients with RR-MS, Th1/17CM cells failed to respond to JCV, but instead proliferated spontaneously with autologous DCs [32]. Consequently, the natalizumab-associated decrease in Th1CM cells might explain the risk of patients with MS developing PML following prolonged natalizumab treatment. Indeed, patients with PML and MS treated with natalizumab have an impaired JCV-specific Th1 response [131], but additional studies are needed to establish whether a decrease in Th1CM cells is associated with the risk of PML.

What could be the mechanism of the selective shift from Th1 to Th1/17 cells in the analyzed patients with MS? Among CD4+ T cells, only the Th1 and Th1/17 subsets express high levels of T-bet [32], which induces not only IFN-γ and CXCR3 [81], but also the IL-2/15Rβ chain (CD122), consequently rendering T cell homeostasis sensitive to IL-15 (Figure 2A) [69,126]. Importantly, persistence of antiviral, but not of conventional, CD4 memory T cells requires IL-15, and they compete with other CD122+ lymphocytes for IL-15 in vivo [126]. In humans, TCM proliferate slowly in the steady state [132], and CXCR3+ ‘pre-Th1’ cells, which contain both Th1CM and Th1/17CM cells, express the highest levels of CD122 among CD4+ TCM, and proliferate most extensively with IL-15 in the absence of TCR stimulation [32,69,84]. Thus, Th1CM and Th1/17CM cells are expected to compete for IL-15 in secondary lymphoid organs [133], and this competition could be intensified when natalizumab limits their access to IL-15-rich peripheral tissues, such as bone marrow or the lungs [134]. Of note, the lung is a niche for resting, myelin-reactive memory T cells in Lewis rats with EAE [135]. Moreover, the bone marrow is a key site for memory T cell maintenance [136,137], and human antiviral CD4+ T cells are enriched at this site [136]. Interestingly, natalizumab inhibits bone marrow homing of stem cells [138], although it is unclear whether it also interferes with T cell homing to bone marrow or the lung [130,139]. In lymph nodes, DCs are expected to expand preferentially autoreactive
Th1/17CM cells in the absence of viral reactivation [32] (Figure 2B). Indeed, an important function of DCs is to present self-MHC to CD4+ T cells at steady state to induce naïve T cell survival [140] and allow secondary expansions of CD4+ memory T cells [141]. Moreover, DCs also trans-present IL-15 to lymphocytes (Figure 2B), including CD4+ T cells [142–144], and could induce the survival and IL-15-dependent proliferation of antiviral Th1 cells [126]. Thus, competition for self-MHC and IL-15 presented by DCs in lymph nodes is a possible mechanism whereby autoreactive, pathogenic Th1/17CM cells could expand selectively at the cost of virus-specific, protective Th1CM cells in patients with natalizumab-treated MS (Figure 2). Whatever the mechanism, such disequilibrium would render patients with MS more vulnerable not only to relapses, but also to JCV [67,131]. In summary, CD4+ T cell homeostasis appears to be disturbed in patients with MS, but more research is needed to understand the maintenance of

Figure 2. Hypothetical Mechanism of Competition between Protective Central Memory T Helper Type 1 (Th1CM) and Pathogenic Th1/17CM Cells. (A) Th1CM and Th1/17CM cells express increased levels of the transcription factor T-bet, which induces the expression of the IL-2/15Rβ-chain that renders T cells responsive to the homeostatic cytokine IL-15, which is required to maintain antiviral CD4 memory in the absence of antigen. (B) In healthy individuals (i) Th1CM and Th1/17CM cells are in equilibrium, and both compete successfully for IL-15, which is most abundant in peripheral tissues, but is also produced by stromal and epithelial cells in lymph nodes. In addition, they occasionally interact with dendritic cells (DCs) in lymph nodes and sense self-major histocompatibility complexes (MHCs). In patients with multiple sclerosis (MS) (ii) autoreactive Th1/17CM cells could expand at the cost of virus-specific Th1CM cells, because they proliferate with self-MHC-presenting DCs in lymph nodes during the remission phase. In addition, natalizumab could limit the access to IL-15 in peripheral tissues and, thus, intensify competition. However, while Th1/17CM cells might have preferential access to IL-15 that is trans-presented on IL-15Rβ by DCs (iii), Th1CM cells might be less fit under these conditions and die by neglect.
antiviral and autoreactive helper T cells in humans, and the equilibrium between Th1_{CM} and Th1/17_{CM} cells.

Relapses Could Be Triggered by Viral Reactivations in the CNS that Induces the Recruitment of Autoreactive Bystander Th1/17 Cells

As discussed above, at least two different pathways could lead to the recruitment of pathogenic T cells to the CNS, and consequently to relapses. On the one hand, autoreactive T cells could enter the CNS in the absence of infections via CCR6 [78,79] and, on the other hand, viral reactivations in the CNS could induce CXCL10/IP10 and consequently attract autoreactive and/or virus-specific CXCR3^+ T cells [82]. Notably, since Th1/17 cells co-express CXCR3 and CCR6, they could use either pathway to reach the CNS. However, antiviral Th1 cells that lack CCR6 expression are strongly enriched in the CSF of patients with active MS [32], suggesting that the IP10/CXCR3 axis is relevant for relapses. Consistent with this notion, in the circulation of patients with MS where CNS homing is blocked by natalizumab, there is a selective increase in CXCR3^+ B cells [145] and CXCR3-expressing Th1/17 cells [32,130]. The requirements for CXCL10/IP10 in different animal models of MS is variable [82], but a role for CXCL10/IP10 in MS is further suggested by the fact that it is expressed in brain lesions of patients with MS [80], and that SNPs in its gene locus are associated with a worse prognosis [146]. In healthy individuals, CXCR3^+ Th1 and CXCR3^+CXCR6^+ Th1/17 cells respond to viruses and express the α4/β1-integrin and, thus, both could contribute to the physiological antiviral immune surveillance in the CNS [147] (Figure 3A, Key Figure). Conversely, in patients with MS, Th1 and Th1/17 cells responded selectively to viral and myelin-derived antigens [32], respectively, suggesting that, while Th1 cells also mediate antiviral immune responses in patients with MS, Th1/17 cells could attack uninfected tissue and promote relapses (Figure 3A). In this scenario, relapses could be triggered by viral reactivation that lead to bystander recruitment of autoreactive Th1/17 cell to the CNS via IP10/CXCR3. EBV is one obvious candidate virus to induce bystander Th1/17 cell recruitment, but the high frequency of JCV-specific Th1 cells in the CSF of patients with active MS [32] also supports a role for JCV reactivation in relapses [15]. This ‘bystander recruitment model’ has important implications for MS therapy, because it predicts that selective targeting of autoreactive Th1/17 cells could be as efficient as natalizumab therapy, but would not induce PML if antiviral Th1 cells were spared. Surprisingly little is known about the signals that induce neurotropic viruses to switch from latency to a lytic stage and, therefore, stress is often suggested as a common explanation [15,148]. In the case of JCV, TNF-α, which is produced by effecter T cells upon antigenic activation, can deliver critical reactivation signals [149]. Therefore, it is possible that autoreactive Th1/17 cells induce de novo viral reactivation in the CNS, thus fueling a vicious feed-forward loop that leads to the recruitment of new waves of pathogenic T cells and possibly also of virus-infected B cells [53]. Alternatively, it is possible that autoreactive Th1/17 cells home first to the CNS during the remission phase of MS via CCR6, and induce then viral reactivation and the recruitment of antiviral Th1 cells via IP-10 (Figure 3B). However, the latter model fails to fully explain why relapses are characteristic for patients with MS, since healthy individuals also harbor autoreactive CCR6^+ T cells [74] that produce substantial amounts of GM-CSF and also some IL-17 [32]. In any case, the concomitant enrichment of virus-specific Th1 and myelin-reactive Th1/17 cells in the CSF of patients with active MS further underlines the close relationship of antiviral immune responses and MS, and warrants further investigation.

Concluding Remarks and Future Perspectives

How infections promote autoimmune diseases is a fascinating and clinically relevant topic. In MS, the field has been dominated by the search for a single causative infectious agent and, due to strong epidemiological evidence, EBV has attracted the most attention. The intriguing molecular mimicry hypothesis has further underlined a possible role of EBV. However,
accumulating evidence indicates that several neurotropic viruses, including JCV, could have a role in MS, and it is also possible that different viruses could be important in individual patients with MS. In this review, we discussed some poorly understood, intensively debated, and understudied aspects in the field. We have proposed possible mechanisms for how viral infections could generate pathogenic Th1/17CM cells from autoreactive memory cells upon bystander activation, how these Th1/17CM cells could progressively expand at the cost of protective, antiviral Th1 cells in the remission phase, and how they could finally be recruited to the CNS upon viral reactivation to promote relapses. Notably, the molecular mimicry concept and this bystander generation/recruitment model are not mutually exclusive. However, the finding that JCV-specific and autoreactive T cells in patients with MS are largely segregated into two different subsets of Th1 and Th1/17 cells with different properties suggests that selective targeting of Th1/17 cells could inhibit relapses without inducing PML. More research on antiviral immune responses in animal models of MS and in patients will be necessary to unravel the
complex relationships between viruses and MS, to predict relapses, and, ultimately, to develop more efficient and/or selective therapies.

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