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Encephalitogenic and regulatory CD8 T cells in multiple sclerosis and its animal models

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Abstract

Multiple sclerosis (MS), a neuroinflammatory disease that affects millions worldwide, is widely thought to be autoimmune in etiology. Historically, research into MS pathogenesis has focused on autoreactive CD4 T cells, due to their critical role in the animal model, experimental autoimmune encephalomyelitis (EAE), and the association between MS susceptibility and single nucleotide polymorphisms in the MHC II region. However, recent studies have revealed prominent clonal expansions of CD8 T cells within the central nervous system (CNS) during MS. Here we review the literature on CD8 T cells in MS, with an emphasis on their potential effector and regulatory properties. We discuss the impact of disease modifying therapies, currently prescribed to reduce MS relapse rates, on CD8 T cell frequency and function. A deeper understanding of the role of CD8 T cells in MS may lead to the development of more effective and selective immunomodulatory drugs for particular subsets of patients.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), characterized by spatiotemporal dissemination of demyelinating lesions that span the optic nerves, brain and spinal cord (1). It is the most common cause of non-traumatic neurological disability among young adults in the Western Hemisphere. As a consequence of the multifocal distribution of lesions, individuals with MS experience diverse neurological symptoms including numbness, weakness, visual loss, double vision, tremor, and gait imbalance (2). MS typically presents with a relapsing-remitting course, although it can also manifest as gradually worsening neurological disability, referred to as progressive disease (1, 3). Clinical relapses correspond with the development of acute inflammatory lesions in neuroanatomically “eloquent” sites. Genome wide association studies (GWAS) implicate multiple adaptive and innate immune system pathways in MS susceptibility, suggesting that MS is likely triggered by a perturbation of peripheral immune responses that is translated to the CNS and leads to a neurodegenerative process (4). Identification of the immune effector

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cells that mediate the CNS damage, and their mechanisms of action, has been a major goal of MS researchers over the past 50 years.

Despite numerous attempts to prove otherwise, there is a dearth of evidence that a local viral infection, or another extraneous threat, drives the destructive neuroinflammatory response during MS. Rather, a large body of circumstantial data supports an autoimmune etiology. Experimental autoimmune encephalomyelitis (EAE), a multifocal demyelinating disease in laboratory rodents and non-human primates that simulates MS, is commonly induced via vaccination against CNS autoantigens, particularly peptide or protein components of the myelin sheath (5). Interestingly, acute inflammatory demyelinating syndromes, with radiological and/or histopathological features reminiscent of MS, have also occurred in human subjects inadvertently exposed to myelin antigens in an immunogenic context (6–8). The genetic architecture of MS susceptibility implicates a broad range of immune cell subsets in MS risk (9). Analyses of GWAS data using system biology approaches indicate that relapsing MS clusters closely with non-CNS diseases also thought to have an autoimmune basis, such as Type 1 diabetes mellitus, Crohn's disease, and rheumatoid arthritis, and not with primary neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (9, 10). Pharmaceutical agents that deplete lymphocytes from the circulation, or block their passage across the blood-brain-barrier (BBB), significantly reduce MS relapse rates (11, 12). Collectively these observations provide a strong argument in support of the importance of autoreactive lymphocytes specific for CNS antigens in MS pathogenesis. The relevance of individual T lymphocyte subsets has yet to be definitively clarified.

Historically, CD4, as opposed to CD8, T cells were depicted as the pivotal effector cells in MS lesion development. There is a growing recognition that CD8 T cells play a more important role than widely appreciated (13–15). Histopathological studies of postmortem brain tissue show that CD8 T cells are actually more prevalent in MS infiltrates than CD4 T cells, across different lesion subtypes and clinical subsets (16). Although less commonly reported than encephalitogenic CD4 T cells, myelin-reactive CD8 T-cell lines are capable of inducing EAE (16–18). More recently, single cell transcriptomic analyses have demonstrated preferential expansion of CD8, compared with CD4, T cell clones in the blood and cerebrospinal fluid (CSF) of people with MS, as well as in individuals at a high risk for the future development of MS (19, 20). Together, these findings indicate that the role of CD8 T cells in MS should be revisited. In this review, we discuss evolving perspectives on the role of CD8 T cells during MS and EAE. We describe the characteristics of CD8 T cells in the CNS and periphery of patients with MS, focusing on clonality, as well as potential pathogenic and regulatory properties. Finally, we highlight how disease modifying therapies (DMT) that attenuate MS disease activity modulate CD8 T cells in a manner that might underlie their mechanism of action.

The role of CD4 versus CD8 T cells

The longstanding focus of many laboratories on the role of CD4 T cells in MS immunopathology is largely based on the fact that the majority of EAE models, induced by active immunization against myelin antigens, are CD4 T cell/MHC class II dependent (21–

24). In certain inbred mouse strains, the adoptive transfer of highly purified myelin-primed CD4 T cells into naïve syngeneic hosts is sufficient to induce full-blown EAE (25, 26). Furthermore, genes relevant to the differentiation and function of CD4 T cells are overrepresented among those mapping close to MS genetic susceptibility loci (4, 10, 27). Nonetheless, the requirement of CD4 T cells for MS lesion development has been brought into question by the failure of a series of clinical trials in which subjects with relapsing remitting disease were treated with monoclonal antibodies that either specifically deplete CD4 T cells or neutralize factors believed to be critical for the polarization of encephalitogenic CD4 T cells (28–30). In contrast, therapies that globally target lymphocytes, such as alemtuzamab and fingolimod, are highly effective at suppressing MS relapses (11, 31). Drugs that specifically target CD8 T cells have yet to be tested in MS.

Numerous published studies on the histopathology of MS have concluded that CD8 T cells at least equal, and in many cases greatly outnumber, CD4 T cells in perivascular and parenchymal infiltrates, as well as at the edge of active plaques (16). CD8:CD4 ratios have been reported to range between 1:1 to 50:1 (32–38). Sparse perivascular cuffs, detected in normal appearing white matter adjacent to lesions, also primarily consist of CD8 T cells (32). The predominance of CD8 T cells in MS lesions has held true irrespective of patient age, clinical subtype, disease duration, tempo of evolution, lesion stage, or history of immunosuppressive treatment (16, 32–37). In the majority of studies, postmortem tissues were primarily obtained from older individuals in the progressive subset with long disease durations. However, a predominance of CNS CD8 T cells was recently reported in 12 cases of acute or relapsing MS (37). Spatially, CD8 T cells within MS lesions interact with microglia, oligodendrocytes, and transected axons (38). Several laboratories have found that the frequency of circulating CD8 T cells falls during clinical MS exacerbations, which might reflect their recruitment from the bloodstream into the inflamed CNS (39–41).

Evidence of CD8 T cell accumulation and expansion in the CNS of individuals with MS

The majority of CD8 T cells in MS lesions have a cell surface phenotype consistent with tissue resident memory cells (T_{RM}; $CD44^{+}CD103^{+/-}CD69^{+}$), a recently recognized subset of memory T cells that do not recirculate and have a low threshold for reactivation (19, 36–38, 42, 43). A subset of intralesional CD8 T cells express markers indicative of recent activation and proliferation (36–38). Macrophages and other immune cells within MS infiltrates express high levels of MHC I and costimulatory molecules, equipping them to present antigen to autoreactive CD8 T cells (44). CD8 T cells are in direct communication with myeloid cells in MS lesions and appear to form immunological synapses (45). In addition, MHC class I is upregulated on cerebrovascular endothelium, neurons, astrocytes, and oligodendrocytes within, and surrounding, MS lesions (46). Although the most prominent MS genetic risk loci reside within the MHC II region, MHC I variability has also been implicated in MS. The MHC class I allele, HLA-A3 (A*0301), is associated with increased susceptibility, while MHC class I allele HLA-A*0201 is associated with increased resistance (16, 47).

Compelling evidence that the CD8 T cells in MS lesions are stimulated with cognate antigen and expand *in situ* comes from T cell receptor gene sequencing analyses of CSF leukocytes

and/or white matter lesion specimens. Although several studies have revealed clonal expansions of CNS-infiltrating B cells and CD4 T cells, the majority of expansions have generally been detected within the CD8 T cell compartment (19, 20, 34, 48). Monozygotic twins of individuals with MS are statistically at high risk of developing clinically definite disease (49). Interestingly, clonal expansions of CD8 T cells were observed in the CSF of the healthy monozygotic twins of MS patients, all of whom had evidence of subclinical disease based on MRI (19). Babbe and colleagues isolated individual T cells from white matter lesional tissue of 2 individuals with MS and performed T cell receptor (TCR) β-chain variable gene (TRBV) sequencing (34). In both patients, the majority of CD8 T cells belonged to relatively few clones. Identical expanded CD8 T-cell clones were detected in the CSF, brain, and blood of each patient. In contrast, CD4 T cells exhibited a more diverse TCR repertoire with limited clonal expansion (34). Similarly, in an independent study, TCR Vβ repertoire analysis of paired peripheral blood CD8 T cells, CSF cells, and CNS lesion samples from several subjects with MS consistently revealed a limited number of predominant clones, most of which were common between the 3 locations (50). Identical CD8 T cell clones have been found in distinct lesions, as well as the normal appearing white matter, of individual MS patients (51). Some CD8 T cell clones detected in the cerebrospinal fluid and/ or blood of individuals with MS persisted for over 5 years (52).

A critical unresolved issue regards the antigenic specificity of the oligoclonally expanded CD8 T cells in the CNS of MS patients. It is widely assumed that those cells are reactive against CNS restricted epitopes. Although some studies have detected myelin antigen-specific CD8 T cells at a higher frequency in the circulation of MS patients compared with age and sex matched healthy controls (53), other studies have found no differences between those groups (54). CD8 T cell lines generated from the peripheral blood mononuclear cells of MS patients produced TNFα and IFNγ upon co-culture with antigen presenting cells bearing myelin antigens and lysed target cells pulsed with myelin peptides (53, 55). Conversely, a panel of CD8 T cell lines, derived from CSF or white matter brain tissue of MS patients, showed no reactivity towards a broad selection of candidate human myelin or neuronal antigens (38). As will be discussed in greater detail below, regulatory CD8 T cell subsets in MS may be specific for TCR peptides expressed by encephalitogenic CD4 T cells.

If the CD8 T cells that infiltrate MS lesions are specific for CNS antigens, the question arises as to how they are initially activated in the periphery in order to upregulate adhesion molecules and chemotactic receptors necessary for passage across the intact BBB. One possibility is that the disease initiating CD8 T cells are cross-reactive against structurally similar microbial and CNS epitopes, and gain the capacity to infiltrate the CNS following stimulation in the context of a systemic infection. Once having breached the BBB, they are reactivated in response to the homologous CNS auto-antigen (56). Consistent with that scenario, MBP-reactive CD8 T cells have been isolated from MS patients that are cross-reactive to the EBV latency antigen (EBNA-1) of Epstein Barr Virus (EBV) (57). In an independent study, multiple short-term CD8 T cell lines, derived from MS lesional tissue, upregulated IFNγ and CD137 in response to co-culture with autologous EBV-transformed B cell lines that express the late lytic viral antigen glycoprotein 350 (38). This might explain why exposure to EBV as an adult is a risk factor for the development of MS (58).

CD8 T cell entry into the CNS

Under homeostatic conditions, immune surveillance of the CNS parenchyma by peripheral cells is limited by the inability of naïve lymphocytes to penetrate the intact BBB (59). Activated CD8 T cells could participate in BBB breakdown via perforin-mediated astrocyte activation, tight junction alteration, and VEGF induction (60–62). In the context of active neuroinflammation, CNS homing of immune cells is facilitated by chemokines and cell adhesion molecules. Migration of CD8 T cells across cerebrovascular endothelial monolayers *in vitro,* or across the BBB *in vivo* during EAE and mouse hepatitis virus encephalitis, is dependent on very late antigen 4 (VLA-4) (63). Melanoma cell adhesion molecule (MCAM/CD116) has also been implicated in CD8 T cell infiltration, specifically in the context of MS. MCAM is up-regulated by circulating CD8 T cells coincident with MS relapses (64). $MCAM^+$ CD8 T cells express higher levels of pro-inflammatory cytokines and cytotoxicity towards cultured oligodendrocytes than their $MCAM^-$ counterparts. MCAM blockade diminishes the severity of EAE induced by the adoptive transfer of encephalitogenic CD8 T cells (64).

Chemokines actively attract lymphocytes to migrate from the blood into the CNS and from perivascular spaces into the parenchyma. CD8 T cell clones that are expanded in the CSF of MS patients strongly upregulate CXCR6 compared with non-expanded CD8 T cells, while intrathecal monocytes and dendritic cells express elevated levels of the CXCR6 ligand, CXCL16 (19). The majority of CD8 T cells isolated from active MS lesions, mixed active/inactive MS lesions, or normal appearing white matter are $CXCR6^+$; CXCL16 is upregulated in the lesion rim (36). CXCR6-CXCL16 interactions are required for the recruitment of pathogenic CD8 T cells in animal models of psoriasis and hepatitis, suggesting that they might play a similar role in MS (65, 66). Therapies that selectively modulate CD8 T cell homing to the CNS might suppress MS relapses with less of an impact on beneficial immunity than currently employed DMT.

Pathogenic properties of CNS-infiltrating CD8 T cells

CNS-infiltrating CD8 T cells could, theoretically, inflict damage to glia and neurons through release of perforin, granzymes and granulysin, or via direct cell-to cell interactions, such as Fas ligand (CD95L)-mediated apoptosis. This is most likely to occur when CD8 T cells are reactivated by MHC I-expressing oligodendrocytes, neurons, and/or microglia *in situ* (67). Circulating CD8 $perforin^+$ T cells are increased in MS, most strikingly in the progressive disease subsets (68). A higher percentage of CD8 T cells in white matter lesions express CD95L compared with CD8 T cells in paired blood (38). Granzyme B-expressing CD8 T cells have been consistently identified in active MS lesions, in some cases adjacent to caspase-3 expressing cells (38, 46).

CD8 T cells in active MS lesions produce pro-inflammatory cytokines that have been linked to destructive neuroinflammation, in general, and oligodendrocyte apoptosis, in particular (69, 70). A high percentage of these CD8 T cells express IL-17, sometimes in combination with IFNγ, compared with CD8 T cells in adjacent normal-appearing white matter or inactive lesions (71). IFNγ, produced by infiltrating CD8 T cells and/or CD4 T cells, could upregulate MHC I expression on oligodendrocyte precursor cells (OPCs) and microglia,

thereby amplifying local autoreactive CD8 responses in a positive feedback loop (72). CD8 T cells may promote CNS pathology in synergy with CD4 T cells via a number of additional mechanisms. For example, in some EAE models, IL-17 secretion by CNS-infiltrating CD8 T cells drives the local accumulation of IL-17 producing, encephalitogenic CD4 T cells (73, 74). Conversely, CD4 T cells can prime microglia and CNS macrophages to activate CD8 T cells via CD40-CD40 ligand interactions (75, 76).

There is circumstantial evidence that CD8 T cells mediate axonal pathology that occurs during MS. Axon transections and spheroids are prominent features of MS lesions from the earliest stages of development and are believed to be a major cause of chronic disability (77). Granzyme B-expressing CD8 T cells have been observed in close proximity to demyelinated axons in MS tissue, with the cytotoxic granules polarized towards axons (78). The extent of axonal damage in active MS lesions correlates with the frequency of infiltrating CD8 T cells (78). In two independent experimental systems, CD8 T cell lines formed stable adhesions with neurites of dissociated neurons, and subsequently induced neuritic spheroids and cytoskeletal breaks in a MHC I/peptide dependent fashion (79, 80). Lytic granules, isolated from antigen-activated murine CD8 T cells, drive microtubule destabilization in axons *ex vivo* (81). CD8 T cells are critical and selective mediators of axonopathy in encephalomyelitis secondary to Theiler's Murine Encephalomyelitis Virus (TMEV) infection, an alternative rodent model of inflammatory demyelinating disease. Hence, MHC I deficiency or CD8 T cell blockade protects TMEV-inoculated mice from axonal degeneration and the development of functional and physiological neurological deficits, without impacting the degree of neuroinflammation or demyelination (82). Perforin-deficient mice exhibit a similar phenotype, suggesting that CD8 T cells inflict axonal damage during TMEV infection via a perforin-dependent pathway (83).

CD8 T cells may also play a direct role in promoting demyelination and suppressing remyelination. Mature oligodendrocytes isolated from postmortem MS tissue express MHC I, making them susceptible to CD8 cytotoxicity (78). Alloreactive and MBP-specific CD8 T cell lines have been shown to lyse human oligodendrocytes in co-cultures (84, 85). Interestingly, immature OPCs upregulate MHC I upon stimulation with IFNγ and engulf, process, and present antigen to CD8 T cells *in vitro* (72). This presentation not only results in the activation of cytotoxic CD8 T cells, but also in the direct death of the presenting OPC. Hence, CD8 mediated apoptosis of OPC could underlie, in part, the failure of remyelination that has been observed in MS lesions.

Regulatory CD8 T cells in MS

Although cytotoxic CD8 T cells exhibit gliotoxic and neuro-toxic properties in *in vitro* assays and in some animal models of inflammatory demyelination, alternative CD8 T cell subsets have been identified that possess anti-inflammatory functions (Fig. 1). Immunization of C57BL/6 mice with an immunodominant peptide of myelin oligodendrocyte glycoprotein (MOG) elicits the early expansion of encephalitogenic CD4 T cells in the periphery and CNS, followed by the delayed expansion of $CD44^+$ $Ly49^+$ regulatory CD8 T cells in both compartments (20). These expanded CD8 T cells suppress MOG-specific CD4 T cells *ex vivo* and are reactive against foreign peptides (as opposed to MOG) complexed to classic

MHC I. Furthermore, CD8 T cells isolated from the spleens of Lewis rats that had recovered from adoptively transferred EAE selectively lyse myelin-specific CD4 T cell lines *ex vivo*, and counter their encephalitogenic functions *in vivo* (86). The presence of an endogenous pool of regulatory CD8 T cells in wildtype mice, that expand during EAE and can suppress neuroinflammatory responses, is reinforced by the observation that CD8 knock-out mice are more prone to EAE relapse than their WT counterparts (87). In a separate EAE model, CD8 T cell depletion facilitated the induction of clinical relapses following an initial episode of inflammatory demyelination (88). An array of regulatory CD8 T cell subsets have been isolated from both human subjects and laboratory animals that suppress myelin reactive CD4 responses *ex vivo*, but differ in cell surface phenotype (ex. $FoxP3^+CD25^+$ versus $LAP\text{-}1^+$), antigenic specificity (neuroantigen versus CD4 T cell receptor epitopes), MHC restriction (classical versus non-classical MHC I) and mechanism of action (direct lysis of encephalitogenic CD4 T cells versus bystander suppression via release of soluble factors).

$CD25^+FoxP3^+$ CD8 T cell clones (TCC), isolated from the peripheral blood or CSF of MS patients, and expanded in the presence of irradiated myelin-specific CD4 T cells, inhibit the proliferation and cytokine expression of autologous myelin-reactive CD4 Th1 and Th17 cell clones in co-cultures (89). The cloning frequency of these regulatory CD8 T cells is lower during MS exacerbations compared with remissions. In an independent study, the frequency of circulating $FoxP3^+CD8$ T cells was reduced in relapsing remitting patients during relapses, but not remissions, when compared with healthy controls (90). Terminally differentiated CD8 T cells isolated from the blood of MS patients lyse autologous, neuroantigen-specific CD4 T cells in an IFNγ, Granzyme B, and perforin dependent manner (91). The antigenic specificities and CNS homing capacity of human $FoxP3^+CD8$ T cells or terminally differentiated regulatory CD8 T cells have yet to be demonstrated.

Unconventional subpopulations of CD8 T cells that are restricted to non-classical MHC Class Ib molecules (HLA-E in humans and Qa-1b in mice) can also suppress myelin-reactive CD4 T cell responses. Qa1-deficient mice develop exaggerated CD4 T cell responses to myelin peptides and experience an earlier onset of clinical EAE than WT mice (92). Murine CD8 T cell lines and clones reactive against a TCR Vβ8.2 peptide complexed to Qa-1 directly kill activated myelin-specific $V\beta8.2^+$ T cells *ex vivo*, and are protective when transferred into mice with a form of EAE that is primarily mediated by encephalitogenic $V\beta8.2^+$ CD4 T cells (93). Similarly, Qa-1 restricted CD8 T cells reactive to a non-classical epitope of myelin oligodendrocyte glycoprotein transfer EAE suppression (94). There is circumstantial evidence for a role of HLA-E restricted regulatory CD8 T cells in MS. HLA-E expression is enhanced on T cells, as well as on B cells and myeloid cells, in MS lesions (95, 96). HLA-E restricted CD8 T cell clones, isolated from the CSF or blood of MS patients and healthy controls, and enriched by expansion with irradiated neuroantigen-specific CD4 TCC, lyse autologous myelin-reactive CD4 T cells via a Granzyme B and perforin dependent pathway (97). These regulatory cells are decreased in MS patients during exacerbations, particularly in the CSF compartment. Consistent with these results, intrathecal synthesis of soluble HLA-E is reduced in clinically active versus clinically stable relapsing remitting MS (RRMS) patients (96).

Efficacy of immunomodulatory treatments on CD8 T cells

At present, there are over 15 FDA-approved disease modifying therapies (DMT) that decrease the rate of clinical relapses in individuals with MS (Table I). All of these drugs modulate peripheral immune responses in a manner believed to deplete or inactivate pathogenic lymphocytes, or to block the entry of pathogenic lymphocytes into the CNS. Although none selectively targets CD8 T cells, they all impact the CD8 T cell compartment.

DMT such as dimethyl fumarate, fingolimod, and alemtuzumab, reduce the absolute number of peripheral blood CD8 T cells by 53%, 70%, and over 80%, respectively (98–100). However, each of these agents has distinctive effects on CD8 T cell subsets. MS patients responsive to dimethyl fumarate treatment showed a reduction in the frequency of circulating IL-17$^+$ or TNFα^+ CD8 T cells after treatment as compared to pre-treatment levels, while the frequency of cytokine producing CD8 T cells was not significantly changed in non-responders (101, 102). Fingolimod, a sphingosine-1-phosphate inhibitor that sequesters naïve and central memory T cells in secondary lymphoid tissues, preferentially depletes CCR7$^+$ CD8 T cells from the blood, consistent with its mechanism of action (99). In contrast, senescent CD8 T cells (CD28$^-$CD27$^-$CD57$^+$) were not decreased in number in fingolimod treated patients and, therefore, were significantly increased in frequency within the remaining CD8 T cell pools. Fingolimod has also been shown to preferentially deplete CD8 and CD4 T cells that double produce IFNγ and IL-17 (103). Alemtuzamab significantly reduces the absolute numbers of circulating naïve and memory CD8 T cells, but naïve CD8 T cells are disproportionately impacted (104). Although anti-CD20 antibodies, such as rituximab and ocrelizumab, were initially used in the treatment of autoimmune diseases based on their effects on B cells, these drugs also deplete a subset of CD8 T cells that express CD20 (105). Interestingly, a high percentage of myelin-specific CD8 T cells in MS patients express CD20, and are preferentially reduced following anti-CD20 treatment (105). Administration of alemtuzumab to individuals with MS also results in long term depletion of CD20$^+$ T cells from the blood and CSF (106). In contrast to DMT that reduce the frequency of circulating CD8 T cells, treatment with the anti-α4 integrin antibody, natalizumab, raises their numbers (107–109). This might reflect blockade of CD8 T cell entry into the CNS via $\alpha4\beta1$ integrin/VCAM-1 interactions.

Two first line DMT, beta interferon and glatiramer acetate, both curtail the reactivity of CD8 T cells to CNS antigens *in vitro* (110, 111). Treatment of EAE mice with glatiramer acetate, which is an MBP analog, triggers the priming of CD8 T cells that suppress encephalitogenic CD4 T cells (110). Prophylactic infusion of glatiramer acetate-treated CD8 T cells prevents EAE via a mechanism dependent on MHCI, IFNγ, and perforin (110). In animal models, glatiramer acetate induced Qa-1 restricted regulatory CD* T cells (112).

CONCLUSIONS

Numerous studies demonstrate that CD8 T cells accumulate in active MS lesions, often exceeding the number of CD4 T cells, and preferentially undergo clonal expansion within the CNS during MS. DMTs that suppress MS relapses deplete or modulate CD8 lymphocytes, which might reflect the mechanisms of action of those drugs. Collectively, these observations are highly suggestive of an important role of CD8 T cells in MS.

However, we are just beginning to understand their significance. There are conflicting data about the specificity of the expanded CD8 T cells in MS, with different studies implicating neuroantigens, foreign antigens or the TCR hypervariable region of encephalitogenic CD4 T cells. Similarly, their biological function remains to be elucidated. They might be pathogenic effectors that mediate BBB breakdown, promote the activities of encephalitogenic CD4 T cells, lyse oligodendrocytes and OPCs, and/ or directly inflict axonal damage. Conversely, they may limit destructive neuroinflammation by disarming or killing encephalitogenic CD4 T cells. It is likely that the CD8 T cells in MS are heterogeneous, and have different effects that vary depending their location in the periphery versus specific CNS compartments, the stage of lesion evolution, and the clinical phase/ subtype of disease, among a multitude of other factors. However, there is now clear justification to support the investigation of CD8 T cells and related factors as putative biomarkers and therapeutic targets in MS.

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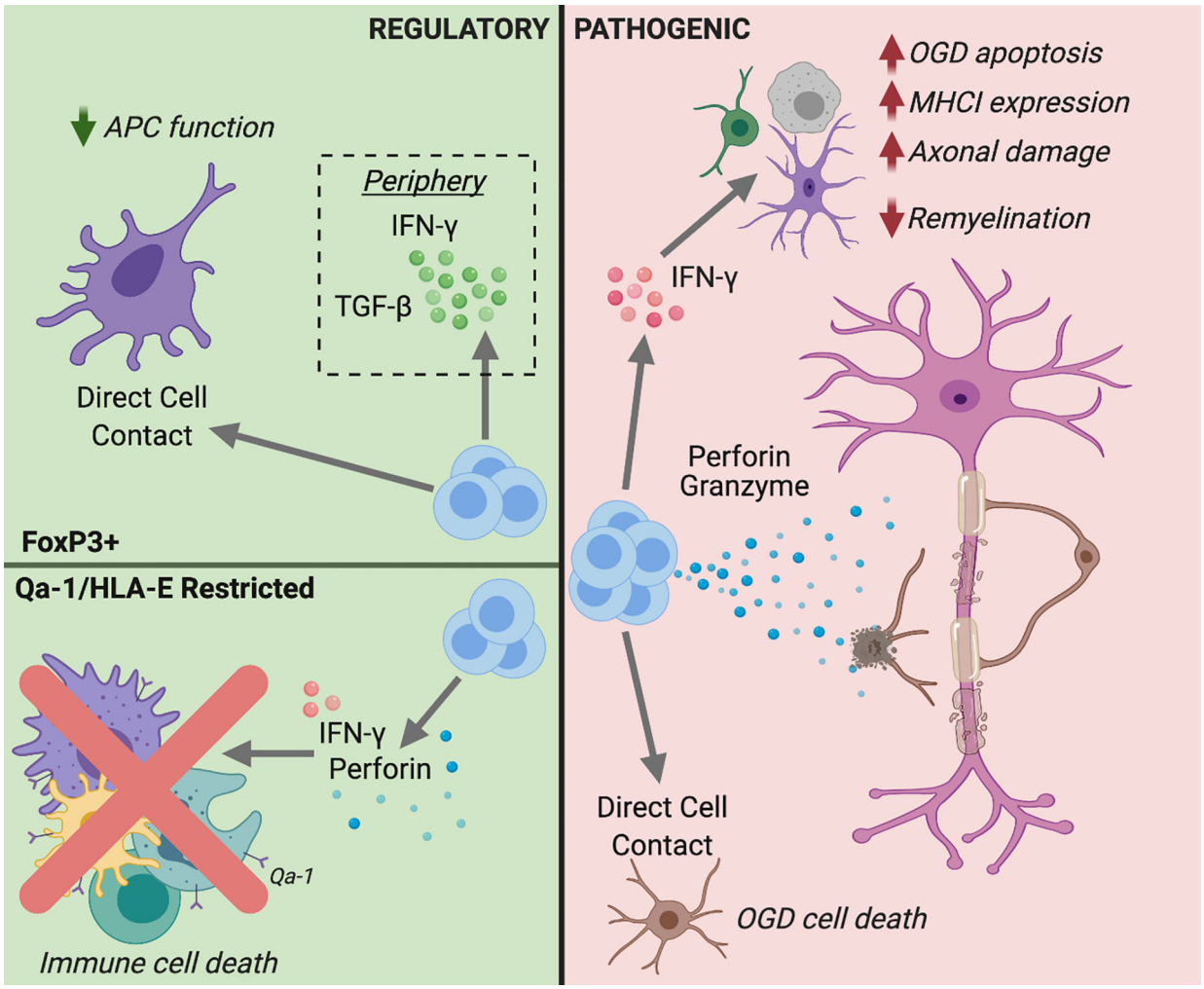

Figure 1: Potential roles of CD8 T cells in MS.

CD8 T cells with regulatory (left panel/ green background) or pathogenic (right panel/ pink background) functions might be deployed during MS. FoxP3^{+} regulatory CD8 T cells have been shown to disarm antigen presenting cells (APC), as well as suppress encephalitogenic CD4 T cells directly, via cell-to-cell interactions or the release of immunosuppressive cytokines. Qa-1- (mouse) or HLA-E- (human) restricted CD8 T cells could curtail neuroinflammation by killing APC or CD4 effector cells via FasL, IFNγ,and/ or Perforin mediated pathways. The horizontal line in the left panel separates events in the CNS (above) from the periphery (below). Conversely, pathogenic mechanisms of CNS-infiltrating CD8 T cells include lysing oligodendrocytes and oligodendrocyte precursor cells, inflicting axonal damage, enhancing encephalitogenic CD4 T cell responses, and activating glia. Figure created with BioRender.com.

Table I:

Disease modifying therapies and their effects on CD8 T cells.

Therapy	Proposed Biological Activity	Effect on CD8 T cells
Plasma exchange	Exchange of pathogenic plasma components	• No known effect on CD8 T cells
Beta interferons	unknown	• Suppresses effector CD8 T cell reactivity (111)
Glatiramer acetate (Copaxone, Glatopa)	MBP analog	• Possibly induces regulatory CD8 T cells (110, 112) • Reduces reactivity to CNS antigens *in vitro* (110)
Fingolimod (Gileyna) Siponimod (Mayzent)	Sphingosine I phosphate receptor modulator	• Retains lymphocytes in lymph nodes, reducing the number of circulating CD8 T cells (31, 99, 103)
Dimethyl fumarate (Tecfidera)	Nrf2 activation to reduce inflammation and oxidative damage	• Depletes circulating CD8 T cells and suppresses their effector functions (98, 101, 102)
Ocrelizumab (Ocrevus)	Anti-CD20 monoclonal antibody	• Depletes $CD20^+$ CD8 T cells (105)
Natalizumab (Tysabri)	Anti-α4 integrin monoclonal antibody	• Prevents trafficking of CD8 T cells across the BBB (12, 107–109)
Alemtuzumab (Campath, Lemtrada)	Anti-CD52 monoclonal antibody	• Depletes global CD8 T cells globally, including CD20+CD8 T cells (100, 104, 106)
Terifllunomide (Aubagio)	Pyrimidine synthesis inhibitor	• Reduces CD8 lymphocyte proliferation and cytokine production (113)