Role of CD8 T cell subsets in the pathogenesis of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system leading to demyelination and axonal/neuronal loss. Cumulating evidence points to a key role for CD8 T cells in this disabling disease. Oligoclonal CD8 T cells reside in demyelinating plaques where they are likely to contribute to tissue destruction. Histopathological analyses and compelling observations from animal models indicate that cytotoxic CD8 T cells target neural cell populations with the potential of causing lesions reminiscent of MS. However, CD8 T cell differentiation results in several subsets of effector CD8 T cells that could be differentially implicated in the mechanisms contributing to tissue damage. Moreover CD8 regulatory T cells arise as important populations involved in restoring immune homeostasis and in maintaining immune privileged sites. Here we examine the current literature pertaining to the role of CD8 effector and regulatory T cell subsets in the pathogenesis of MS.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) [1]. This disabling disease is characterized by multi-focal demyelination, axonal loss, activation of glial cells and infiltration by immune cells [1]. During the early phases of lesion formation CD4 and CD8 T cells, as well as macrophages, are recruited to the CNS white matter. The antigens that trigger this immune response to cause tissue damage are currently unknown but may include myelin self-antigens [1,2]. The predisposition to MS is in part genetically determined. The strongest known genetic risk-factor is the DRB1*1501–DQB1*0602 haplotype which encodes for the human leukocyte antigen (HLA)-DR2 and DQ6 molecules, thus implicating HLA class II molecules and CD4 T cells in MS pathogenesis [3,4]. Nevertheless, treatment of relapsing-remitting MS patients with a depleting anti-CD4 antibody did not alleviate relapse rate, neither progression of new lesions [5,6], in contrast to depleting all lymphocyte populations, significantly reduced relapse rate and new lesion formation [7].

Among the additional lymphocytic populations CD8 T cells are emerging as important effector cells in MS. Recent genetic studies strongly advocate an independent association between specific major histocompatibility complex (MHC) class I alleles and MS [8]. The exact contribution of CD8 T cells in the pathogenesis of MS remains ambivalent as the HLA-A*0301 allele is reported to increase susceptibility [9,10], whereas the HLA-A*0201 allele confers protection from the disease [4,11]. This review discusses the recent advances regarding functionally distinct CD8 T cell subsets and their implication in the pathogenesis of MS.

2. Effector CD8 T cell subsets in MS and its animal models

2.1. Generalities on CD8 T cells and their subsets

CD8 T cells are essential players of the adaptive immune system. Their intrinsic ability to perceive very few peptide–MHC class I complexes and thereby mediate direct killing of antigen-presenting target cells underlie their capacity to provide defense against intracellular pathogens [12].

Sallusto et al. described different subsets of CD8 T cells in human peripheral blood based on the expression of CD45RA and the chemokine receptor CCR7: (i) a CD45RA+ CCR7+ subset, composed of naive cells that lack effector functions, (ii) a
CD45RA–CCR7+ subset, which represents antigen-experienced cells without active effector function, also referred to as “central memory” (T_{CM}), (ii) a CD45RA−, CCR7– memory cell subset, which bears effector functions, termed “effector memory” (T_{EM}), (iv) a CD45RA+, CCR7− subset that includes highly differentiated, antigen-experienced cells with effector functions (T_{Eeff}) [13].

In order to acquire effector functions naive CD8 T cells undergo a series of events which include recognition of peptide:MHC class I complexes on antigen-presenting cells, co-stimulatory signals provided by CD28–B7 interaction in presence of inflammatory cytokines and the antigen-driven diversification of the CD8 T cell response is in a stochastic manner [35,36]. Collectively, these data suggest that CD8 T cell clones with shared specificity have trafficked to the CNS independently and have responded locally to a given set of antigens.

In blood, even though myelin-specific CD8 T cells lines could be derived from MS patients as well as healthy controls [38–41], a higher frequency of CD8 T cells recognizing myelin proteins has been reported in MS patients [41,42]. These data are however controversial [43]. MBP-specific CD8 T cells clones isolated from MS patients, as well as healthy individuals, secrete the pro-inflammatory cytokines IL-6, IL-21 and TNF-α and specifically lyse freshly isolated HLA-matched human oligodendrocytes, without the addition of exogenous peptide [44]. These observations however are either “unique” or follow strong in vitro manipulation of cell lines, which might have influenced their functional properties. An unbiased approach determining the nature and phenotype of the CNS-infiltrating CD8 T cells in MS is highly needed.

A recent report argues for IL-17-producing CD8 T cells (T_{Tc17}) being involved in MS pathogenesis [45]. This is based on the observation that the vast majority of the CD4 and CD8 T cells detected in the perivascular spaces of active MS lesions were labeled for IL-17 by immunohistology and in situ hybridization. In contrast, inactive lesions contained only few IL-17-producing T cells [45]. Furthermore, Annibali et al. have identified significant up-regulation of the perivascular spaces of active MS lesions [46]. This subset of CD8 T cells includes most of the CCR6+, effector memory T cells with pro-inflammatory properties. Interestingly, CCR6 has been implicated in the transmigration of T cells into the uninfamed CNS through the choroid plexus [47].

Moreover, all the circulating Tc17 cells are contained within this CD161^{high} subset, further suggesting a role for this subset of CD8 T cells in MS pathogenesis [46]. It is at present unclear whether these CD161^{high} CD8 T cells are conventional HLA class I-restricted T cells or whether they belong to an innate-like T cell subset.

Recent studies revealed enrichment of activated effector memory CD8 T cells in CSF [48]. These effector memory CD8 T cells do not express CCR7 [49] and can therefore be retained in the tissue and carry out their effector functions [13,50,51]. Moreover, enriched numbers of CCR7−CD45RA+/−CD8 T cells has been shown in the CSF of early-diagnosed MS patients suggesting that CD8 T cells are implicated early on in the development of relapsing-remitting MS [48].

As together these findings converge to support the concept of a pathogenic role for CD8 T cells in MS. However, association is not causation and the final proof of their pathogenic involvement is still lacking.
2.3. CD8 T cells in animal models of MS

To better understand the functional contribution of CD8 T cells in CNS tissue damage, several experimental models were generated. Among the virally induced models, the Theiler's murine encephalomyelitis virus (TMEV) mouse model reproducing several histological features of MS. Indeed, the intra-cerebral injection of TMEV in susceptible mouse strains (SJL) elicits chronic inflammatory demyelinating lesions, involving macrophagic and lymphocytic infiltration, degradation of myelin, axonal damage and gliosis. Both CD8 and CD4 contribute to the disease process; CD8 T cells by killing of infected oligodendrocytes and CD4 T cells through bystander mechanisms in response to viral and myelin antigens [52,53]. However, in resistant mouse strains (C57BL/6), the infection is cleared within 3 weeks by a strong anti-viral CD8 T cells response that controls viral spread by both lytic and non-lytic mechanisms. Effector CD8 T cells can use these mechanisms to target resident CNS cells[9,54,55].

Much emphasis has been put recently on the contribution of CD8 T cells in animal models of CNS autoimmunity. Huseby et al. have demonstrated that adoptive transfer of H-2K<sup>d</sup>-restricted CD8 T cells specific for MBP<sub>79–87</sub> induces clinical experimental autoimmune encephalomyelitis (EAE) in C3H mice, reproducing features of MS lesions usually not observed in CD4 T cell-driven EAE [56]. Furthermore, adoptive transfer of MOG<sub>35–55</sub> specific CD8 T cells induces progressive EAE in C57Bl/6 mice, independent of CD4 T cells [57]. The adoptive transfer of H-2D<sup>d</sup>-restricted CD8 T cells specific for the short MOG<sub>37–46</sub> peptide also induces EAE into C57Bl/6 recipients [58]. Therefore, MOG<sub>35–55</sub> is thought to contain at least 2 nested encephalitogenic epitopes: MOG<sub>40–48</sub> that elicits a CD4 T cell response in the context of H-2I-Ab [59], and MOG<sub>37–46</sub> inducing a CD8 T cell response restricted to H-2Db [58]. Most recently, MOG<sub>42–50</sub> was found to bind to H-2D<sup>b</sup> molecule to elicit a CD8 T cell responses in MOG-deficient animals. However, CD8<sup>+</sup> T cells responsive to this MOG peptide could neither initiate CNS inflammation upon passive transfer nor exacerbate EAE once it is underway in MOG-expressing animals [60].

To further investigate the damage caused by CD8 T cells recognizing an oligodendroglial antigen, we developed an original murine model. This transgenic model combines the MOG-HA mice, expressing the influenza virus hemagglutinin (HA) selectively in oligodendrocytes using the MOG promoter, with TcR-transgenic mice expressing an H-2K<sup>d</sup>-restricted HA<sub>512–520</sub>-specific TcR on most CD8 T cells [61,62]. The adoptive transfer of HA-specific Tc1 cells in MOG-HA mice induces inflammatory lesions in the optic nerve, spinal cord, and brain. These lesions associate CD8 T cell infiltration with focal loss of oligodendrocytes, demyelination, axonal damage, and microglia activation, features that are very reminiscent of active MS lesions [62]. A similar transgenic model introduced ovalbumin (OVA) under the proximal MBP promoter (ODC-OVA mice) to induce the expression of a neo-self antigen in the optic nerve, spinal cord, and brain. These lesions associate CD8 T cell infiltration with focal loss of oligodendrocytes, demyelination, axonal damage, and microglia activation, features that are very reminiscent of active MS lesions [62]. A similar transgenic model introduced ovalbumin (OVA) under the proximal MBP promoter (ODC-OVA mice) to induce the expression of a neo-self antigen in the optic nerve, spinal cord, and brain. These lesions associate CD8 T cell infiltration with focal loss of oligodendrocytes, demyelination, axonal damage, and microglia activation, features that are very reminiscent of active MS lesions [62].
mediated tissue damage can be neutralized in this model by blocking antigen presentation of OVA257–264 through administration of a monoclonal antibody specific for the H-2Kb/OVA257–264 complex [65]. These findings document the nature of the CNS tissue damage mediated by CD8 T cells specific for a sequestered self-antigen expressed by oligodendrocytes.

In addition, humanized mouse models have served as a cutting edge tool to study the functional relevance of human MHC class I genes [8]. To this goal, murine MHC class I expression has been invalidated to impose the restriction of the CD8 T cell repertoire to transgenic human HLA class I molecules. To gain insight into the functional relevance of HLA-A3 in MS pathogenesis, humanized transgenic mice expressing both HLA-A-0301 and an HLA-A-0301:PLP45–53-specific TcR (2D1) isolated from MS patients were generated [66]. A small fraction (4%) of these humanized mice developed spontaneous EAE driven by CD8 T cells. PLP45–53 immunization in complete Freund adjuvant induces mild disease in 71% of these mice, followed in 25% of them by a severe disease leading to hind limb paralysis. The PLP45–53-specific CD8 T cells mediate the first phase of this disease, whereas the second phase is due to CD4 T cells targeting the MOG35–55 epitope in the context of the murine I-Aa molecule [66]. Therefore, this study demonstrates that CD8-driven autoimmune demyelination can initiate epitope spreading. We have shown in a transgenic mouse model that HLA-A2-restricted autoreactive CD8 T cells recognizing MOG181–190 could worsen the outcome of MOG35–55-induced EAE [67]. Conversely, humanized mice expressing the 2D1 TcR along with the disease protective HLA-A2 molecule were completely protected from both spontaneous and active EAE due to thymic negative selection of 2D1-expressing developing CD8 T cells induced by HLA-A2 [66]. The hypothesis that the MS-protective effect of HLA-A-0201 is related to negative selection of myelin-reactive CD8 T cells is appealing but would need to be tested for other clonotypes.

These studies document that autoreactive CD8 T cells are detrimental in animal models of MS, further advocating their potential contribution in MS pathogenesis.

3. Regulatory CD8 T cells

3.1. Generalities

Regulatory T cells (Tregs) play an essential role in contending immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host [68]. Several subsets of natural CD8 Tregs have been identified based on the expression of CD25 [69], Foxp3 [70,71], CD122 [72] and/or HLA-G [73], or lack of CD28 expression [74]. CD8+CD122+ αβTCR Tregs could sense activated T cells by interacting with cell surface molecules including classical MHC class I [75] and directly constrain proliferation and IFN-γ production of CD8 T cells presumably via production of IL-10 [76]. Moreover, in human peripheral blood a novel immunoregulatory population was identified among CD4 and CD8 T cells expressing HLA-G in the absence of Foxp3. This population exhibits potent suppressive properties that are partially mediated by HLA-G, immunoglobulin-like transcript-2 (ILT-2) and IL-10 [73,77]. In addition, Mayer et al. showed that CD8+Foxp3+ T cells have reduced suppressive activity while they share developmental and phenotypic features with CD4+Foxp3+ Tregs [78]. Furthermore, a population of CD8+CD28− cells has the capacity to suppress immune responses by directly interacting with APCs and rendering them tolerogenic [74]. Menager-Marcq et al. demonstrated that naturally occurring CD8+CD28− Tregs can block gut inflammation by the secretion of IL-10 in a murine model of inflammatory bowel disease [79]. In human, CD8+CD28− T cells trigger the up-regulation of ILT-3 and ILT-4 on monocytes and dendritic cells, which was responsible for the propagation of antigen-specific CD4 Treg mediated suppression [80,81]. A regulatory subset of TCRα/β CD8 T cells has been shown to recognize activation-induced peptides (VIP peptides, HSP60) in the context of Qa-1, a non-classical MHC class Ib molecule [82]. Their positive selection in the thymus requires interaction with Qa-1, which can be provided by hematopoietic, rather than epithelial cells [83]. Qa-1-restricted CD8 T cells appear to control secondary, rather than primary, CD4 T cell responses. These Qa-1-restricted CD8 Tregs could control effector CD4 T cells through several mechanisms: direct killing of CD4 T cells and/or inactivation of APCs. Recently, Qa-1-restricted CD8 T cells have been shown to maintain self-tolerance primarily through elimination of follicular helper CD4 T cells, which, upon activation, express high levels of Qa-1 [84]. The integrin αEβ7 (CD103) has been identified as a marker for alloreactive induced CD8 Tregs. When exposed to alloantigens and expanded in vitro CD8+CD103+ T cells produced significant quantities of IL-10 and suppressed T-cell proliferation through a cell contact dependent mechanism, even though their cytotoxic potential was limited [85,86].

3.2. CD8 Tregs in MS and its animal models

The immunoregulatory functions of CD8 T cells have been studied during the course of EAE. Based on antibody-mediated depletion experiments, CD8 T cells were found to be a major factor in the resistance to a second induction of EAE after recovery from the first episode [87]. Various regulatory CD8 T cell subsets could account for this impact. Mice knock-out for the non-classical MHC class Ib molecule Qa-1 exhibit little aggravation of EAE severity, but are more susceptible to EAE re-induction following initial suboptimal PLP immunization, again pointing at an inhibitory effect role of Qa-1-restricted CD8 T cells on secondary responses [88]. Interestingly, Qa-1-restricted T cells elicited by a previous expansion of Vj8.2+ CD4 T cells directed to a foreign antigen can also inhibit EAE mediated by Vj8.2+ MOG-specific CD4 T cells [89]. Naturally occurring CD8+CD122+ Tregs produce IL-10 and suppress IFN-γ production and T-cell proliferation. In vivo depletion of these cells by anti-CD122 mAb in MOG35–55 immunized mice increases the duration of EAE, while the adoptive transfer of purified CD8+CD122+ T cells at the peak of disease provide clinical benefit [90]. Furthermore, CD8 Tregs actively contribute to the resistance of CD28−/− to CNS autoimmunity [74]. Indeed, both depletion of CD8 T cells and CD8 gene inactivation restore susceptibility of CD28−/− mice to MOG35–55-induced EAE. Resistance to EAE is restored by the adoptive transfer of CD8+ CD28− T cells in CD8−/− mice, demonstrating their regulatory function in vivo [74].

Several studies have pointed out that MS could be favored by an impaired suppressive function of Tregs, including CD8 Tregs [91–93]. More recently, a study pointed out that CD8 T cell clones isolated from MS patients can kill myelin-specific CD4 T cells using a mechanism dependent on HLA-E, the human homolog of mouse Qa-1 [94]. However, HLA-E can also interact with CD94/NKG2 receptors expressed on CD8 T cells and this interaction can inhibit CD8 T cell cytotoxicity. In MS patients, a significantly elevated expression of CD94/NKG2 on CD8 T cells was observed during clinical exacerbation, presumably inhibiting the killing of pathogenic CD4 T cells [94]. The suppressive function of HLA-E-restricted CD8 T cells was also observed in MS patients treated with glatiramer acetate (GA, Copaxone®), a pool of synthetic polypeptides with immunomodulatory properties [95]. CD8 Tregs from treated MS patients express high levels of perforin and could kill GA-reactive CD4 T cells in a cell contact dependent mechanism. This suppressive activity of GA-induced CD8 Treg is directly correlated with clinical remission [96,97].
Another subset of regulatory CD8 T cells, the HLA-G-expressing CD8 Tregs, could also be involved in the MS pathogenesis. These cells accumulate at sites of inflammation during relapses of MS and can suppress either CD4 or CD8 T cell responses through a contact-independent mechanism. These patients uniformly show higher frequencies of HLA-G-expressing cells in the CSF as compared to peripheral blood [73,77]. Furthermore, Airas et al. pointed out that a drop in the number of HLA-G expressing CD4 and CD8 T cells is associated with an increased risk of postpartum relapses in females with MS [98].

These studies clearly point out that, although FoxP3+CD4+ Tregs are essential regulators of the immune system, certain CD8 T cell populations possess immunoregulatory functions that might influence the progression of MS.

4. Concluding remarks

Effector CD8 T cells may have a major detrimental effect in MS, given their unique ability to recognize self-peptides presented by MHC class I molecules on almost any nucleated cell type. Experimental models serve as cutting edge tools to assess the potential of these effector CD8 T cells to mediate tissue damage and to investigate the mechanisms involved. There is also evidence to suggest a role for CD8 T cells in the pathogenesis of MS. In addition, understanding their specific function and antigen specificity will be helpful to uncover the role of these CD8 T cell subsets in MS pathogenesis.

Several fundamental questions remain to be addressed. How do pathogenic CD8 T cells become activated to target self? Do they follow the same rules as CD4 T cells for activation and migration into the CNS? How are the autoreactive CD8 T cell responses regulated and how do these mechanisms fail in MS patients? How do the genetic polymorphisms associated with MS [4] alter the biology of CD8 T cells?

Most current therapies in MS have been designed to target pathogenic CD4 T cells. There is however little doubts that they may also impact on other immune cell subsets such as the CD8 T cells. A better understanding of the pathogenic and regulatory potential of CD8 T cells may help develop more focused therapeutic strategies for MS.

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