FEBS Letters 585 (2011) 3758–3763

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

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

A. Saxena, G. Martin-Blondel, L.T. Mars, R.S. Liblau *

INSERM U1043 – CNRS UMR 5282, Centre de Physiopathologie Toulouse-Purpan, France
Université Toulouse III, Toulouse F-31000, France

ARTICLE INFO

Article history:
Received 19 August 2011
Revised 30 August 2011
Accepted 31 August 2011
Available online 8 September 2011

Edited by Richard Williams, Alexander Flügel and Wilhelm Just

Keywords:
Multiple sclerosis
CD8 T cell
Autoimmunity
Central nervous system
Experimental autoimmune encephalomyelitis

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 homoeostasis 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.

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 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

Abbreviations: MS, multiple sclerosis; CNS, central nervous system; MHC, major histocompatibility complex; EAE, experimental autoimmune encephalomyelitis; CTLs, cytotoxic CD8 T lymphocytes; Tregs, regulatory T cells; HLA, human leukocyte antigen

* Corresponding author. Address: INSERM U1043 – CNRS UMR 5282, Centre de Physiopathologie Toulouse-Purpan, CHU Purpan, BP 3028, 31024 Toulouse Cedex 3, France. Fax: +33 561 774 558.

E-mail address: rolandliblau@hotmail.com (R.S. Liblau).

0014-5793 © 2011 Federation of European Biochemical Societies. Published by Elsevier B.V. Open access under CC BY-NC-ND license.
doi:10.1016/j.febslet.2011.08.047

CD45RA− CCR7+ subset, which represents antigen-experienced cells without active effector function, also referred to as "central memory" (T_{CM}), (iii) 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_{Eff}) [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 leading to activation, proliferation and differentiation into a heterogeneous pool of effector CD8 T cells [12,14,15]. The commitment of naïve T cells to functionally distinct subsets is dictated by the composition of the local cytokine milieu. The influence of cytokine signaling on the differentiation of CD8 T cells resembles that of their CD4 counterparts. For instance, T-bet expression is induced by IL-12 for Tc1 differentiation, GATA-3 is induced by IL-4 for Tc2 differentiation [16]. It has recently been shown that the IL-17-producing subset of CD8 T cells (Tc17) follows a similar differentiation program as Th17 cells [17]. Th17 cell differentiation requires retinoid-related orphan receptor (ROR)γt, a transcription factor that is induced by TGF-β in combination with the pro-inflammatory cytokines IL-6, IL-21 and IL-23 [18]. Taken together, these findings suggest that the local microenvironment, through provision of specific cytokines, directs the multiple possible alternate fates that CD8 T cells can adopt.

Differentiated subsets of CD8 T cells acquire distinct migratory properties to survey extra lymphoid tissues [19]. Moreover, cytotoxic CD8 T lymphocytes (CTLs) may acquire a distinct tissue-specific phenotype. For instance, T cells isolated from the skin uniquely express E-selectin and CCR4, while T cells isolated from the small intestine express CCR9 and the α4β7 integrin [20]. Several studies have demonstrated that the tissue environment and the local dendritic cells themselves imprint this tissue-specific signature to the T cells [20–22]. This differential homing potential associated with distinct effector functions advocates that the antigen-driven diversification of the CD8 T cell response is instructed rather than stochastic, implicitly questioning the role of these CD8 T cell subsets in immune-mediated diseases, such as MS.

Effector CD8 T cells use both cytotoxic and non-cytotoxic functions to affect their target cells: (i) cytotoxic molecules such as granzyme and perforin mediate direct contact-dependent cytotoxicity [23], (ii) expression of Fas ligand (CD95L) induces apoptosis in a Fas–Fas ligand dependent manner [23] and (iii) immediate secretion of pro-inflammatory cytokines, including IFN-γ and TNF-α, sustains local inflammation [24].

2.2. CD8 T cells and their subsets in MS

Although the implication of CD4 T cells in the pathogenesis of MS has been largely investigated, several arguments support a key role for CD8 T cells. The independent association between the MHC class I allele HLA-A*0301 and MS susceptibility argues for a potential role of MHC class I-restricted CD8 T cells in MS pathogenesis. However, the contribution of CD8 T cells in MS is likely complex as the HLA-A*0201 allele confers significant protection from the disease (see Fig. 1).

Most CNS resident cells such as astrocytes, oligodendrocytes and neurons do express MHC class I molecules, at least under inflammatory conditions, making them potential targets for CD8 T cells. Moreover, up-regulation of MHC class I molecules can be observed early during the course of MS, before demyelination develops [25–27]. Furthermore, activated microglial cells have been shown to cross-present exogenous peptides on MHC-I molecules, thereby supporting the persistence and expansion of the CD8 T cell response [28].

In post-mortem material from acute or relapsing-remitting MS patients, CD8 T cells are consistently detected within perivascular cuffs and parenchymal lesions [29] where they frequently outnumber CD4 T cells [30–33]. Within parenchymal lesions cytotoxic T cells can be detected with their cytolytic granules polarized towards demyelinated axons indicative of imminent T cell mediated killing [34]. Furthermore, there is a positive correlation between the abundance of CD8 T cells and the intensity of axonal damage [35,36].

TcR usage analyses of CNS-infiltrating CD8 T cells have revealed oligoclonal expansion of CD8 T cells within MS lesions [30,33] and the CSF [37], suggesting an antigen-driven activation of CD8 T cell clones during the course of MS. Moreover, CDR3 nucleotide sequences encoding TcRs isolated from different lesions of individual MS brains revealed silent nucleotide changes implying that distinct T cell clones with identical antigen-specificity can be detected within MS lesions [33]. This CDR3 spectratyping confirms that infiltration of CD8 T cells in the lesions is selective, rather than stochastic. 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 IFN-γ 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 (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 natural killer receptor protein 1a/CD161 and increased numbers of $CD161^{high}$ CD8 T cells in the peripheral blood of MS patients [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 uninflamed 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].

Altogether 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.

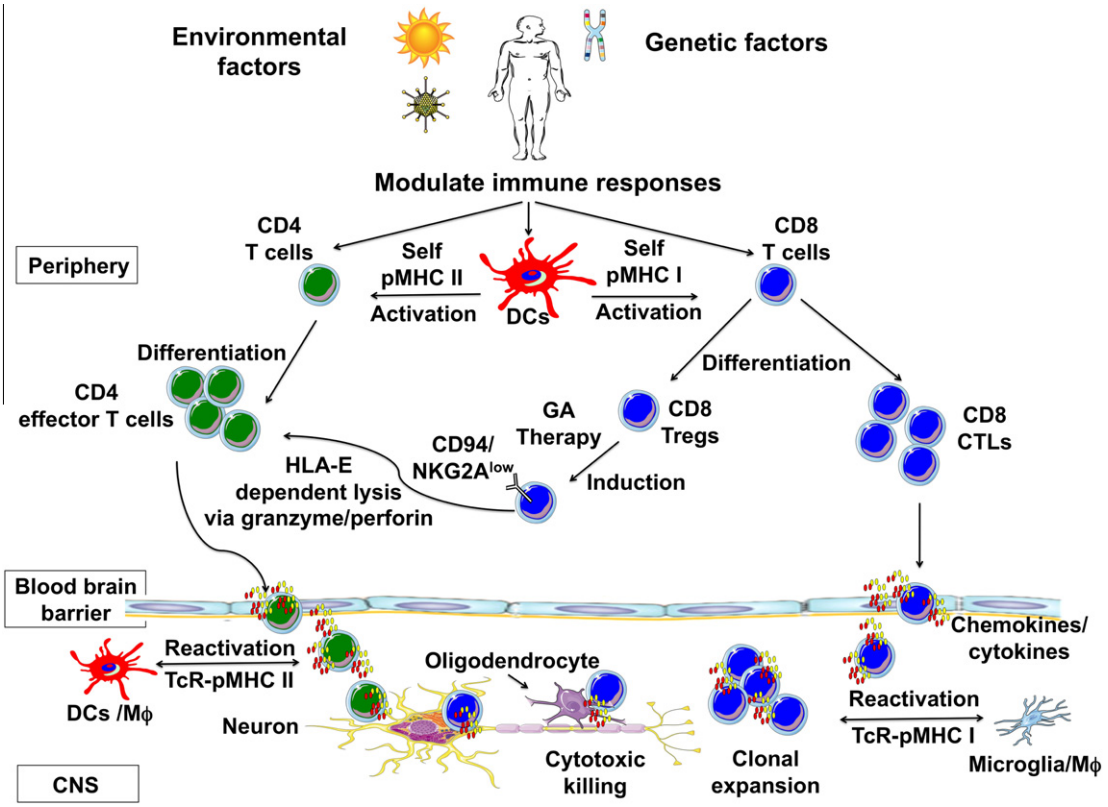

Fig. 1. Hypothetical scheme of the contribution of CD8 T cells in MS pathogenesis. Numerous genetic and environmental factors modulate the immune response so that dendritic cells (DCs) productively present self-antigens to autoreactive T cells. These autoreactive T cells differentiate into different effector subsets. CD8 T cells differentiate into regulatory and effector (including CTLs) subsets that can transmigrate into the CNS through the BBB. Microglia and recruited macrophages (Mϕ) present self-peptide:MHC-I complexes and promote clonal expansion of autoreactive CTLs. These activated CTLs directly target MHC-I expressing oligodendrocytes and axons/neurons, leading to irreversible tissue damage. Chemokines and cytokines produced by effector CD8 T cells contribute to sustain the inflammatory reaction. Regulatory CD8 T cells may play a major role in the pathogenesis of MS by directly killing pathogenic CD4 T cells in an HLA-E-dependent manner, therefore reducing CNS inflammation and promoting remission.

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^k-restricted CD8 T cells specific for MBP$_{79-87}$ 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$_{35-55}$ specific CD8 T cells induces progressive EAE in C57BL/6 mice, independent of CD4 T cells [57]. The adoptive transfer of H-2D^b-restricted CD8 T cells specific for the short MOG$_{37-46}$ peptide also induces EAE into C57Bl/6 recipients [58]. Therefore, MOG$_{35-55}$ is thought to contain at least 2 nested encephalitogenic epitopes: MOG$_{40-48}$ that elicits a CD4 T cell response in the context of H-2I-A^b [59], and MOG$_{37-46}$ inducing a CD8 T cell response restricted to H-2D^b [58]. Most recently, MOG$_{42-50}$ was found to bind to H-2D^b molecule to elicit a CD8 T cell responses in MOG-deficient animals. However, CD8+ 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^d-restricted HA$_{512-520}$-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 cytosol of oligodendrocytes. Crossing these mice with mice expressing H-2K^b-restricted OVA$_{257-264}$-specific TcR on CD8 T cells (OT-1 mice) induces a spontaneous disease characterized by noxious demyelinating lesions [63] that combine the specific loss of oligodendrocytes with bystander damage to axons [64]. CD8

mediated tissue damage can be neutralized in this model by blocking antigen presentation of $OVA_{257-264}$ through administration of a monoclonal antibody specific for the H-$2K^b$:$OVA_{257-264}$ 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:PLP_{45-53}-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. PLP_{45-53} 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 PLP_{45-53}-specific CD8 T cells mediate the first phase of this disease, whereas the second phase is due to CD4 T cells targeting the MOG_{35-55} epitope in the context of the murine I-A^b 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 $MOG_{181-189}$ could worsen the outcome of MOG_{35-55}-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 (Vβ 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 Vβ8.2+ CD4 T cells directed to a foreign antigen can also inhibit EAE mediated by Vβ8.2+ 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 MOG_{35-55} 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 invalidation restore susceptibility of CD28−/− mice to MOG_{35-55}-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 regulatory function of CD8 T cells during the course of MS. Given these opposite functions that CD8 T cells may carry in MS, it is essential to better characterize the various subsets of CD8 T cells, identify specific markers, and investigate their changes as disease evolves. 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 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.

References

[1] Compston, A. and Coles, A. (2008) Multiple sclerosis. Lancet 372, 1502–1517.
[2] Sospedra, M. and Martin, R. (2005) Immunology of multiple sclerosis. Annu. Rev. Immunol. 23, 683–747.
[3] Lincoln, M.R. et al. (2005) A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. Nat. Genet. 37, 1108–1112.
[4] Sawcer, S. et al. (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476, 214–219.
[5] Lindsey, J.W., Hodgkinson, S., Mehta, R., Mitchell, D., Enzmann, D. and Steinman, L. (1994) Repeated treatment with chimeric anti-CD4 antibody in multiple sclerosis. Ann. Neurol. 36, 183–189.
[6] van Oosten, B.W. et al. (1997) Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial. Neurology 49, 351–357.
[7] Coles, A.J., Compston, D.A., Selmaj, K.W., Lake, S.L., Moran, S., Margolin, D.H., Norris, K. and Tandon, P.K. (2008) Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N. Engl. J. Med. 359, 1786–1801.
[8] Fugger, L., Friese, M.A. and Bell, J.I. (2009) From genes to function: the next challenge to understanding multiple sclerosis. Nat. Rev. Immunol. 9, 408–417.
[9] Fogdell-Hahn, A., Ligers, A., Gronning, M., Hillert, J. and Olerup, O. (2000) Multiple sclerosis: a modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. Tissue Antigens 55, 140–148.
[10] Harbo, H.F. et al. (2004) Genes in the HLA class I region may contribute to the HLA class II-associated genetic susceptibility to multiple sclerosis. Tissue Antigens 63, 237–247.
[11] Brynedal, B., Duvefelt, K., Jonasdottir, G., Roos, I.M., Akesson, E., Palmgren, J. and Hillert, J. (2007) HLA-A confers an HLA-DRB1 independent influence on the risk of multiple sclerosis. PLoS ONE 2, e664.
[12] Zhang, N. and Bevan, M.J. (2011) CD8(+) T cells: foot soldiers of the immune system. Immunity 35, 161–168.
[13] Sallusto, F., Lenig, D., Forster, R., Lipp, M. and Lanzavecchia, A. (1999) Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature 401, 708–712.
[14] Curtsinger, J.M., Schmidt, C.S., Mondino, A., Lins, D.C., Kedl, R.M., Jenkins, M.K. and Mescher, M.F. (1999) Inflammatory cytokines provide a third signal for activation of naive CD4+ and CD8+ T cells. J. Immunol. 162, 3256–3262.
[15] van Stipdonk, M.J., Lemmens, E.E. and Schoenberger, S.P. (2001) Naive CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. Nat. Immunol. 2, 423–429.
[16] Sad, S., Marcotte, R. and Mosmann, T.R. (1995) Cytokine-induced differentiation of precursor mouse CD8+ T cells into cytotoxic CD8+ T cells secreting Th1 or Th2 cytokines. Immunity 2, 271–279.
[17] Huber, M. et al. (2009) A Th17-like developmental process leads to CD8(+) Tc17 cells with reduced cytotoxic activity. Eur. J. Immunol. 39, 1716–1725.
[18] McGeachy, M.J. et al. (2009) The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat. Immunol. 10, 314–324.
[19] Masopust, D., Vezys, V., Marzo, A.L. and Lefrancois, L. (2001) Preferential localization of effector memory cells in nonlymphoid tissue. Science 291, 2413–2417.
[20] Sheridan, B.S. and Lefrancois, L. (2011) Regional and mucosal memory T cells. Nat. Immunol. 12, 485–491.
[21] Dudda, J.C., Simon, J.C. and Martin, S. (2004) Dendritic cell immunization route determines CD8+ T cell trafficking to inflamed skin: role for tissue microenvironment and dendritic cells in establishment of T cell-homing subsets. J. Immunol. 172, 857–863.
[22] Liu, L., Fuhlbrigge, R.C., Karibian, K., Tian, T. and Kupper, T.S. (2006) Dynamic programming of CD8+ T cell trafficking after live viral immunization. Immunity 25, 511–520.
[23] Chavez-Galan, L., Arenas-Del Angel, M.C., Zenteno, E., Chavez, R. and Lascurain, R. (2009) Cell death mechanisms induced by cytotoxic lymphocytes. Cell. Mol. Immunol. 6, 15–25.
[24] Slifka, M.K., Rodriguez, F. and Whitton, J.L. (1999) Rapid on/off cycling of cytokine production by virus-specific CD8+ T cells. Nature 401, 76–79.
[25] Hayashi, T., Morimoto, C., Burks, J.S., Kerr, C. and Hauser, S.L. (1988) Dual-label immunocytochemistry of the active multiple sclerosis lesion: major histocompatibility complex and activation antigens. Ann. Neurol. 24, 523–531.
[26] Ransohoff, R.M. and Estes, M.L. (1991) Astrocyte expression of major histocompatibility complex gene products in multiple sclerosis brain tissue obtained by stereotactic biopsy. Arch. Neurol. 48, 1244–1246.
[27] Gobin, S.J., Montagne, L., Van Zutphen, M., Van Der Valk, P., Van Den Elsen, P.J. and De Groot, C.J. (2001) Upregulation of transcription factors controlling MHC expression in multiple sclerosis lesions. Glia 36, 68–77.
[28] Beauvillain, C. et al. (2008) Neonatal and adult microglia cross-present exogenous antigens. Glia 56, 69–77.
[29] Traugott, U., Reinherz, E.L. and Raine, C.S. (1983) Multiple sclerosis. Distribution of T cells, T cell subsets and Ia-positive macrophages in lesions of different ages. J. Neuroimmunol. 4, 201–221.
[30] Babbe, H. et al. (2000) Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. J. Exp. Med. 192, 393–404.
[31] Frischer, J.M. et al. (2009) The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 132, 1175–1189.
[32] Hauser, S.L., Bhan, A.K., Gilles, F., Kemp, M., Kerr, C. and Weiner, H.L. (1986) Immunohistochemical analysis of the cellular infiltrate in multiple sclerosis lesions. Ann. Neurol. 19, 578–587.
[33] Junker, A. et al. (2007) Multiple sclerosis: T-cell receptor expression in distinct brain regions. Brain 130, 2789–2799.
[34] Neumann, H., Medana, I.M., Bauer, J. and Lassmann, H. (2002) Cytotoxic T lymphocytes in autoimmune and degenerative CNS diseases. Trends Neurosci. 25, 313–319.
[35] Bitsch, A., Schuchardt, J., Bunkowski, S., Kuhlmann, T. and Bruck, W. (2000) Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain 123 (Pt 6), 1174–1183.
[36] Kuhlmann, T., Lingfeld, G., Bitsch, A., Schuchardt, J. and Bruck, W. (2002) Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. Brain 125, 2202–2212.
[37] Jacobsen, M. et al. (2002) Oligoclonal expansion of memory CD8+ T cells in cerebrospinal fluid from multiple sclerosis patients. Brain 125, 538–550.
[38] Tsuchida, T., Parker, K.C., Turner, R.V., McFarland, H.F., Coligan, J.E. and Biddison, W.E. (1994) Autoreactive CD8+ T-cell responses to human myelin protein-derived peptides. Proc. Natl. Acad. Sci. USA 91, 10859–10863.
[39] Honma, K., Parker, K.C., Becker, K.G., McFarland, H.F., Coligan, J.E. and Biddison, W.E. (1997) Identification of an epitope derived from human proteolipid protein that can induce autoreactive CD8+ cytotoxic T lymphocytes restricted by HLA-A3: evidence for cross-reactivity with an environmental microorganism. J. Neuroimmunol. 73, 7–14.
[40] Dressel, A., Chin, J.L., Sette, A., Gausling, R., Hollsberg, P. and Hafler, D.A. (1997) Autoantigen recognition by human CD8 T cell clones: enhanced agonist response induced by altered peptide ligands. J. Immunol. 159, 4943–4951.

[41] Crawford, M.P. et al. (2004) High prevalence of autoreactive, neuroantigen-specific CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. Blood 103, 4222–4231.
[42] Zang, Y.C., Li, S., Rivera, V.M., Hong, J., Robinson, R.R., Breitbach, W.T., Killian, J. and Zhang, J.Z. (2004) Increased CD8+ cytotoxic T cell responses to myelin basic protein in multiple sclerosis. J. Immunol. 172, 5120–5127.
[43] Berthelot, L. et al. (2008) Blood CD8+ T cell responses against myelin determinants in multiple sclerosis and healthy individuals. Eur. J. Immunol. 38, 1889–1899.
[44] Jurewicz, A., Biddison, W.E. and Antel, J.P. (1998) MHC class I-restricted lysis of human oligodendrocytes by myelin basic protein peptide-specific CD8 T lymphocytes. J. Immunol. 160, 3056–3059.
[45] Tzartos, J.S., Friese, M.A., Craner, M.J., Palace, J., Newcombe, J., Esiri, M.M. and Fugger, L. (2008) Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. Am. J. Pathol. 172, 146–155.
[46] Annibali, V. et al. (2011) CD161(high)CD8+T cells bear pathogenetic potential in multiple sclerosis. Brain 134, 542–554.
[47] Reboldi, A. et al. (2009) C–C chemokine receptor 6-regulated entry of TH-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. Nat. Immunol. 10, 514–523.
[48] Jilek, S., Schluep, M., Rossetti, A.O., Guignard, L., Le Goff, G., Pantaleo, G. and Du Pasquier, R.A. (2007) CSF enrichment of highly differentiated CD8+ T cells in early multiple sclerosis. Clin. Immunol. 123, 105–113.
[49] Kivisakk, P. et al. (2004) Expression of CCR7 in multiple sclerosis: implications for CNS immunity. Ann. Neurol. 55, 627–638.
[50] Debes, G.F., Arnold, C.N., Young, A.J., Krautwald, S., Lipp, M., Hay, J.B. and Butcher, E.C. (2005) Chemokine receptor CCR7 required for T lymphocyte exit from peripheral tissues. Nat. Immunol. 6, 889–894.
[51] Bromley, S.K., Thomas, S.Y. and Luster, A.D. (2005) Chemokine receptor CCR7 guides T cell exit from peripheral tissues and entry into afferent lymphatics. Nat. Immunol. 6, 895–901.
[52] Brahic, M., Bureau, J.F. and Michiels, T. (2005) The genetics of the persistent infection and demyelinating disease caused by Theiler's virus. Annu. Rev. Microbiol. 59, 279–298.
[53] Munz, C., Lunemann, J.D., Getts, M.T. and Miller, S.D. (2009) Antiviral immune responses: triggers of or triggered by autoimmunity? Nat. Rev. Immunol. 9, 246–258.
[54] Medana, I., Martinic, M.A., Wekerle, H. and Neumann, H. (2001) Transection of major histocompatibility complex class I-induced neurites by cytotoxic T lymphocytes. Am. J. Pathol. 159, 809–815.
[55] Wang, T. et al. (2006) Granzyme B mediates neurotoxicity through a G-protein-coupled receptor. FASEB J. 20, 1209–1211.
[56] Huseby, E.S., Liggitt, D., Brabb, T., Schnabel, B., Ohlen, C. and Goverman, J. (2001) A pathogenic role for myelin-specific CD8(+) T cells in a model for multiple sclerosis. J. Exp. Med. 194, 669–676.
[57] Sun, D., Whitaker, J.N., Huang, Z., Liu, D., Coleclough, C., Wekerle, H. and Raine, C.S. (2001) Myelin antigen-specific CD8+ T cells are encephalitogenic and produce severe disease in C57BL/6 mice. J. Immunol. 166, 7579–7587.
[58] Ford, M.L. and Evavold, B.D. (2005) Specificity, magnitude, and kinetics of MOG-specific CD8+ T cell responses during experimental autoimmune encephalomyelitis. Eur. J. Immunol. 35, 76–85.
[59] Ben-Nun, A., Kerlero de Rosbo, N., Kaushansky, N., Eisenstein, M., Cohen, L., Kaye, J.F. and Mendel, I. (2006) Anatomy of T cell autoimmunity to myelin oligodendrocyte glycoprotein (MOG): prime role of MOG44F in selection and control of MOG-reactive T cells in H-2b mice. Eur. J. Immunol. 36, 478–493.
[60] Leech, M.D., Carrillo-Vico, A., Liblau, R.S. and Anderton, S.M. (2011) Recognition of a high affinity MHC class I-restricted epitope of myelin oligodendrocyte glycoprotein by CD8+ T cells derived from autoantigen-deficient mice. Front. Immunol. 2, 17.
[61] Morgan, D.J., Liblau, R., Scott, B., Fleck, S., McDevitt, H.O., Sarvetnick, N., Lo, D. and Sherman, L.A. (1996) CD8(+) T cell-mediated spontaneous diabetes in neonatal mice. J. Immunol. 157, 978–983.
[62] Saxena, A. et al. (2008) Cutting edge: Multiple sclerosis-like lesions induced by effector CD8 T cells recognizing a sequestered antigen on oligodendrocytes. J. Immunol. 181, 1617–1621.
[63] Na, S.Y., Cao, Y., Toben, C., Nitschke, L., Stadelmann, C., Gold, R., Schimpl, A. and Hunig, T. (2008) Naive CD8 T-cells initiate spontaneous autoimmunity to a sequestered model antigen of the central nervous system. Brain 131, 2353–2365.
[64] Sobottka, B., Harrer, M.D., Ziegler, U., Fischer, K., Wiendl, H., Hunig, T., Becher, B. and Goebels, N. (2009) Collateral bystander damage by myelin-directed CD8+ T cells causes axonal loss. Am. J. Pathol. 175, 1160–1166.
[65] Na, S.Y., Eujen, H., Gobel, K., Meuth, S.G., Martens, K., Wiendl, H. and Hunig, T. (2009) Antigen-specific blockade of lethal CD8 T-cell mediated autoimmunity in a mouse model of multiple sclerosis. J. Immunol. 182, 6569–6575.
[66] Friese, M.A. et al. (2008) Opposing effects of HLA class I molecules in tuning autoreactive CD8+ T cells in multiple sclerosis. Nat. Med. 14, 1227–1235.
[67] Mars, L.T. et al. (2007) CD8 T cell responses to myelin oligodendrocyte glycoprotein-derived peptides in humanized HLA-A*0201-transgenic mice. J. Immunol. 179, 5090–5098.
[68] Sakaguchi, S., Yamaguchi, T., Nomura, T. and Ono, M. (2008) Regulatory T cells and immune tolerance. Cell 133, 775–787.
[69] Cosmi, L. et al. (2003) Human CD8+CD25+ thymocytes share phenotypic and functional features with CD4+CD25+ regulatory thymocytes. Blood 102, 4107–4114.
[70] Xystrakis, E., Dejean, A.S., Bernard, I., Druet, P., Liblau, R., Gonzalez-Dunia, D. and Saoudi, A. (2004) Identification of a novel natural regulatory CD8 T-cell subset and analysis of its mechanism of regulation. Blood 104, 3294–3301.
[71] Jarvis, L.B., Matyszak, M.K., Duggleby, R.C., Goodall, J.C., Hall, F.C. and Gaston, J.S. (2005) Autoreactive human peripheral blood CD8+ T cells with a regulatory phenotype and function. Eur. J. Immunol. 35, 2896–2908.
[72] Rifa'i, M., Kawamoto, Y., Nakashima, I. and Suzuki, H. (2004) Essential roles of CD8+CD122+ regulatory T cells in the maintenance of T cell homeostasis. J. Exp. Med. 200, 1123–1134.
[73] Feger, U., Tolosa, E., Huang, Y.H., Waschbisch, A., Biedermann, T., Melms, A. and Wiendl, H. (2007) HLA-G expression defines a novel regulatory T-cell subset present in human peripheral blood and sites of inflammation. Blood 110, 568–577.
[74] Najafian, N. et al. (2003) Regulatory functions of CD8+CD28− T cells in an autoimmune disease model. J. Clin. Invest. 112, 1037–1048.
[75] Rifa'i, M., Shi, Z., Zhang, S.Y., Lee, Y.H., Shiku, H., Isobe, K. and Suzuki, H. (2008) CD8+CD122+ regulatory T cells recognize activated T cells via conventional MHC class I-alphabetaTCR interaction and become IL-10-producing active regulatory cells. Int. Immunol. 20, 937–947.
[76] Endharti, A.T. et al. (2005) Cutting edge: CD8+CD122+ regulatory T cells produce IL-10 to suppress IFN-gamma production and proliferation of CD8+ T cells. J. Immunol. 175, 7093–7097.
[77] Wiendl, H. et al. (2005) Expression of the immune-tolerogenic major histocompatibility molecule HLA-G in multiple sclerosis: implications for CNS immunity. Brain 128, 2689–2704.
[78] Mayer, C.T., Floess, S., Baru, A.M., Lahl, K., Huehn, J. and Sparwasser, T. (2011) CD8(+) Foxp3(+) T cells share developmental and phenotypic features with classical CD4(+) Foxp3(+) regulatory T cells but lack potent suppressive activity. Eur. J. Immunol. 41, 716–725.
[79] Menager-Marcq, I., Pomie, C., Romagnoli, P. and van Meerwijk, J.P. (2006) CD8+CD28− regulatory T lymphocytes prevent experimental inflammatory bowel disease in mice. Gastroenterology 131, 1775–1785.
[80] Chang, C.C. et al. (2002) Tolerization of dendritic cells by T(S) cells: the crucial role of inhibitory receptors ILT3 and ILT4. Nat. Immunol. 3, 237–243.
[81] Vlad, G., Cortesini, R. and Suciu-Foca, N. (2005) License to heal: bidirectional interaction of antigen-specific regulatory T cells and tolerogenic APC. J. Immunol. 174, 5907–5914.
[82] Varthaman, A. et al. (2010) Control of T cell reactivation by regulatory Qa-1-restricted CD8+ T cells. J. Immunol. 184, 6585–6591.
[83] Sullivan, B.A., Kraj, P., Weber, D.A., Ignatowicz, L. and Jensen, P.E. (2002) Positive selection of a Qa-1-restricted T cell receptor with specificity for insulin. Immunity 17, 95–105.
[84] Kim, H.J., Verbinnen, B., Tang, X., Lu, L. and Cantor, H. (2010) Inhibition of follicular T-helper cells by CD8(+) regulatory T cells is essential for self tolerance. Nature 467, 328–332.
[85] Uss, E., Rowshani, A.T., Hooibrink, B., Lardy, N.M., van Lier, R.A. and ten Berge, I.J. (2006) CD103 is a marker for alloantigen-induced regulatory CD8+ T cells. J. Immunol. 177, 2775–2783.
[86] Koch, S.D., Uss, E., van Lier, R.A. and ten Berge, I.J. (2008) Alloantigen-induced regulatory CD8+CD103+ T cells. Hum. Immunol. 69, 737–744.
[87] Jiang, H., Zhang, S.I. and Pernis, B. (1992) Role of CD8+ T cells in murine experimental allergic encephalomyelitis. Science 256, 1213–1215.
[88] Hu, D., Ikizawa, K., Lu, L., Sanchirico, M.E., Shinohara, M.L. and Cantor, H. (2004) Analysis of regulatory CD8 T cells in Qa-1-deficient mice. Nat. Immunol. 5, 516–523.
[89] Varthaman, A. et al. (2011) Physiological induction of regulatory Qa-1-restricted CD8+ T cells triggered by endogenous CD4+ T cell responses. PLoS ONE 6, e21628.
[90] Lee, Y.H., Ishida, Y., Rifa'i, M., Shi, Z., Isobe, K. and Suzuki, H. (2008) Essential role of CD8+CD122+ regulatory T cells in the recovery from experimental autoimmune encephalomyelitis. J. Immunol. 180, 825–832.
[91] Antel, J., Bania, M., Noronha, A. and Neely, S. (1986) Defective suppressor cell function mediated by T8+ cell lines from patients with progressive multiple sclerosis. J. Immunol. 137, 3436–3439.
[92] Bania, M.B., Antel, J.P., Reder, A.T., Nicholas, M.K. and Arnason, B.G. (1986) Suppressor and cytolytic cell function in multiple sclerosis. Effects of cyclosporine A and interleukin 2. J. Clin. Invest. 78, 582–586.
[93] Zozulya, A.L. and Wiendl, H. (2008) The role of regulatory T cells in multiple sclerosis. Nat. Clin. Pract. Neurol. 4, 384–398.
[94] Correale, J. and Villa, A. (2008) Isolation and characterization of CD8+ regulatory T cells in multiple sclerosis. J. Neuroimmunol. 195, 121–134.
[95] Liblau, R. (2009) Glatiramer acetate for the treatment of multiple sclerosis: evidence for a dual anti-inflammatory and neuroprotective role. J. Neurol. Sci. 287 (Suppl. 1), S17–S23.
[96] Karandikar, N.J. et al. (2002) Glatiramer acetate (Copaxone) therapy induces CD8(+) T cell responses in patients with multiple sclerosis. J. Clin. Invest. 109, 641–649.
[97] Tennakoon, D.K., Mehta, R.S., Ortega, S.B., Bhoj, V., Racke, M.K. and Karandikar, N.J. (2006) Therapeutic induction of regulatory, cytotoxic CD8+ T cells in multiple sclerosis. J. Immunol. 176, 7119–7129.
[98] Airas, L., Nikula, T., Huang, Y.H., Lahesmaa, R. and Wiendl, H. (2007) Postpartum-activation of multiple sclerosis is associated with down-regulation of tolerogenic HLA-G. J. Neuroimmunol. 187, 205–211.