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Review Article

Immunopathology of CD4+ T Cell-Mediated Autoimmune Responses to Central Nervous System Antigens: Role of IL-16

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Abstract

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and degenerative disease of the central nervous system (CNS). While etiology of the disease remains unknown, genetic susceptibility and autoimmune mechanisms in the initiation and progression of the disease have been strongly suggested. Experimental autoimmune encephalomyelitis (EAE) is commonly used to study immune regulation of MS. Infiltration by $CD4^+$ T cells, through blood-brain barrier (BBB), precedes the onset and relapses of MS. CNS migration and homing patterns of T cells are tightly synchronized by astrocyte and microglia derived cytokines and chemokines. Autoimmune, CNS antigen-reactive, infiltrating T cells produce and locally release cytokines including but not limited to IFNγ, IL-2, IL-6, IL-16, IL-17, TNFα, and chemokines including CCL2, CCL5 and CXCL10. Chemokine mediated chemotaxis is exclusive for activated cell state and most chemokines do not discriminate between distinct cell types. Conversely, a cytokine IL-16 is a CD4-specific cytokine-ligand and exclusively induces chemotaxis of $CD4^+$T cells, by binding and signaling through CD4, regardless of T cell activation state. In this article we focus on $CD4^+$ T cell-mediated autoimmune responses to CNS antigens because of their importance for immunopathology of MS and EAE. We focus on autoimmune responses to myelin oligodendrocyte glycoprotein (MOG) because of its relevance for immunopathology of MS. We emphasize a role of IL-16 in regulation of $CD4^+$T cell mediated autoimmune responses to MOG in EAE and MS. While a role of IL-16 in regulation of other $CD4^+$T cell mediated autoimmune diseases has been established, its role in regulation of MS remains to be determined. Emerging data from our laboratories have indicated that IL-16-mediated $CD4^+$ T cell chemoattraction has a significant role in regulation of $CD4^+$ T cell-mediated autoimmune responses to CNS antigens. We propose an important function of this cytokine in regulation of relapsing-remitting EAE.

T CELL RESPONSES IN CNS AUTOIMMUNITY

Multiple sclerosis (MS) is an immunepathologically-mediated, putative autoimmune disease. It ranks among the leading causes of disability in North America. Autoimmune mechanisms of central nervous system (CNS) damage are primarily mediated by auto-reactive $CD4^+$ T cells, which are specific for encephalitogenic epitopes of myelin peptides. Migration of autoimmune T cells from the periphery into CNS parenchyma leads to inflammation, demyelination and damage of axons, oligodendrocytes and neurons [1]. This autoimmune T cell mediated tissue damage results in impairment of motor function leading to paralysis. Disease is progressive and often takes a relapsing-remitting course. Progression and severity of the disease as well as types of CNS lesions are highly heterogeneous among patients with MS [2]. In an effort to replicate heterogeneity of clinical course and CNS lesions observed in MS patients, different types of experimental models have been developed.

In experimental autoimmune encephalomyelitis (EAE), an autoimmune model of MS, major effector mechanisms of autoimmune demyelination in the CNS are mainly, but

not exclusively, mediated by Th1 helper/inducer CD4+ encephalitogenic T cells [3], and followed by the phagocytosis of myelin debris by macrophages. Roles for cytotoxic CD8+ T cell, B cell and NK cell mediated regulation of immune response to myelin antigens have been proposed [4,5]. B cell-mediated mechanisms are of particular interest as auto-antibodies to myelin oligodendrocyte glycoprotein (MOG) play a significant role in regulation of CNS demyelination, especially in pediatric MS patients [6].

Development and progression of an autoimmune response to myelin specific antigens results from a fine balance and interactions between the effector and regulatory T cells (Treg) in the periphery [7]. Once activated and clonally expanded, auto-aggressive myelin antigen-specific CD4+ effector T cells, Th1, Th17 and Th9 coordinate CNS inflammation and induce tissue damage. Conversely, regulatory T cells (Treg) and Th2 CD4+ T cells have roles in controlling and downregulating effector T cell mediated inflammation. CD4+ T cell infiltration into CNS precedes onset of clinical signs of disease. Similarly, relapses of disease are based upon the reappearance of activated CD4+ T effector cells into the CNS, which subsequently leads to demyelination and axonal damage [8]. Transmigration of encephalitogenic CD4+ T cells through the blood-brain barrier (BBB) is a process tightly regulated by the production of chemoattractant chemokines and expression of their cognate receptors by both, glial and inflammatory cells [9]. Timing and levels of produced chemokines and their corresponding cognate receptors are primarily regulated by cytokines, produced by activated mononuclear cells and glia [10]. These chemokines and their cognate receptors associated with MS include: CCL2 (MCP-1) /CCR2, CCL3 (MIP-1α) /CCR1/CCR5, CCL4 (MIP-1β) /CCR5 and CCL5 (RANTES) / CCR1/CCR3/CCR5 [11,12]. Similar to MS, a role for chemokines in regulation of macrophage and activated CD4+ T cell migration has been documented in different models of EAE [13,14].

T CELL RESPONSES TO MYELIN OLIGODENDROCYTE GLYCOPROTEIN (MOG) IN RELAPSING- REMITTING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

Immune regulation of EAE relapses is not completely understood. Contribution of local microenvironment in immunomodulation of encephalitogenic cell responses remains in the focus of investigation. We originally demonstrated presence of encephalitogenic cells and revealed their trafficking patterns and distribution throughout the entire course (389 days – 10 relapses) of relapsing-remitting EAE in SJL Thy-1 congenic mice. We analyzed homing of T cells to the CNS throughout the course of relapsing-remitting EAE. The SJL-Thy1^a mouse strain was derived by crossing SJL (Thy1^b) and AKR (Thy1^a) mice and by twelve subsequent successive backcrosses of SJL to select breeders expressing the Thy1.1 phenotype [15] . EAE was induced by adoptive transfer of sensitized and *in vitro* restimulated myelin basic protein (MBP) -specific lymph node cells from SJL (Thy1.2+) mice into SJL-Thy^a (Thy1.1+) congenic hosts. In CNS of SJL-Thy 1^a recipients, we observed donor Thy 1.2+ cells in small infiltrates disseminated throughout the white matter, beginning prior the onset of clinical signs. Seven days post cell transfer, Thy1.2+ donor cells constituted 2.5% of the infiltrating cells and reached peak value of approximately 10% during the first attack. This five-fold increase in numbers of Thy1.2+ donor cells raises the question of intrinsic mechanisms driving either local or peripheral expansion of Thy 1.2+ cells [16,17].

Understanding the regulation of CD4+ T cell infiltration in response to MOG_{35-55} is of great importance for MS [18]. Studies of immunoregulatory mechanisms underlying heterogeneity of MS lesions [2] and clinical course require use of different EAE models, which closely replicate heterogeneous immunopathology of the human disease. Development of appropriate models is the major challenge in enhancing MS related research [19,20]. Strong immune responses to MOG_{35-55} by CD4+ Th1 cells are found in patients with MS. The encephalitogenic epitope of myelin oligodendrocyte glycoprotein (MOG) p35-55 is highly conserved among species, including mouse and human. In EAE, CD4+ T cell immune responses to MOG_{35-55} are restricted by MHC class II (H-2^b) expression. Following immunization with MOG_{35-55}, most B6 (H-2^b) mice fully recover after the acute disease, with one or no relapse, or develop chronic sustained disease [21] . Studies of mechanisms regulating relapsing disease in response to MOG_{35-55} have been hampered by the lack of appropriate animal models. Our laboratory originally described relapsing-remitting EAE model in (B6 x SJL) F1 (H-2$^{b/s}$) mice [22], which compared to B6 (H-2^b) non-relapsing model, shares great similarity with clinical course and histopathology of human MS. We observed a profound depletion of myelin associated glycoprotein (MAG), concomitant with depletion of axonal neurofilament (NF160), and sharp elevations of PARPp85, which is a 85 kD caspase cleaved fragment of a DNA binding enzyme, poly (ADP-ribose) polymerase (PARP) and whose presence indicate irreversible apoptosis, occurring exclusively in relapsing H-2$^{b/s}$ mice. Our data implicate genetic factors as main regulators of preferential myelin-associated glycoprotein (MAG) depletion and axonal damage in (B6 x SJL) F1 (H-2$^{b/s}$) mice with MOG_{35-55} induced EAE [23]. An excessive loss of MAG, believed to result from a distal oligodendrogliopathy is observed in the subtype III of MS lesions [2]. Similar to our observations in EAE model, a recent study in neuromyelitis optica reports histopathology of demyelinating lesions with preferential decrease of MAG and oligodendrocyte apoptosis [24]. We propose that MOG-induced EAE in (B6 x SJL) F1 (H-2$^{b/s}$) mice may serve as a useful animal model in studying mechanisms, which govern autoimmune-induced preferential loss of MAG, and its impact on oligodendroglial pathology. Therefore, a specific contribution of SJL background in (B6 x SJL) F1 (H-2$^{b/s}$) mice have a potential to modulate an H-2^b restricted immune response to encephalitogenic epitope. This specific immune modulation leads to distinct clinical EAE, immunopathology of relapsing lesions and T cell responses to MOG_{35-55}. H-2$^{b/s}$ mice developed consistently more severe relapsing remitting disease, compared to H-2^b mice, which develop less severe non-relapsing disease. In relapsing H-2$^{b/s}$ mice, we observed extensive demyelination and small inflammatory infiltrates scattered throughout the white matter. Infiltrating cell phenotypes in CNS lesions were skewed towards CD4+ T cells and B220+ B cells with fewer Mac-3+ macrophages. To investigate mechanisms underlying preferential accumulation of CD4+ T cells and B220+ B cells over macrophages in relapsing lesions of H-2$^{b/s}$ mice, we analyzed a macrophage chemoattractant protein (CCL2, MCP-1) chemokine and its

corresponding receptor CCR2 expression throughout disease in H-$2^{b/s}$ and H-2^{b} mice. We noted less abundant levels of CCL2 message in acute and relapsing lesions of H-$2^{b/s}$ mice compared to H-2^{b}. Conversly, CCR2 levels did not differ significantly between the strains in acute and relapsing disease. Surprisingly, a switch of CCL2 positive immunostaimig from GFAP^{+} astrocytes, which are considered a main CCL2 producing cell in EAE, to a CD3^{+} T cells, was observed. By two-color immunostaining, we further identified CD3^{+}CD4^{+} T cells as major sources of CCL2 production in relapsing lesions of H-$2^{b/s}$ mice. Our data point to existence of locally derived factors that facilitate intra CNS migration of CD4^{+} T cell compared to macrophages during relapsing stages of disease. We further examined whether the significantly higher incidence of relapses in H-$2^{b/s}$ rather than H-2^{b} mice might be the result of either higher numbers of long term memory cells or their facilitated recall responses to MOG_{35-55}, in the peripheral lymphoid organs of H-$2^{b/s}$ and H-2^{b} mice. MOG_{35-55} induced recall T cell responses were notably higher in H-$2^{b/s}$ mice during the relapse, suggesting the existence of mechanisms that facilitate clonal expansion of MOG_{35-55} specific T cells. We proposed that this specific enhancement of CD4^{+} T cells mediated mechanisms play a major role in relapsing disease in H-$2^{b/s}$ mice.

In a search for factors, which favor local enrichment of CD4^{+} T cells, we decided to study IL-16 over other known CD4^{+} T cell chemoattractant chemokines because IL-16 selectively chemoattracts CD4^{+} T cells [25,26]. Also, IL-16 has a potential to modulate chemokine mediated T cell migration. Reciprocal desensitization of a chemokine receptor CCR5 and CD4 molecule by IL-16 and chemokine MIP-1, respectively, has been demonstrated [27]. Chemokines known to regulate inflammation in EAE through their chemoattractant properties, such as CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES) are not exclusive for CD4^{+} T cells. More importantly, these chemokines regulate migration of activated mononuclear cells, including CD4^{+} T cells, which express corresponding chemokine receptors. Even though IL-16 attracts CD4^{+} monocytes, only a fraction of monocyte/macrophages expresses CD4 on their surface and therefore it was feasible to hypothesize that IL-16-mediated chemoattraction would contribute primarily to CD4^{+} T cell dominated infiltration. The fact that IL-16 chemoattraction is not related to CD4^{+} T cell activation state was especially interesting because such non-selectivity might provide recruitment from the pool of long-term Th1 memory (peripheral memory) cells [28] in our MOG_{35-55} EAE model [22] which do not readily express activation markers and activation induced chemokine receptors. The existence of peripheral memory cells to MOG_{35-55} is suggested by our finding of strong lymph node and splenic T cell proliferation to MOG_{35-55} in relapsing H-$2^{b/s}$ mice.

While a role of IL-16 in regulation of inflammatory infiltration in several autoimmune diseases, including rheumatoid arthritis [29] has been established, there were no data available prior to our studies on the role of IL-16 in MS and EAE.

ROLE OF IL-16 IN IMMUNE REGULATION OF AUTOIMMUNE RESPONSES

IL-16 is an exclusive chemoattractant cytokine for CD4^{+}T cells [30]. IL-16 preferentially induces chemoattraction of CD4^{+} Th1 over Th2 cells with a requirement of CCR5 chemokine receptor [31]. Among other immunomodulatory properties, IL-16 has an important role in regulation of CD4^{+} T cell – dendritic cell and T – B cell communication [32]. Immunotherapy of MS with anti-CD4 antibodies showed beneficial effects in ameliorating severity of disease by abrogating CD4^{+} T cell mediated immune responses. Major pitfalls of such therapy were due to overall T cell depletion and immune-compromised defense from infection [33,34]. . In EAE, non-depleting anti-CD4 antibody therapy protected from disease through induction of peripheral T-cell tolerance to myelin basic protein (MBP) in PL/J mice [35]. In general antibody-based therapies face a challenge of the requirement for humanized antibodies to be successfully used for human. Therapy with two different types of humanized CD3 antibodies was used in treatment of autoimmune diabetes type I (T1D). Overall, this treatment showed beneficial results in ameliorating disease over two-year period. It was noted that response to treatment was highly heterogeneous between patients with T1D. Underlying mechanisms of protection were governed through reduction of T cell mediated responses and likely through modulation of regulatory T cell responses [36]. Our laboratory demonstrated in relapsing (B6 x SJL) F1 (H-$2^{b/s}$) EAE mice that therapy with monoclonal anti-IL-16 antibody, administered 24-48 hour after relapse, reversed paralysis. When such therapy was delayed beyond 48 - hour period, it did not have an effect in ameliorating the disease. Our data suggest that success of anti-inflammatory therapy depends on timing with relapsing episode and that the opportune therapeutic window is narrow, following shortly after relapse development. In treated mice, mononuclear cell infiltration within the white matter was significantly reduced, while infiltration in the meninges seemed comparable to that in control, non-treated EAE mice. This pattern of mononuclear cell infiltrates scattered throughout the white matter is consistent with our previous findings [22] and is clearly different from that found in EAE models in other strains of mice, including B6 (H-2^{b}) mice, where large perivascular and meningeal infiltrates were observed. With quantitative analysis of cell phenotypes, we demonstrated that anti-IL-16 therapy had most profound effect in decreasing the numbers of infiltrating CD4^{+} T cell, where a fivefold decrease was observed. Therapy exhibited less robust effect on B cell infiltration, where approximately two-fold decrease was observed. Therapy with anti-IL-16 antibody did not significantly reduce numbers of infiltrating Mac3^{+} macrophages. Overall, anti-IL-16 therapy was successful in reducing CD4^{+} T cell infiltration, ameliorating severity of established and relapsing disease. Repeated treatment showed more sustained effect by diminishing severity and frequency of relapses and enabling longer and more successful recovery during remission. Treatments with IL-16 neutralizing antibody reduced numbers of infiltrating CD4^{+} T cells, in the spinal cord white matter, reduced demyelination and fostered better preservation of axons in treated mice. Taken together, our results show an important role of IL-16 in regulation of CD4^{+} T cell inflammation, demyelination, axonal degeneration and progression and severity of relapsing EAE. We described a novel therapeutic approach to specifically decrease CD4^{+} T cell infiltration in EAE based on IL-16 neutralization. Our findings have high relevance for the development of new therapies for relapsing EAE and potentially MS [37].

IL-16 mRNA expression and protein production have been detected in Th1- and Th2-mediated human and experimental diseases. We demonstrated increased IL-16 mRNA expression and protein levels in CNS lesions in EAE and MS [38,39]. We observed increased levels of IL-16 co-localized with $CD4^+$ T cells in pancreatic isles of spontaneously diabetic BB/W rats, with type1 diabetes mellitus (T1D) [40]. *In vivo* neutralization studies performed to assess the role of IL-16 in pathogenesis of T1D, demonstrated that neutralization of IL-16 prevented nonobese diabetic (NOD) mice from developing the disease by interfering with recruitment of $CD4^+$ T cell. In NOD mice, increased production of IL-16 correlated with invasive insulitis. IL-16 immunoreactivity was observed in infiltrating CD4+ T cells [41]. We found that elevated levels of IL-16 along with increase in active caspase-3 and CD4 levels correlated with stages of clinically active disease in both (B6 x SJL) F1 ($H\text{-}2^{b/s}$) and B6 ($H\text{-}2^{b}$) mice. CNS levels of bioactive IL-16 were notably higher in $H\text{-}2^{b/s}$ compare with $H\text{-}2^{b}$ mice at all stages, being most prominent during relapse. We observed similar patterns of regulation for IL-16 and active caspase-3 in peripheral lymphoid organs and in T cells isolated from lymph nodes following T-cell activation *in vitro*. We co-immunoprecipitated IL-16 with CD4 from CNS of relapsing $H\text{-}2^{b/s}$ mice. Our data suggest that caspse-3 mediated production of IL-16 by infiltrating $CD4^+$ T cells, contributes to ongoing neuroinflammation by chemoattraction of additional waves of $CD4^+$ T cells [38]. In MS lesions, analyzed from post-mortem snap frozen tissue, we made the original observation of markedly increased levels of pro- and secreted IL-16 (80 kD and 22 kD, respectively) compared with control. IL-16 levels were highest in acute, diminished in subacute and peaked again in chronic active lesions. Compared to lesions, lower but still appreciable IL-16 levels were found in normal-appearing white matter adjacent to active lesions. We further found that increased levels of IL-16 corresponded to increase in active caspase-3, T-bet and phosphorylated Stat-1. We co-localzed IL-16 immunoreactivity to $CD3^+$, $Tbet^+$ and active $caspase\text{-}3^+$ mononuclear cells. We further observed the correlation between increased levels of secreted IL-16, $CD4^+$ Th1 cell inflammation, and phosphorylation of axonal neurofilament (medium and heavy chain) [NF (M+H)], in MS lesions. All together, our data suggest that IL-16 production occurs in MS lesions. Our data indicate a role for IL-16 in regulation of $CD4^+$ Th1 inflammation and subsequent changes in the axonal cytoskeleton in MS lesions [39].

CONCLUSIONS

Role of $CD4^+$T cells in regulation of relapsing disease is not completely understood. IL-16 is a specific cytokine-ligand for CD4, which chemoattracts exclusively $CD4^+$ T cells. Other biological properties of IL-16 important for regulation of autoimmune responses to CNS antigens include regulation of: CD25 expression by $CD4^+$ T cells; T cell-dendritic cell, and T cell-B cell communication; chemokine production and modulation of chemokine-mediated chemotaxis. IL-16 has an important role in regulation of $CD4^+$ T cell infiltration in $MOG_{35\text{-}55}$ induced relapsing-remitting EAE in (B6 x SJL) F1 ($H\text{-}2^{b/s}$) mice. Encephalitogenic epitope (p35-55) of myelin oligodendrocyte protein (MOG) is highly conserved among species, including mice and humans. Relapsing-remitting EAE model in (B6 x SJL) F1 ($H\text{-}2^{b/s}$) mice resembles closely human pathohistology and clinical course of relapsing MS. The model of relapsing-remitting EAE in (B6 x SJL) F1 mice provides a good choice to study effects of single gene deficiencies on relapsing phenotype, as most gene disruptions were done in B6 mice.

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