

# $\gamma\delta$ T cells and IL-17/IL-17R signaling axis in CNS inflammation

Jayasri Das Sarma

Department of Biological Sciences,  
Indian Institute of Science Education  
and Research – Kolkata, Mohanpur,  
Nadia, West Bengal, India

**Abstract:** Lymphocytes expressing  $\gamma\delta$  T-cell receptors constitute an entire system of functionally specialized subsets that have been implicated in the regulation of immune responses, including responses to pathogens and allergens, and in tissue repair.  $\gamma\delta$  T cells represent a small subpopulation of T cells that, unlike  $\alpha\beta$  T cells, function more as cells of the innate immune system.  $\gamma\delta$  T cells are known to mediate the production of inflammatory cytokines, including interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and interleukin (IL)-17, and thus enable the activation of other subsets of infiltrating effector cells. However, not much attention was paid to  $\gamma\delta$  T cells until the recent discovery of a distinct CD4<sup>+</sup> T helper ( $T_H$ ) cell,  $T_H17$  cell. CD4<sup>+</sup> T cells, upon activation and expansion, develop into different  $T_H$ -cell subsets with different cytokine profiles and distinct effector functions. T cells were earlier divided into  $T_H1$  or  $T_H2$  cells, depending on the cytokines they produce. A third subset of IL-17-producing effector  $T_H$  cells, called  $T_H17$  cells, has been discovered and characterized recently. Since then the literature on IL-17-producing cells has grown steadily, and several studies have focused on  $\gamma\delta$  T cells. Cytokine-mediated modulation of central nervous system (CNS) inflammatory diseases by  $\gamma\delta$  T cells in humans or in animal models is currently the subject of many studies. IL-17 and its receptor IL-17R have been implicated in the pathogenesis of immune-mediated CNS diseases, and attention has been paid to understand the mechanisms by which IL-17 cytokines and its receptor (IL-17R) family mediate the effects at a molecular level. This article reviews the studies that cover earlier aspects of  $\gamma\delta$  T cell/IL-17 biology and the new dimension of  $\gamma\delta$  T cells, IL-17, and IL-17/IL-17R signaling axis in CNS inflammation. Understanding the role of  $\gamma\delta$  T cells, IL-17, and IL-17/IL-17R signaling axis in infection and immunity could open a new avenue for immunomodulation.

**Keywords:** cytokine,  $\gamma\delta$  T cells,  $T_H17$  cells, IL-17, IL-17R, multiple sclerosis, EAE, autoimmunity, CNS, viral infection, virus-induced demyelination

## Introduction

Interleukin (IL)-17A and its receptor IL-17RA are the founding members of a newly described family of cytokines (IL-17A–IL-17F) and their receptors (IL-17RA–IL-17RE; known as the IL-17R family).<sup>1–3</sup> Receptors belonging to the IL-17R family have unique structural features and mediate signaling events that are surprisingly distinct from those triggered by other cytokine receptors, particularly those usually involved in adaptive immunity. IL-17A plays a critical role in the pathogenesis of many autoimmune diseases, including multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). IL-17 has also been shown to exacerbate autoimmune diseases.  $T_H17$  cells are a newly defined  $\alpha\beta$  T-cell lineage

Correspondence: Jayasri Das Sarma  
Department of Biological Sciences,  
Indian Institute of Science Education  
and Research – Kolkata, Mohanpur  
Campus, PO: BCKV Campus Main Office,  
Mohanpur, Nadia, West Bengal  
741252, India  
Tel +91 33 25873019  
Fax +91 33 25873020  
Email [dassarmaj@iiserkol.ac.in](mailto:dassarmaj@iiserkol.ac.in)

characterized by IL-17 production. However,  $\gamma\delta$  T cells are often the major source of IL-17.<sup>4,5</sup> Recent studies have demonstrated that  $\gamma\delta$  T cells play a role in the development of demyelinating central nervous system (CNS) inflammation. As multifaceted cells,  $\gamma\delta$  T cells have the potential to influence all levels of inflammation by the rapid production of inflammatory mediators, by recruiting inflammatory cells via chemokines, influencing T-cell differentiation by cytokine production, and/or direct killing via production of cytotoxic effectors.<sup>6</sup> Although the roles of  $\gamma\delta$  T cells and  $T_H17$  cells/IL-17 in EAE and MS are to some extent clear, it is unknown whether the activation cascade of  $\gamma\delta$  T cells and  $T_H17$  cells/IL-17 has any function in virus-induced demyelination. Very few studies are available on the inflammatory cascade of  $\gamma\delta$  T cells and  $T_H17$  cells/IL-17 and IL-17/IL-17R signaling mechanisms in virus-induced CNS demyelination. In this review, we have attempted to gather data from published articles and our own findings to examine the role of  $\gamma\delta$  T cells, IL-17-producing  $T_H17$ -cell lineage, and IL-17/IL-17R signaling system in the virus-induced demyelination model of MS.

MS is one of the major chronic inflammatory CNS diseases in humans with heterogeneous clinical presentations and course.<sup>7</sup> The major manifestation of MS is demyelination with and without axonal preservation. Demyelination is a complex process, and while the precise mechanisms of this pathology are unclear, inflammatory demyelination is thought to be the result of adaptive immune-mediated responses to myelin antigens in the myelin sheaths of axons and/or in the myelin-forming oligodendrocytes. However, the contribution of innate immune cells in mediating MS pathogenesis has recently gained attention, as several studies demonstrated the role of various innate immune cells in mediating MS pathogenesis, in particular, the potential anti-inflammatory or proinflammatory function of dendritic cells, microglial cells, natural killer (NK) cells, NKT cells, and  $\gamma\delta$  T cells along with their interaction among themselves and with myelin.<sup>8–11</sup>

MS is best studied in some experimental models such as EAE, Theiler's murine encephalomyelitis virus (TMEV), and mouse hepatitis virus (MHV). The primary emphasis has been on understanding CD<sup>+</sup> T cell-mediated or T cell and antibody-mediated autoimmune encephalomyelitis. Virtually all types of immune response have been proposed to play important roles in the pathogenesis of EAE<sup>7,12</sup> and TMEV.<sup>13–15</sup> Infection of mice with MHV, strain JHM,<sup>16,17</sup> results in acute and chronic demyelination, mimicking the pathogenesis of the MS. This pathological process is primarily T cell-mediated, and MHV infection of mice lacking B and

T cells does not result in demyelination. Contrary to these results, robust demyelination is detected in MHV-infected young nude (athymic) mice, which demonstrates that demyelination in nude mice could be mediated by  $\gamma\delta$  T cells.<sup>18</sup>  $\gamma\delta$  T cells, but not conventional CD4 or CD8  $\alpha\beta$  T cells, were detected in the CNS of MHV-infected nude mice, and their depletion with neutralizing antibody resulted in an 80% reduction in demyelination. Moreover, demyelination induced by MHV-A59, another neurotropic strain of MHV, has been shown to develop in adult immunocompromised mice lacking B and T cells.<sup>19</sup> It has also been demonstrated that the depletion of CD4<sup>+</sup> or CD8<sup>+</sup> T cells after the acute stage of infection does not reduce demyelination.<sup>20,21</sup> Indeed, recent studies on MHV-A59 or the demyelination induced by its isogenic spike protein (host-attachment protein) recombinant strain, RSA59, exhibit that inflammatory CNS demyelination consists of a mixed population of inflammatory cells, predominantly macrophages/microglia and a smaller population of T lymphocytes but not conventional CD4<sup>+</sup> or CD8<sup>+</sup>  $\alpha\beta$  T cells.<sup>22–24</sup> These results illustrate that  $\gamma\delta$  T cells can substitute for T cells in a virus model of demyelination, but not much is known about the mechanism of action of effectors.

## $\gamma\delta$ T cells in infection and immunity

Because of their immune response against viral infection, macrophages, NK cells, and interferons are mostly known as immune effectors, and slow-generating, adaptive Ag-specific  $\alpha\beta$  T-cell and B-cell responses are known to be often crucial for the clearance of the pathogen and establishment of adaptive immunity. Although the existence of  $\gamma\delta$  T cells has been known for a long time, their significance in this paradigm of protective immunity has not been well documented until some recent studies have suggested that  $\gamma\delta$  T cells may play a role in the control of parasitic infections such as malaria and *Eimeria veriformis* and bacterial infections such as *Listeria monocytogenes* and *Klebsiella pneumoniae*.<sup>25–34</sup> Information about these cells in viral infections still remains elusive,<sup>35–40</sup> although there is an ongoing critical reappraisal of the protective role of  $\gamma\delta$  T cells in viral infection. Recently, it has been reported that there is an increased number of  $\gamma\delta$  T cells in the peripheral blood of individuals infected with HIV and Epstein–Barr virus,<sup>37,41</sup> and some human  $\gamma\delta$  T cell clones preferentially lyse targets infected with vaccinia virus 3 or herpes simplex virus.<sup>35</sup> In some viral infection, antiviral function of  $\gamma\delta$  T cells can be substituted and masked by  $\alpha\beta$  T cells,<sup>28,38,39</sup> which explain why the role of  $\gamma\delta$  T cells has been concealed in the field of protective immunity. However, with the advent of the novel cytokine IL-17 and a new subset of

T<sub>H</sub>17 cells,  $\gamma\delta$  T cells attain a new dimension in the field of infection and immunity.

In addition to the innate immune function, growing evidence from both human and primate studies suggest that  $\gamma\delta$  T cells are involved in inducing adaptive immunity by regulating CD8 T-cell memory responses. It has been proposed that in West Nile (WN) virus infection,  $\gamma\delta$  T cells contribute to the development of adaptive immunity.<sup>42</sup> However, the development of CD8 T-cell memory response to WN virus infection is not fully understood. Several attempts are being made to determine whether  $\gamma\delta$  T cells can directly link innate and adaptive immunity in viral infection and contribute to memory response, thus playing a potential role in future vaccine development.

$\gamma\delta$  T cells are known to have a role in the pathogenesis of various autoimmune diseases and diseases of unknown etiology, as elevated levels of  $\gamma\delta$  T cells have been reported in rheumatoid arthritis,<sup>43</sup> MS,<sup>44,45</sup> pulmonary sarcoidosis,<sup>46</sup> inflammatory bowel disease,<sup>47</sup> and polymyositis.<sup>48</sup> Some of these diseases might be precipitated or exacerbated by viral infections, and recent evidence has indicated that  $\gamma\delta$  T cells may contribute to myocarditis in mice infected with encephalomyocarditis virus.<sup>49</sup> Recent studies have also found  $\gamma\delta$  T cells in the cerebrospinal fluid (CSF) and lesions of patients with MS.<sup>50</sup> These findings showed that  $\gamma\delta$  T cells may play a role in regulating autoimmune inflammation in the CNS; however, a causal relationship has not yet been established. In summary,  $\gamma\delta$  T cells are a multifaceted group of cells that might have both innate and adaptive characteristics and functions.

## IL-17 in CNS inflammation

IL-17 is a cytokine that plays an important role in orchestrating innate and adaptive immune function.<sup>51</sup> IL-17 has also been shown to exacerbate experimental autoimmune diseases;<sup>52</sup> CD4<sup>+</sup>  $\alpha\beta$  T cells,  $\gamma\delta$  T cells, NK cells, and LTI-like cells all produce IL-17.<sup>5,53,54</sup> However,  $\gamma\delta$  T cells are often the major source of IL-17.<sup>4,5</sup> Recently, it has been found that  $\gamma\delta$  T cells infiltrate the CNS during the development of EAE, and a very high frequency of these cells secretes IL-17.<sup>5</sup>

IL-17A was described earlier,<sup>55</sup> but became a major focus of research only recently, after the discovery of a novel IL-17A-producing T<sub>H</sub>-cell lineage (T<sub>H</sub>17).<sup>56–60</sup> CD4<sup>+</sup> T cells, upon activation and expansion, develop into various T<sub>H</sub>-cell subsets with different cytokine profiles and distinct effector functions. T cells were earlier divided into T<sub>H</sub>1 or T<sub>H</sub>2 cells, depending on the cytokines they produce. A third subset of IL-17-producing effector T<sub>H</sub> cells, called T<sub>H</sub>17 cells, has recently been

discovered and characterized.<sup>54,61–63</sup> T<sub>H</sub>17 cells are generated in response to polarizing cytokines, where TGF- $\beta$  plus IL-1 $\beta$ , IL-6, or IL-21 act as differentiation factors, IL-23 as growth and stabilization factor, and STAT3, ROR $\gamma$ , and ROR $\alpha$  as transcription factors. Although the mechanism of activation of T<sub>H</sub>17 cells and CD4<sup>+</sup> T cells that secrete IL-17 is known to some extent, much less is known about the ability of innate cell subpopulations to produce IL-17.

The transcription factor ROR $\gamma$ t and IL-23 receptor (IL-23R), the master regulator of T<sub>H</sub>17-cell differentiation, which has been associated with the development and differentiation of CD4<sup>+</sup> T<sub>H</sub>17 cells,<sup>64</sup> are also constitutively expressed by NKT cells and CD4<sup>+</sup>CD3<sup>-</sup> LTI-like cells.<sup>53,64,65</sup>  $\gamma\delta$  T cells constitutively express IL-23R and the transcription factor ROR $\gamma$ t and produce IL-17, in response to activation by IL-1 and IL-23, without T-cell receptor engagement.<sup>65</sup> IL-17-producing  $\gamma\delta$  T cells were found at high frequency in the brain of mice with EAE.  $\gamma\delta$  T cells activated by IL-1 $\beta$  and IL-23 promoted IL-17 production by CD4<sup>+</sup> T cells and increased susceptibility to EAE, suggesting that  $\gamma\delta$  T cells act in an amplification loop for IL-17 production by T<sub>H</sub>17 cells.  $\gamma\delta$  T cells activated by IL-1 $\beta$  and IL-23 are an important source of innate IL-17.<sup>65</sup>

Recently published studies on MS and EAE have demonstrated an association between the development of demyelinating plaques and the accumulation of T<sub>H</sub>17 cells at the center and periphery of the lesions.<sup>66–68</sup> Similarly, IL-17-producing  $\gamma\delta$  T cells were also found at high frequency in the brain of mice with EAE.<sup>5</sup>

Like other inflammatory cytokines, IL-17A has both protective and pathogenic roles. IL-17A is important for host defense against infectious organisms.<sup>67,69–71</sup> However, elevated IL-17A levels in several autoimmune diseases, including MS and EAE, contribute to disease pathogenesis.<sup>52,72–74</sup> Deficiency or neutralization of IL-17A in EAE reduces disease susceptibility and clinical severity.<sup>52</sup> IL-17A can induce the expression of a range of inflammatory mediators and thus can modulate the activities of inflammatory cells through production of numerous cytokines and chemokines involved in inflammatory responses.<sup>75,76</sup> Infiltration of inflammatory cells and encephalitogenic T cells in the CNS is the hallmark of EAE.<sup>10</sup> IL-17A expression is increased in lymphocytes derived from EAE mice, and anti-IL-17A antibody treatment during the recovery phase in a relapsing–remitting EAE model delays the onset and reduces incidence and severity of relapses.<sup>77,78</sup> In patients with MS, IL-17A mRNA and protein are increased in both brain lesions and mononuclear cells isolated from blood and

CSF.<sup>79,80</sup> Recently, it was demonstrated that IL-17A produced by T<sub>H</sub>17 cells is detectable at the blood–brain barrier in MS lesions and that IL-17A can promote blood–brain barrier disruption *in vitro*.<sup>81</sup>

## IL-17 receptor signaling in CNS inflammation

IL-17A functions through a distinct ligand–receptor signaling system.<sup>2,3</sup> IL-17A is the founding member of a recently described cytokine family with unique sequences and functions in the immune system and elsewhere.<sup>82</sup> These cytokine molecules, consisting of six ligands (IL-17A–F) and five receptors (IL-17RA–IL-17RE) in mammals, has distinct primary amino acid structures with only minimal homology to other cytokine families. By far the best studied of these cytokines are IL-17A and its receptor, IL-17RA. In contrast to the restricted expression of IL-17A, the IL-17RA is ubiquitously expressed, and thus most cells are potential physiological targets of IL-17A.

The unique structural features of IL-17R family receptors are also known to mediate signaling events that are surprisingly distinct from those triggered by other cytokine receptors, particularly those usually involved in adaptive immunity. The signature cytokines involved in the T<sub>H</sub>1- and T<sub>H</sub>2-cell responses trigger Janus kinase signaling pathways, whereas IL-17R family cytokines mediate signaling through a distinct pathway that depends on ACT1 (also known as CIKS), resulting in the activation of proinflammatory mediators that are usually associated with innate immune signaling, such as nuclear factor- $\kappa$ B. Thus, because of the unusual signaling properties of IL-17, T<sub>H</sub>17 cells act as a bridge between adaptive and innate immunity. Studies have been initiated to define the architecture of the IL-17R family with its ligand–receptor relationships and signal transduction pathways. Current discoveries in the field of IL-17 cytokine receptor biology and its potential implications with respect to emerging therapeutics have been discussed elegantly in a very recent reviews by Gaffen.<sup>1,83</sup>

IL-17RA is a widely expressed receptor that binds IL-17A with high affinity.<sup>2,3</sup> Leukocytes from mice lacking IL-17RA fail to bind IL-17A, and antibodies against IL-17RA inhibit the activity of IL-17A on human epithelial cells, indicating that IL-17RA is critical for IL-17A function.<sup>84</sup> Recently, it has been demonstrated that in infectious models in which neutrophils are crucial for host defense, IL-17RA deficiency results in reduced chemokine levels, reduced neutrophil numbers, and increased susceptibility to infection.<sup>67,71</sup> IL-17RA signaling is implicated in both innate and adaptive

elements of infectious and autoimmune diseases;<sup>72</sup> however, little is known about its signaling in the CNS. One reason may be that IL-17RA is expressed in the CNS at a very low level. Expression of IL-17RA in the CNS of healthy human subjects is undetectable by immunofluorescence, but the receptor was expressed in CNS endothelial cells within heavily infiltrated MS lesions.<sup>81</sup> Given the important role that IL-17A plays in autoimmune diseases of the CNS, it is important to understand responses of CNS cells to IL-17RA signaling.

Human CNS cells express very little IL-17 receptors.<sup>81</sup> Recently, IL-17RA expression in the mouse CNS was documented and compared between control and EAE mice using RT-PCR, *in situ* hybridization, and immunohistochemistry.<sup>85</sup> Results indicated increased IL-17RA expression in the CNS of mice with EAE and constitutive expression of functional IL-17RA in mouse CNS tissue. In humans, it has been demonstrated that IL-17RA is expressed on CNS endothelial cells in MS lesions although it has not been possible to detect IL-17RA expression *in situ* in healthy CNS.<sup>81</sup> CNS cell type-specific expression of IL-17RA was examined in a highly purified, isolated astrocytes and microglial cell cultures (culture technique was adopted from Marek et al<sup>86</sup>), and cytokine/chemokine production was measured in IL-17A-treated cultures to evaluate the functional status of IL-17RA. Experiment on isolated glial cells demonstrated that astrocyte and microglia specifically express IL-17RA *in vitro*, and IL-17A treatment induces biological responses in these cells, including significant upregulation of monocyte chemoattractant protein (MCP-1), MCP-5, macrophage inflammatory protein-2, and KC chemokine secretion. Exogenous IL-17A does not significantly alter the expression of IL-17RA in glial cells, suggesting that upregulation of chemokines by glial cells is due to IL-17A signaling through constitutively expressed IL-17RA. The cellular response elicited in glial cells by IL-17A will likely differ depending on the inflammatory status of the tissue. In addition, cross-communication between IL-17A and other cytokine signaling systems would likely modify the response of glial cells to IL-17A.

## Conclusions

Constitutive expression of IL-17RA in mouse CNS, upregulation during EAE, and its expression on astrocytes and microglia suggest a role for glial IL-17A signaling in mediating CNS inflammation and may be a potential pathway to be targeted by therapeutic interventions. Infiltration of IL-17A-secreting T cells ( $\gamma\delta$  T cells and T<sub>H</sub>17 cells) has clearly been demonstrated to be a pathogenic event in EAE. The resultant cellular and chemokine milieu and its effect on IL-17RA signaling in glial

cells warrant detailed study in the future. Moreover, to date, the fundamental signaling mechanisms used by the IL-17R complex are still unclear. Although the current structure–function studies have primarily focused on the IL-17RA subunit, recent research indicates that the IL-17RC subunit plays a key role in modulating IL-17 responses.<sup>87</sup> Proper regulation of the IL-17 signaling axis results in effective host defense against extracellular pathogens, while aberrant signaling can drive autoimmune pathology. Elucidating the molecular mechanisms underlying IL-17 signal transduction can enhance our understanding of inflammatory immune processes and also create an avenue for therapeutic intervention in the treatment of IL-17-dependent diseases. Recent studies have focused on the role of  $\gamma\delta$  T cells/ $T_H17$  cells and their possible contribution in  $T_H17$ /IL-17 inflammation in MS and EAE. Understanding the role of  $\gamma\delta$  T cells in concurrence with  $T_H17$  cells/IL-17 in virus-induced CNS inflammation also require immediate attention. In sum,  $T_H17$  cells has opened up a new framework for future studies on IL-17 and  $\gamma\delta$  T cells in infection and immunity.

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## Disclosure

The author reports no conflict of interest.

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