

The direct deleterious effect of Th17 cells in the nervous system compartment in multiple sclerosis and experimental autoimmune encephalomyelitis: one possible link between neuroinflammation and neurodegeneration

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Abstract

The processes of demyelination and neurodegeneration in the central nervous system (CNS) of multiple sclerosis (MS) patients and experimental autoimmune encephalomyelitis (EAE) are secondary to numerous pathophysiological mechanisms. One of the main cellular players is the Th17 lymphocyte. One of the major functions described for Th17 cells is the upregulation of pro-inflammatory cytokines, such as IL-17 at the level of peripheral and CNS inflammation. This review will focus on the newly described and unexpected, direct role played by the Th17 cells in the CNS of MS patients and EAE models. Th17 and their main cytokine, IL-17, are actively involved in the onset and maintenance of the immune cascade in the CNS compartment as Th17 were found to achieve brain-homing potential. Direct interaction of myelin oligodendrocyte glycoprotein - specific Th17 with the neuronal cells firstly induces demyelination and secondly, extensive axonal damage. The Th17 cells promote an inflammatory B cell response beyond the BBB through the presence of infiltrating Th follicles. Due to their role in preventing remyelination and direct neurotoxic effect, Th17 cells might stand for an important connection between neuroinflammation and neurodegeneration in a devastating disease like MS. The Th17 cell populations have different mechanisms of provoking an autoimmune attack not only in the periphery but also in the CNS of MS patients.

Keywords: multiple sclerosis, T helper 17, blood brain barrier, ectopic lymphoid structure NG2+

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Introduction

Multiple sclerosis (MS), an autoimmune and neurodegenerative disease of the central nervous system (CNS) is caused partially by a genetic polymorphism and various environmental factors (1).

A major component of the immunopathology of MS is the T cell-driven inflammatory attack from the peripheral immune system towards the CNS (2). MS inflammatory demyelination is buckled with neurodegeneration, albeit the primary mechanism underlying this phenomenon remains in debate.

T helper (Th) 17 cells were described in 2005 by Harrington et al (3). Ever since, various clinical and experimental research studies have attributed numerous roles for this group of Th cells in the immunopathology of MS and experimental autoimmune encephalomyelitis (EAE). The Th17 cells are key players in MS pathogenesis during all the disease phases. Until recently, the medical literature has attributed to the Th17 cells the delineation of initiation and maintenance of the immune attack in MS and EAE. The scientific works regarding the two most important aspects of the implication of Th17 cells in MS immunopathogenesis are chronologically as follows: in 2009, Durelli et al. reported that Th17 lymphocytes increase and expand in the peripheral blood of patients with active MS; in 2013, Rostami et al. demonstrated that the blood-brain barrier (BBB) can be efficiently crossed by the Th17 cells using different pathways from Th1 cells, thus promoting its disruption. The BBB breakthrough is a complex process, sustained by the involvement of Th17 cells. The possibility of Th17 cells to induce the activation of other inflammatory cells in the CNS, to maintain the immune process inside the CNS and to inhibit the remyelination of demyelinated axons was recently described (4-8). Undoubtedly, Th17 cells contribute both to the onset and to the progression of immunological

mechanisms in MS/EAE. Th17 lymphocytes are involved in the self-entertainment of the brain inflammation in MS patients with sustained myelin and axonal damage (8-10).

In EAE, the presence of Th17 cells into the parenchymal CNS white matter that mediates CNS inflammation is possible according to a two-wave proposed hypothesis. First wave is represented by the cell traffic through the choroid plexus into the subarachnoid space, where the Th17 cells encounter antigen presenting macrophages (meningeal antigen presenting cells); the second wave is formed by these re-stimulated Th17 cells that undergo clonal expansion and migrate across the glia limitans basement membrane. Once they reach the white matter, the Th17 cells will initiate tissular destruction, demyelination and axonal injury, that will subsequently lead to neurodegeneration (11-13).

The present review will focus on the recently described and unexpected role of the Th17 cells in the CNS of MS and EAE. These cells and their main secreted cytokine, IL-17 are actively involved in the maintenance of the immune cascade in the CNS compartment as Th17 cells were found to achieve brain-homing potential (11). The levels of Th17 lymphocytes are elevated in the cerebrospinal fluid (CSF) and in the perivascular tissue of clinically isolated syndrome or MS patients during the relapses, and respectively, in the demyelinating brain lesions (11, 14, 15).

1. Th17 cell induce direct neuronal dysfunction

The Th17 cells attack neurons during the acute phase of EAE through the formation of synapse-like contacts with neurons. Kebir et al. described a prevalence of Th17-mediated attacks in MS types with main cerebral involvement unlike spinal forms of MS, where Th1 lymphocytes are predominant (8). Siffrin et al. found direct

interactions between Th17 cells and neuronal cells at the level of the brainstem, mainly during the EAE peak. The direct interaction between myelin oligodendrocyte glycoprotein - specific Th17 with the neuronal cells induces demyelinating lesions and secondary extensive axonal damage. The Th17 cells induce fluctuations in the neuronal intracellular Ca^{2+} concentration, marking the initial neuronal damage. In neuroinflammatory lesions, the major phenomenon found in the early neuronal damage processes was excitotoxicity (Figure1). Numerous different pathophysiologic conditions (traumatic brain injury, stroke, autoimmune diseases) share the same pathways that lead to neurodegeneration through the sustained influx of Ca^{2+} that induces Wallerian degeneration and protease activation that cause cytoskeletal and neurofilament degradation. Th17 cells exhibit a preferential ability to engage in sustained contacts with neurons (16).

In EAE, the neuron/Th17 cell interactions lead to localized Ca^{2+} oscillations provoking axonal and perikaryonal injuries. These injuries are reversible to the administration of the N-methyl-D-aspartate receptor antagonist MK801. This finding demonstrates that Th17 cells have an important, pivotal role in neuronal loss, and not only in demyelination. These data might be the missing piece of the puzzle in immune-mediated neurodegeneration. There is a very complex immune-neuronal dynamics during demyelinating pathologies like MS or EAE (8, 17, 18).

2. Th17 cells and ectopic lymphoid-like structures

In 2007, Magliozzi et al. found that clustered populations of infiltrating immune cells can be found in the brain of about 40% of the secondary progressive MS patients, especially in the

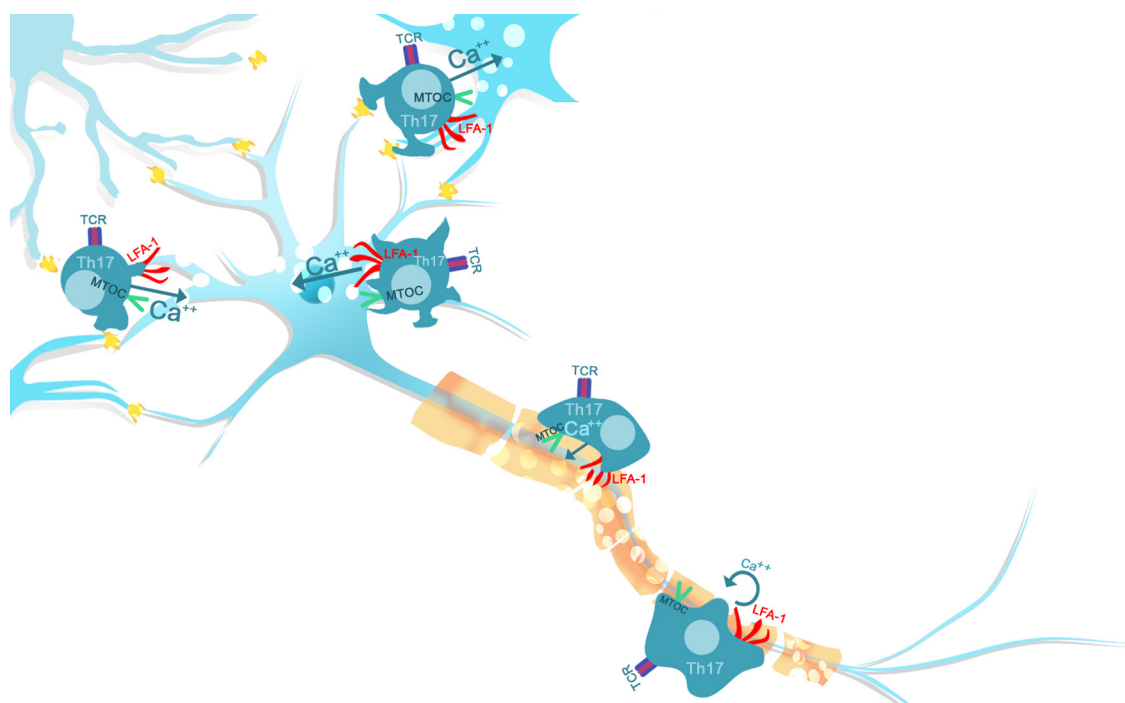


Fig. 1. Direct Th17 cell attack on neurons (MTOC: microtubule organizing center; TCR: T-cell receptor; LFA-1: Lymphocyte function-associated antigen 1; Th17: T helper 17 lymphocyte)

meningeal regions, forming lymphocyte-rich aggregates (19). These aggregates stimulate the cortical demyelination and axonal atrophy that are associated with the progression of neurological dysfunction in MS cases. Ectopic lymphoid structures (ELS) are found in the brain regions with numerous cortical demyelinating lesions (20). These 'follicles' resemble the follicles found in spleen or tonsils, known as secondary lymphoid tissues (19). Th17 cells that produce IL-17 play important roles in the development of these ELS as was demonstrated in animal models of chronic demyelination. Inside these follicles, in the presence of IL-21, B cells differentiate, they promote inflammation and maintain an autoreactive T and B cell population beyond the BBB. This microenvironment of 'germinal centres' supports and balances the interactions of B cells with follicular Th cells. A number of experimental studies performed on mice that express more IL-17, showed that blocking IL-17 signalling decreased the interactions between B cells and CD4⁺ cells needed for the formation of ELS (21, 22). A research performed on transferred Th17 cells showed that these cells begin to take a Th follicular-like phenotype in the mice brain during EAE and also, when transferred into healthy mice recipients, spontaneous ELS formation was obtained (23). IL-17 and IL-21 are important for the formation of spontaneous ELS but also for the development of pathogenic autoantibodies in the CNS. The mechanism through which IL-17 is involved in this process is the following: IL17 upregulates signalling proteins that promote the capacity of follicular Th cells to form conjugates with B cells in the light zone of germinal centres in CNS and promotes follicular Th cells differentiation and stabilisation (21, 22, 24).

Furthermore, the germinal centres include both follicular T cells and follicular regulatory T cells that maintain an optimal response in preventing the auto-emergence of the autoreactive B cells

(25, 26). In MS patients, follicular regulatory cells appear suppressed compared to healthy controls, most likely secondary to a proinflammatory phenotype of circulating Th cells or due to a deficit in CTLA-4 signalling, which is essential for the follicular regulatory Th cell function. Dhaeze T et al, (2015) reports that the ratio between follicular T cells and follicular regulatory T cells is increased in patients compared to controls, indirectly translated as a deficit of pro-inflammatory Th suppression (27, 28).

There is a close relationship between B cells and Th17 cells, leading to an elevated number of B cells and ELS as a mark for Th17 signature in MS (22, 24). Th17 cells promote an inflammatory B cell response inside the CNS through the presence of infiltrating Th follicles (29). Likewise, B cells can support the survival and activities of Th17 cells in MS. In vitro assays showed that the B cells from MS patients display the capacity of coordinating Th17 response against neuro-antigens (30). As a result, in 2018 Quinn and Axtell described an 'inflammatory axis' consisting of Th17 cells, B cells and follicular Th cells (31). Th17 cells through their implication in the formation of the subpial follicles, have a contributory role in the underlying subpial grey matter pathology (4). The propagation of neuroinflammation inside the CNS compartment is done by Th17 cells through the interaction between the lymphotoxin $\alpha\beta$ (LT $\alpha\beta$), a ligand situated on Th17 cells and the receptor LT β R situated on stromal cells. The Th17 cells promote the meningeal microenvironmental re-modelation that has a deleterious effect in MS evolution by inducing the production of proinflammatory cytokines, chemokines and various extracellular matrix proteins. There are speculations that the circulation of these LT $\alpha\beta$ -Th17 cells through the CSF might remodel the meningeal stroma in MS patients and increase the severity of the disease even in the early cases of MS (32) (Figure 2).

3. Th17 and IL-17 inhibits remyelination through downregulation of NG2⁺ cells

Since the description of MS made by Charcot, demyelination is the hallmark of this disease (33, 34). Oligodendrocyte progenitor cells (OPC) are able to differentiate into myelinating oligodendrocytes but also to proliferate and migrate in the demyelinated regions of the CNS. Neuroplasticity is a rather general and blurry term but it is certain that one constituent mechanism is the capacity of OPC to proliferate, to advance to the demyelinated region and to induce the genesis of new myelinating oligodendrocytes. Over the course of MS, OPC tend to gradually lose their remyelination capacity. One of the responsible phenomena is represented by the difficulty of the OPC to be “activated.” Initially, remyelination often follows demyelination. In order for this process to take place, newly recruited OPCs secrete new myelin and restore the myelin sheath around the

axons, protecting them from neurodegeneration. Unfortunately, after a variable period of time, the remyelinating process is exceeded by the speed of demyelination that creates a milieu that limits the efficacy of the reparatory process (35).

The OPCs express gangliosides that are recognized by the neuron-glial antigen2 (NG2, a surface proteoglycan) and the receptor of platelet-derived growth factor alpha. The maturation and the proliferation of NG2 cells generate the remyelination process. NG2 cells are extensively dispersed throughout the CNS. NG2 are a distinct cell population residing inside the CNS. They are distinct from neuronal cells, oligodendrocytes and astrocytes and close to OPCs, and during development they can generate either oligodendrocytes or astrocytes (35).

NG2⁺ glial cells are a specific macroglia population in CNS. The proliferation and maturation of NG2⁺ cells are at the base of the remyelina-

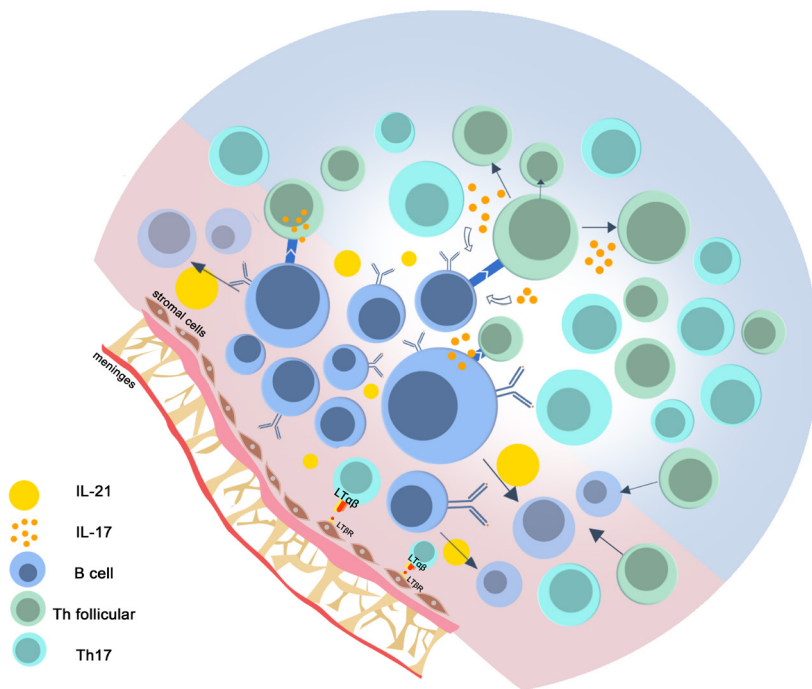


Fig. 2. Involvement of Th17 together with B cells and Th follicular in the “inflammatory axis” of the CNS

tion process. Following demyelination, NG2⁺ glia proliferates and expresses NG2 that furthermore contributes to myelin repair indirectly by giving rise to the oligodendrocytes but also directly by resolution of the glial scar (36, 37). IL-17 participates in the pathogenesis and development of EAE by contributing to brain destruction through demyelination and neurodegeneration (axonal injury). IL-17-mediated proinflammatory effects are supplemented by the role of IL-17 in preventing the remyelination processes of demyelinated axons. It was stated that IL-17 also influences the remyelinating processes, by stimulating oligodendrocyte apoptosis. From this point of view, in EAE, one of the main CNS cellular targets of IL-17 is NG2⁺ glia. Act1, an adaptor for IL-17 receptors also known as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B activator 1) is necessary for IL-17-mediated inflammatory responses. Kang et al. showed that in experimental murine models, IL-17 induced in NG2⁺ glial cells typical inflammatory mediated expressions through

Act1. A reduced EAE severity was experimentally obtained by the deletion of Act1 from NG2⁺ glia (35, 37) (Figure 3). The results published by Zhang et al, determined that in forms of EAE that are IL-17-mediated, NG2⁺ glia might be a CNS cellular target (38). Secondary to neuroinflammation, many studies have found morphological transformation of NG2⁺ glia (39, 40). During the crosstalk between oligodendrocyte, astrocyte and microglia throughout demyelination and remyelination in MS brain, it seems that the Th17 cells play an important role towards neurodegeneration (41).

IL-17 also displays crucial inhibitory effects on the *in vitro* development of oligodendrocyte lineage cells by reducing their survivability through the stimulation of the tumour necrosis factor (TNF)- α -mediated cell death cascade that furthermore induces oligodendrocyte loss through apoptosis. Active oligodendrocytes substantially contribute to the repair processes in demyelinated CNS demyelinated lesions. Lately, there has been increased evidence that one important play-

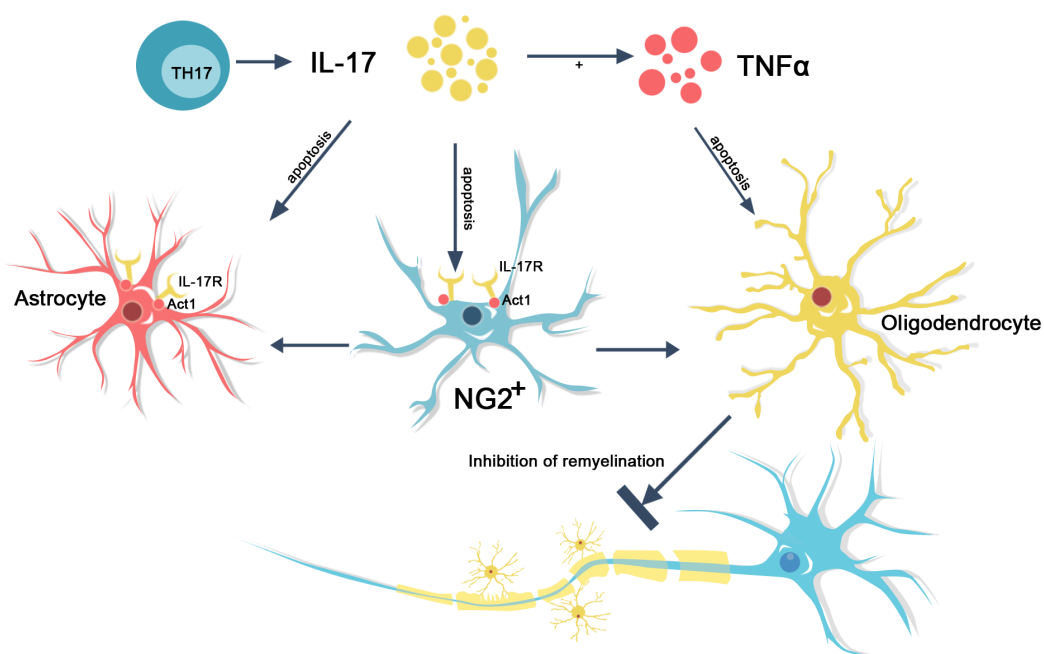


Fig. 3. Th17 – Induced neurodegeneration through inhibition of remyelination

er in the vascular pathology in MS might be the IL-17R, receptor located on astrocytes and microglia, therefore IL-17 can also interact directly with these cells (9). This might represent the one link between inflammation and neurodegeneration in MS and also the explanation for the heterogeneous progressive neurological deficits (42). Of course, the essential question remains open: is oligodendrocyte injury in MS the cause or the consequence of the inflammation? (Figure 3)

Conclusions

In the immunopathology of MS/EAE, Th17 cells are involved early carrying deleterious effects on two very important compartments: the peripheral immune compartment that is activated towards a proinflammatory status and the BBB, which is profoundly disrupted. In the central nervous compartment, Th17 cells continue to have a self-maintained proinflammatory (but also a neurodegenerative) role. Direct interaction of myelin oligodendrocyte glycoprotein - specific Th17 with neuronal cells creates demyelinating lesions and secondary extensive axonal damage. The development of ELS found in the brain of the early but severe cases of MS is supported by interleukins that are secreted by the Th17 cells, such as IL-17 and IL-21 and is a cause of local CNS demyelination. Another effect of the Th17 cells/IL-17 beyond the BBB is the interference with the remyelination process by inhibiting the oligodendrocytes through different mechanisms. Due to their role in preventing remyelination and direct neurotoxic effect, Th17 cells might stand for an important connection between neuroinflammation and neurodegeneration in a devastating disease such as MS. Some of the immune-mediated mechanisms presented might be therapeutically accessible in order to prevent dysfunction in the central nervous compartment.

Abbreviations

Act1 – IL-17R adaptor
 BBB - blood-brain barrier
 CNS - central nervous system
 CSF - cerebrospinal fluid
 EAE - experimental autoimmune encephalomyelitis
 ELS - ectopic lymphoid structures
 LT $\alpha\beta$ - lymphotoxin $\alpha\beta$
 LT β R – lymphotoxin β receptor
 MS – multiple sclerosis
 NF - κ B activator 1 - kappa-light-chain-enhancer of activated B cells
 NG2+ - neuron-glia antigen 2+
 NMDA - N-methyl-D-aspartate
 OPC - oligodendrocyte progenitor cells
 Th – T helper

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Authors contribution

BR (Conceptualization, Methodology, Writing – original draft preparation, Funding Acquisition)
 BL (Investigation, Resources, Software, Conceptualization of the figures and drawings)
 MS (Investigation, Resources, Visualisation)
 SA (Investigation, Formal Analysis)
 MA (Conceptualization, Writing – review and editing, Supervision)

Conflict of interest

The authors declare no conflict of interest.

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