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Role of Effector T-cell Subsets in Multiple Sclerosis: A Comprehensive Review

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Abstract: Neurons are essential components of the nervous system, playing a key role in controlling and coordinating the functions of higher vertebrates. The nervous system also includes the brain and spinal cord, which are crucial for transmitting nerve impulses throughout the body. Over time, neurons can become vulnerable to autoimmune processes, leading to diseases such as multiple sclerosis (MS). In MS, certain subsets of T-cells within the immune system are instrumental in driving the disease. These T-cells mistakenly identify the myelin sheath—the protective covering of nerve fibres—as a threat and attack it. This destruction of myelin disrupts the normal transmission of nerve impulses, resulting in a range of neurological symptoms, including muscle weakness, coordination problems, and cognitive impairments.

The body does have mechanisms to defend against these autoimmune attacks. One such mechanism involves regulatory T-cells (Tregs), which help modulate the immune response and prevent the immune system from attacking the body's own tissues. Additionally, the body can produce anti-inflammatory cytokines and other molecules that work to reduce inflammation and promote repair of damaged tissues.

In this review, we will delve into the specific roles that different T-cell subsets play in the degeneration of neurons, with a focus on the pathogenesis of multiple sclerosis. We will also explore the body's natural defense mechanisms against these harmful T-cells, including the role of regulatory T-cells and other immune-modulating factors. Understanding these processes is crucial for developing new therapeutic strategies to combat multiple sclerosis and potentially other autoimmune diseases affecting the nervous system.

Keywords: Neurons, Multiple sclerosis, T-cells, Neurological symptoms, Natural defense, Cytokines, Autoimmune diseases

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune disease that targets the neurons (nerve cells) of the central nervous system (CNS) and peripheral nervous system (PNS) resulting in

nerve cell damage and thus disrupting the communication between the brain and the body (Thompson *et al*., 2018). MS attacks the myelin sheath on the axon resulting in its degradation and lowering of impulse transmission (Weinshenker, 1996).

It has been observed that the T cells of an individual's immune system attack its neuronsand infiltrate the CNS and by breaking down the blood-brain barrier (BBB), enter into the brain parenchyma, targeting the Schwann cells and oligodendrocytes of the myelin sheath and tears them which results in the formation of naked neurons which leads to the formation of lesions. This tearing of the myelin sheath mainly prolongs the impulse transmission along with various symptoms in the individual like vision loss, pain, fatigue and impaired coordination (Frischer *et al*., 2009).

On a world scale Northern European descent are at high risk of developing MS. Twice as many women as men are affected with the disease (Hauser *et al*., 2008). The onset of MS has been reported in all age groups and individuals aged 18 to 50 make the most susceptibility to the disease (Naseri *et al*., 2021).

Environmental factors like migration are seen to be a vital cause of MS. Genetic factors can lead to the development of MS in an individual. The main concept in the development of autoimmune diseases is the break in T-cell tolerance (Cheng and Anderson, 2018). The AIRE (autoimmune regulator) gene present in the medullary thymic epithelial cells (MTECs) controls the mechanism of tolerance of T-cells in the thymus also known as the central tolerance or negative selection. This gene synthesizes the peripheral tissue peptides (autoantigens) within the thymus and present them to the immature self-reactive T-cells, eliminating those with high avidity towards these autoantigens (Fig. 1)(Anderson and Su, 2016).

In case the immature T cells reactive to autoantigens escape negative selection in the thymus traffic to the periphery and attack self-tissues causing autoimmune diseases. The mechanism of negative selection is of high importance in humans as mutations in the AIRE gene lead to the occurrence of Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED), a severe multi-organ autoimmune disease (Cheng and Anderson, 2018).

Mature T-cells that are reactive to antigens become activated, differentiate into various subsets, responding by releasing cytokines such as IFN-γ, IL-4, IL-5, IL-13, IL-17, IL-21, and IL-22 (Fig. 2). Multiple sclerosis (MS) is identified as a CD4+ specific disease, where activated CD4+ Th1 and Th17 cells, which are specific to myelin peptide antigens, recognize and bind to these antigens, causing damage to nerve axons (Axisa and Hafler, 2016).

FOXP3+ regulatory T-cells (Tregs) are produced in abundance through negative selection, maintaining immune homeostasis by suppressing reactive T-cells in the peripheral tissues (Fig. 1) (Sakaguchi *et al*., 2007). The FOXP3+ gene is crucial for the production and maintenance of Tregs. A deficiency or mutation in this gene can inhibit the suppression of self-reactive T-cells that bind to myelin peptide antigens, thereby promoting the development of MS.

Pathogenesis of MS

Proinflammatory CD4+ Th1 and Th17 cells are majorly involved in the development of autoimmune diseases by the release of IFN-γ, TNF-α and IL-17 (Zhu *et al*., 2010). According to studies it has been observed that both IFN-γ and IL-17 tend to escalate the immune activation by inducing the release of additional proinflammatory mediators either by augmenting antigen presentation or by directly affecting the viability or function of CNS resident cells. *In vitro* studies have reported that naïve T-cells are induced to differentiate into Th-17 in response to IL-6 and TGF-β whereas, IL-12 tend to induce differentiation of T-cells into Th1 cell type (Damsker *et al*., 2010). IL-6 and IL-12 are

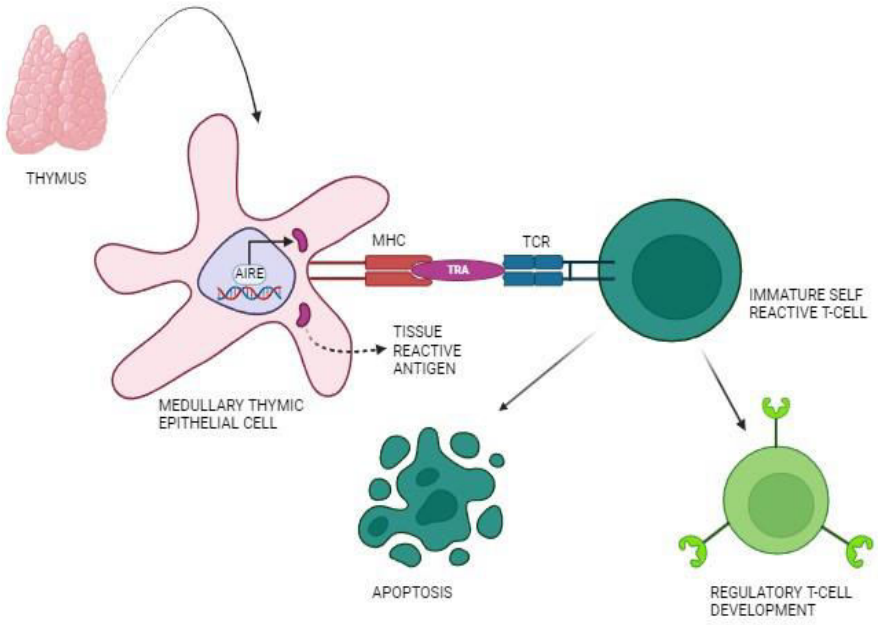

Fig. 1: Central tolerance.

primarily produced by APCs of the myeloid lineage such as microglia and infiltrating macrophages; astrocytes can also secrete proinflammatory cytokines potentially contributing to the differentiation and activation of the Th1 and Th17 cells in the CNS (Choi *et al*., 2014).

CD4+ Th1

IFN-γ is the primary and signature cytokine secreted by Th1 T-cells (Table 1) which increases the expression of MHC molecules by cells in the CNS (Ottum *et al*., 2015) and directly affects the activation and viability of other CNS resident cells.

IFN-γ is seen to activate microglia to become phagocytic in MS susceptible patients which present myelin protein antigens to T-cells. IFN-γ can also directly kill oligodendrocytes (Fig. 3) (Aloisi *et al*., 2000). In the MS patients the increased level of IFN-γ elevates the frequency of active lesions in the brain (Olsson, 1992). IFN-γ also induces dendritic retraction and inhibits the formation of synapse which effects the faster transmission of the impulse (Kim *et al*., 2002). IFN-γ augments the expression of MHC-molecules and enhances the antigen presenting ability of myeloid cells in the meningeal or perivascular sites to restimulate myelin-antigen-specific CD4 or CD8 T.

In EAE models it has been reported that Th17 cells get converted into ex-Th17 cells which lack in IL-17 but can express IFN-γ at high levels which follows the same fate of attacking the myelin protein on axon (Hirota *et al*., 2011).

CD4+ Th17

Th17 T-cells secrete the proinflammatory cytokine IL-17 and inflammatory subtype IL-17A, IL-22 and IL-21 (Table 1) which usually provide defence against bacteria and fungi (O'Quinn *et al*., 2008). The immune pathological responses get promoted by IL-17 through its combining ability with other cytokines, increasing the secretion of proinflammatory cytokines, chemokines, and complement proteins (Onishi and Gaffen, 2010). These effects of IL-17 help to maintain the Th17 population and also activates microglia to initiate the recruitment of lymphocyte, macrophages and neutrophiles which causes inflammatory damage to the neurons by attacking the myelin sheath (Fig. 3) (Steinman, 2007). Th17 cells efficiently migrate

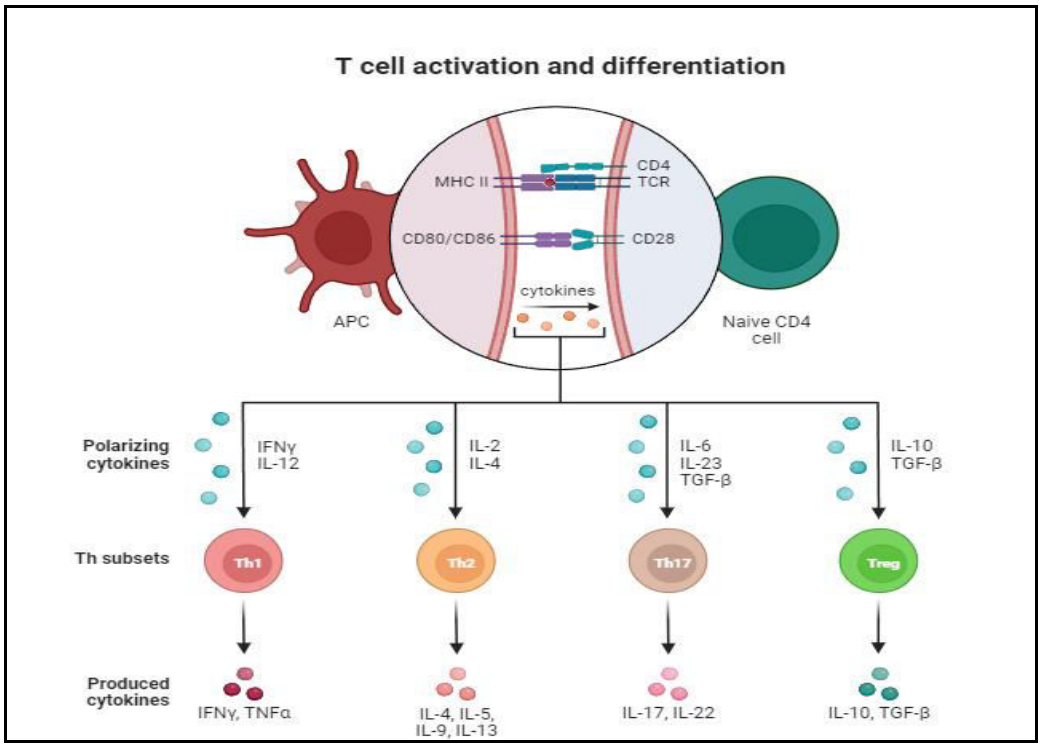

Fig. 2: T-cell activation and differentiation by formation of immunological synapse.

Table.1: The subsets of mature T-cells

CD4+Th1 T-cells	**CD4+ Th2 T-cells**	**CD4+Th17 T-cells**	**CD4+ T-reg cells**	**CD8+ T-cells**
The major proinflammatory CD4 T-cell populations. Produce IFN-γ and tumor necrosis factor (TNF-α). In MS, Th1 cells are found at increased frequency in CNS lesions.	Associated with allergic reactions. Produce IL-4, IL-5 and IL-13.	The major proinflammatory CD4 T-cell populations. Secrete interleukin; IL-17, IL-21, and IL-22. In MS, Th17 cells are also found at increased frequency in CNS lesions.	suppress immune response and maintain homeostasis and self-tolerance. Tregs are able to inhibit T cell proliferation and cytokine production and play a critical role in preventing autoimmunity.	Classical function-killing of target cells via granzyme and perforin release in cytosol.

across the BBB in comparison to Th1 cells, bind and recognise the self-antigens of myelin protein and secrete high levels of IL-17 (Kebir *et al*., 2007). An increased level of IL-17A cytokine in the cerebrospinal fluid leads to neutrophil expansion and BBB disruption (Kostic *et al*., 2015).

The other cytokines IL-21 and IL-22 produced By Th-17 cells regulate immune cell activation, survival and promote BBB disruption respectively (Kebir *et al*., 2007; Tzartos *et al*., 2011; Xu *et al*., 2013; Rolla *et al*., 2014; Perriard *et al*., 2015). Th17 cells that express both IL-17A and IL-22 show cytolytic activity on neurons by the secretion of granzyme B (Kebir *et al*., 2007).Also, the extra-cellular secretion of granzyme B is been seen to kill and destroy neurons by targeting the

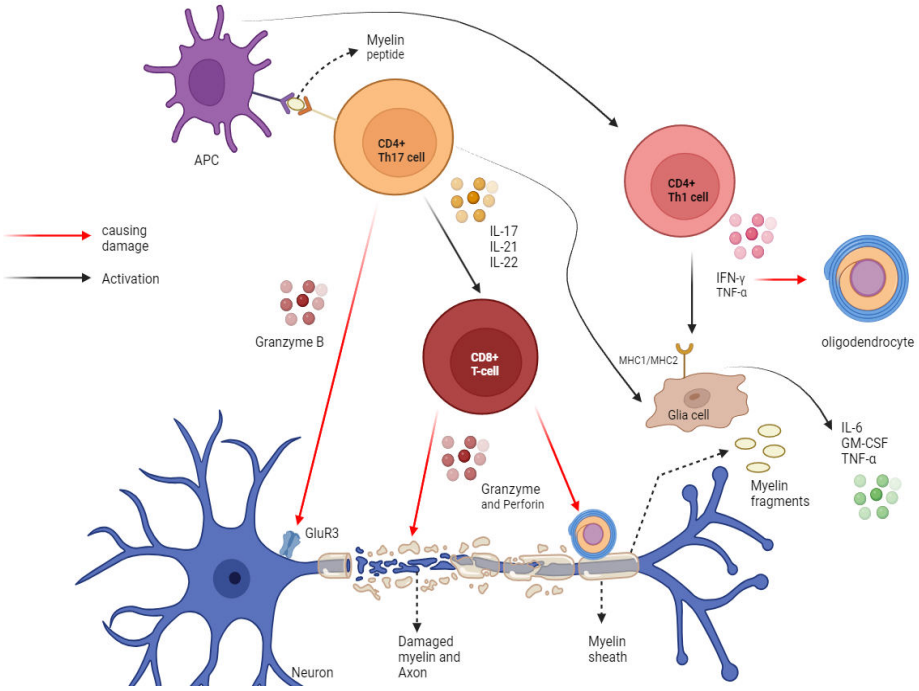

Fig. 3: Effector T-cells in CNS leading to MS.

glutamate receptors i.e. GluR3 (Fig. 3) (Ganor *et al.*, 2007).

CD8+ T-cells

MS patients, in their plaques show biased lineage towards autoreactive CD8+ T-cells (Huseby *et al.*, 2012). The classical and primary function of activated effector CD8+ T-cells is killing through the mechanism of granzyme and perforin (Table 1) (Bevan, 2004). As the CNS is highly susceptible to viral attacks, CD8+ T-cell majorly take upon the role of antiviral defence, but also certain autoreactive CD8+ T-cells can secrete the cytokines IFN-γ and IL-17 (Kish *et al.*, 2009; Salinas *et al.*, 2010).

Initial inflammation caused by the CD4+ T-cells induce the CNS resident cells to express MHC-1 molecule which in turn presents self-antigens to the CD8+ T-cells and make them an easy target for damage and demyelination (Fig. 3) (Gobin *et al.*, 2001). Perivascular space of active MS lesions express cytokine releasing CD8+ T-cells which secrete IL-17 which are all contained within a $CD161^{high}$ subset of CD8 cells and associate with the disease (Annibali *et al.*, 2011).

Regulatory T-cells (*T-reg*)

T-regs play an inhibitory role in manifestation of autoimmune diseases (Table 1). These cells are formed in the medulla of the thymus during central tolerance and possess suppression on the autoreactive T-cells activation in the peripheral tissue region, this is one of the peripheral tolerance mechanisms (Fig. 1) (Dominguez-Villar and Hafler, 2018). FOXP3+ T-reg cells consist of CTLA-4 in high level which is the inhibitory receptor of CD28 family. This receptor interacts with B7-complex on the APC and reduces its availability to CD28 on effector T-cells causing blockage in the activation and differentiation of T-cells by the process of trans- endocytosis (Fig. 4) (Campbell, 2015). Through this interaction the production of inflammatory cytokines is hampered in the peripheral tissue region which eventually helps in checking the manifestation of autoimmune diseases.

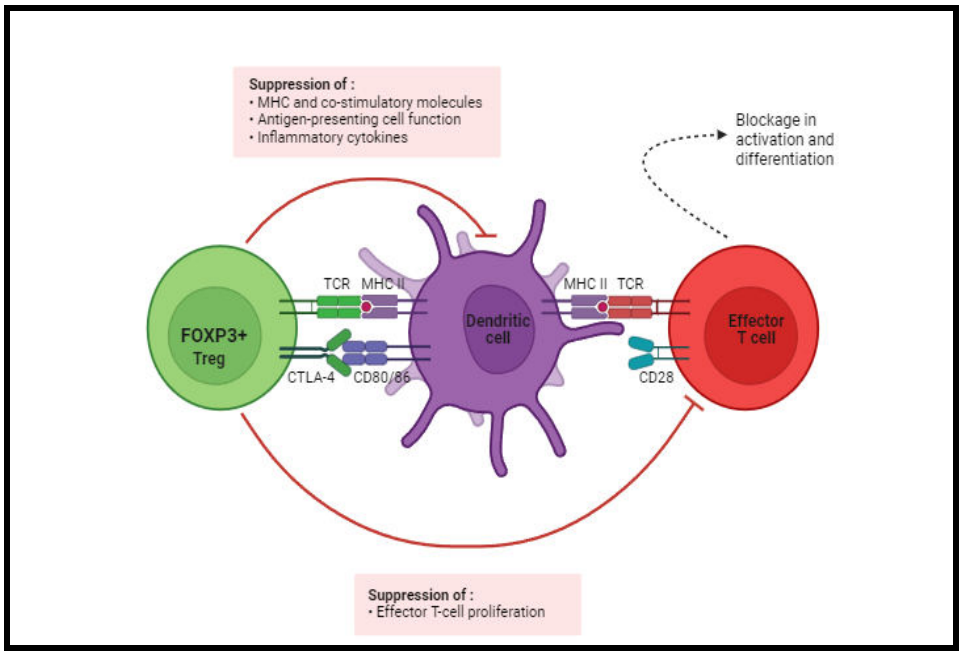

Fig. 4: Role of regulatory T-cells in maintaining homeostasis of immune system.

Escape of effector T-cells from the regulatory T-cells mediated suppression

Effector T-cells become resistant to regulatory T-cell mediated suppression when their ratio to the T-regs is higher because of strong activation of inflammatory cytokine milieu and intracellular modification of signalling pathways due to mutations (Buckner, 2010).

Elevated levels of IL-6 play a pathological role in autoimmune diseases including MS (Yao *et al*., 2014). STAT3, a protein that helps in cell proliferation, cell migration and apoptosis is phosphorylated by IL-6 and thus confer resistance of conventional T-cells to T-reg mediated suppression. Higher level of P-STAT3 serves in the severity of MS (Schneider *et al*., 2013).

Experiment on murine models by activation of DCs through TLRs showed overcoming of T-reg mediated suppression by production of IL-6. Although IL-6 is not alone sufficient for the overcoming it works together with TNF-α produced by TLR-activated DCs to induce resistance to suppression (Pasare and Medzhitov, 2003).

IL-7 and IL-15 having common γ chain play major role together in the induction of resistance in effector T-cells against suppression from T-regs by directly acting on these effector T-cells and activating PI3K-Akt pathway (Hofmeister *et al*., 1999; Ben Ahmed *et al*., 2009; Mishra *et al*., 2014).

Symptoms and Treatments of Multiple sclerosis

Multiple sclerosis causes symptoms like vision loss, weakness, neural in coordination, tremor, sensory loss, pain, fatigue, poor concentration, slowed thinking, poor memory, depression, anxiety, epileptic seizures etc. The brain lesions detected in MRI can be studied in the diagnosis of the disease.

Although there is no permanent cure to MS, reducing or neutralizing Th17 responses by IFN-β treatment in patients can help in the reduction of inflammation in CNS (Sweeney *et al*., 2011). IFN-β medications reduce inflammation and promote nerve growth.

T-reg cell-based therapies to MS patients is an effective therapeutic option (Samuel *et al*., 2019). They are immunosuppressive in nature through various mechanisms such as secretion of inhibitory cytokines such as IL-10 and TGF-β, promotes metabolic disruption of effector T-cells

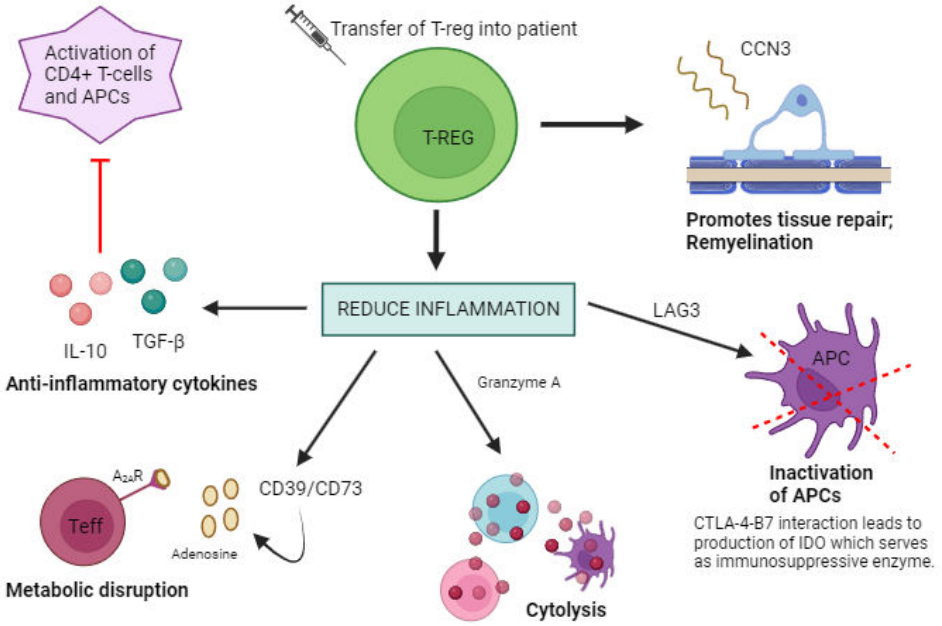

Fig. 5: Immunosuppressive actions of T-reg therapy in multiple sclerosis.

by catalysing the generation of pericellular adenosine which activates the adenosine 2A receptor ($A_{2A}R$), direct cytolysis of cells by granzyme-perforin mediated pathway and APC inactivation (Vignali *et al*., 2008). T-reg cells also induce tissue repair and potentially participate in remyelination by increasing the level of growth regulator CCN3 in the CNS (Fig. 5) (Dombrowski *et al*., 2017).

However, this therapy option may hold a few limitations such as autologous transfer of T-regs may show impaired functioning and unresponsiveness (Schneider *et al*., 2013; Duffy *et al*., 2018). The dose of T-reg administration should be set before administration into the patients to avoid undesirable levels of immunosuppression which may pre-dispose to infection and malignancy (Singer *et al*., 2014). The inflammatory environment of the CNS may affect the suppressive function of T-regs when they are administrated into the patient derailing their immunoregulatory role and hindering their plasticity (Delgoffe *et al*., 2013; Sakaguchi *et al*., 2013).

Oral drugs like corticosteroids are given to the patients to reduce nerve inflammation. Physiotherapy, counseling sessions, and muscle relaxants are given to the patients regularly for maintaining a healthy balanced condition to them.

Conclusion

In conclusion, effector T-cell subsets are pivotal in the development of multiple sclerosis (MS). Self-reactive proinflammatory Th1 and Th17 cells contribute to the disease by recognizing myelin peptides as antigens and releasing cytokines in the central nervous system (CNS), leading to inflammation and destruction of the myelin sheath. This process disrupts nerve impulse transmission and manifests as the symptoms of MS.

Regulatory T-cells (Tregs) play a crucial role in mitigating this autoimmune response. By suppressing the activity of CD4+ and CD8+ T-cells, Tregs help maintain immune homeostasis and prevent excessive autoimmune damage.

Although there is no permanent cure for MS,

numerous therapies have been developed to manage the disease. These treatments aim to control inflammation and enable patients to lead relatively normal, healthy lives under continuous medical supervision. By reducing the frequency and severity of relapses, slowing disease progression, and managing symptoms, these therapies significantly improve the quality of life for those living with MS.

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