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REVIEW OPEN ACCESS

Immunosenescence and Multiple Sclerosis: A Literature Review

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Abstract

Introduction: Multiple sclerosis is a chronic inflammatory disorder characterized by the demyelination of central nervous system neurons, giving rise to various motor and non-motor impairments. Aging has been strongly associated with inflammation and immunosenescence, and it is believed that the dysfunction of regulatory T-cells is the central complication in the maintenance of peripheral immunity. CD4+ T-cells and Th17 cells seem to play a crucial role in autoimmune inflammation and are important in the pathophysiology underlying multiple sclerosis. In this systematic review, the link between aging and T-cell function will be explored as well as its implication in MS pathophysiology.

Methods: A literature review was conducted using databases such as PubMed, NCBI, and Scopus. Relevant primary literature describing theories or results of an experiment and review papers were selected. Data from primary articles were analyzed to explore the association between aging and MS, as well as its contribution to immunosenescence.

Results: There exists a strong association between aging and the pathophysiology of MS which was suggested by a multitude of laboratory studies. Animal models of experimental autoimmune encephalomyelitis have demonstrated the immunological mechanisms of this disease by highlighting differences in T-cell presence and function in healthy people versus MS patients.

Discussion: According to numerous studies, chronic inflammation is recognized as a sign of aging, rendering it one of the key contributors to neurodegenerative diseases like MS. The implication of regulatory T-cells in MS is crucial due to its necessity for the maintenance of immunosuppressive activity, which has been found to deteriorate with age. Myelin antigens supplied by microglial cells reactivate autoreactive CD4+ T-cells infiltrating the CNS, producing a cascade of immunological responses that lead to demyelination and tissue death.

Conclusion: This literature review finds that MS is largely T-cell mediated and that the aging process heightens chronic inflammation, leading to the destruction of neurons in the CNS.

Keywords: multiple sclerosis; immunosenescence; T-cells; inflammation; aging

Introduction

Affecting approximately 2.5 million people worldwide, multiple sclerosis (MS) is the most common neurological disease among those aged 20 to 40 [1]. With an estimated 77 000 Canadians living with MS, Canada has one of the highest incidences of this disease in the world [2]. It is characterized by the demyelination of nerve fibres in the central nervous system (CNS) [3], which occurs when the immune system attacks the myelin sheaths that enable rapid transmission of electrical currents along the axon [4]. MS lesions can emerge anywhere in the CNS, though they are most prominent in the optic nerve, spinal cord, brain stem, and periventricular areas [5]. Impairment of nerve fibres causes varying degrees of symptoms that have been categorized as non-motor and motor. Non-motor symptoms are comprised of fatigue, depression, cognitive dysfunction, and insomnia, while motor symptoms include muscle weakness, spasticity, and impaired balance [5]. A relapsing-remitting phase, called relapsing-remitting multiple sclerosis (RRMS), is common during the start of the disease [6], distinguished by relapses or the emergence of new symptoms followed by periods of remission, during which symptoms may subside or improve [4]. RRMS may later progress into a secondary progressive phase (SPMS) [7], marked by worsening symptoms. RRMS is more prevalent among the younger demographic affected by this disease. However, it is not the case that RRMS will progress into SPMS in every patient [7].

Current literature suggests that chronic inflammation is one of the primary causes of MS [8,9,10]. Aging has proven to have substantial effects on the progression of this disease, since remyelination and other physiological functions become less robust in aging adults [11]. Inflammation in MS is described as a state in which inflammatory cells are not cleared from the CNS [12], and as long as the disease process is active, inflammation is present at all phases of MS [7]. Molecular mimicry is one of the most widely accepted theories for explaining the

induction of autoimmunity, stating that foreign antigens are similar enough to native antigens to launch an autoimmune response [13]. It is hypothesized that active T-cells travel to the CNS and are reactivated by myelin antigens [14] triggering reactive immunological responses and resulting in the generation of self-reactive antibodies that induce inflammation [15]. Therefore, we find that an excessive immune response takes place, emerging in elderly adults as a state of chronic inflammation [16]. It is important to keep in mind that aging does not necessitate the development of autoimmune diseases, but with older age comes an exacerbation of the symptoms of MS.

T-cells are also imperative for adaptive immune system responses [17] and have been implicated in mediating autoimmune inflammation. For instance, it is well documented that effector CD4+ T-cells play a role in supporting the production of antibodies by B-cells and recruiting white blood cells to the site of infection to launch immune responses [18]. The ability for the immune system to encounter new antigens, respond effectively, and develop immunological memory is reflected in the high number of naive CD4+ T-cells [19]. In older adults, a set of functional changes in T-cells emerges [20] and manifests as a reduced efficiency of innate and adaptive immune responses [21]. One example pertains to antigen binding in older adults, in which CD4+ T-cells show diminished T-cell receptor signalling and altered secretion of different cytokines [22].

Other alterations in T-cell populations, such as increased regulatory T-cells and clonal growth of T-cells, can also have a harmful impact on a novel immune response in older people [22]. Moreover, the synthesis of new T-cells in the thymus decreases with age and cannot satisfy the necessary demand for replacement in this demographic [23]. As a result, most of the T-cell population is reduced to memory T-cells, leading to the deregulation of inflammatory responses and immunological self-tolerance [24]. In addition, older adults show a decreased ability in eliciting antigen-specific T-cell responses due to deficiencies in naive T-cells [25]. One explanation is that the number of B cell and T-cell progenitors in the bone marrow and thymus decreases dramatically with age [21]. Therefore, MS is thought to primarily be a T-cell-mediated autoimmune disease [4] since T-cells are critically involved in the immunosenescence of older adults.

In this review, current literature regarding the role of regulatory T-cells in MS will be compiled and the relationship between dysregulated T-cell function in aging adults and MS will be highlighted.

Methods

A comprehensive literature review of a total of 79 papers from the 1930s to 2021 was conducted with the aim of understanding how aging contributes to MS. The databases consulted were PubMed, NCBI, and Scopus for primary research articles and recent reviews. Keywords used in this search included: “Multiple sclerosis”, “MS”, “regulatory T-cells”, “immunosenescence”, “symptoms of MS”, “pathophysiology of MS”, “aging AND multiple sclerosis”, “aging AND T-cells”, “immune system AND multiple sclerosis”, “CD4+ T-cells AND aging”, “immunosenescence AND multiple sclerosis”, “chronic inflammation AND T-cells”, “FOXP3 AND T-cells”, “FOXP3 AND multiple sclerosis”. Data from the last 20 years was rigorously analyzed to be used as part of our results, while data older than 20 years was used to establish the early origins of this disease.

Results

What is MS?

Classified as a neurodegenerative disorder, demyelination is a hallmark trait of MS. Interestingly, axons are greatly preserved despite the loss of myelin with varying amounts of axonal destruction between different patients [26]. Symptoms may occur independently of each other or together and vary from patient to patient. Common symptoms include, but are not limited to cognitive deficits, bladder dysfunction, double vision, limb weakness, fatigue, and ataxia [27]. Although there is no single cause of MS, the environmental [28], genetic [29], and infectious [30] contributions of this disease have been studied. There is no universally accepted marker for the diagnoses of MS, but clinical features and laboratory analyses, such as magnetic resonance imaging (MRI), are often employed [31]. Approximately 85% of patients present a relapsing-remitting form while 15% show steady progression [32]. Some research has found that females have a more positive MS prognosis compared to males [33] but some have found no significantly relevant gender differences in this disease [34]. Immunological dysfunction is believed to underly MS pathology, namely, T-lymphocytes [35], which enter the CNS from the periphery and induce inflammation resulting in the demyelination of neurons and axonal loss [36]. Patients with MS have distinct problems as they age, owing to an increasing prevalence of age-related and MS-related comorbidities, as well as the move from an inflammatory to a neurodegenerative character [37].

CD4+CD25 T-cells and MS

It was once speculated that lead absorption into the body [38] or *Spirochaeta mylophthora* infection [39] were causes of MS, but the discovery of T-cells in 1961 by Jacques Miller turned the tide, and the role of T-cells in MS pathology became increasingly explored. The findings that lower amounts of T-cells in the cerebrospinal fluid (CSF) was detected in MS patients as compared to healthy patients were detailed by Kam-Hansen [40] in 1970, contributing to the growing body of T-cell literature and its role in MS disease occurrence. That same year, Bach and colleagues [41] performed indirect immunofluorescence using monoclonal antibodies to understand the role of suppressor T-cells in MS patients They found reduced suppressor T-cell numbers in these patients, though they

were unsure of the necessity of suppressor T-cells in the pathology of MS. Later in 1992, Zhang and colleagues [42] noted that MS plaques are marked by the presence of activated T-cells, which expressed IL-2 receptors and class II MHC positive macrophages. Thus, in the 20th century, it slowly became understood that there was an underlying immunopathogenesis exacerbating this disease.

CD4+ CD25+ cells constitute a subset of regulatory T-cells (Treg) that emerge throughout the prenatal period, functioning to prevent autoimmune diseases in humans [44]. Necessary for immunological tolerance, they control autoimmunity by reducing the number of self-reactive T-cells [44]. Viglietta and colleagues [45] were among the first to examine CD4+CD25+ regulatory and CD4+CD25+ responder cell populations in MS patients, reporting that individuals with MS exhibited reduced CD4+CD25+ Treg activity. When compared to healthy people, they discovered that the Treg population's effector activities were markedly lower in patients with MS. Additionally, they were able to demonstrate that defects in CD4+ CD25+ Treg cells may trigger autoimmune diseases. Huan *et al* [46] were the first to establish a direct link between MS patients and aberrations in transcription factor forkhead box P3 (FOXP3protein expression levels in CD4+CD25+ Tregs, suggesting that deficient FOXP3 levels indicate a problem with Treg immunoregulation. Accordingly it was also reported by Frisullo *et al* [47] that increased FOXP3 expression in circulating CD4+ CD25+ T-cells and an increase in Tregs may affect the sustainability of tolerance in the relapsing-remitting phase of MS. In addition, a lower percentage of CD4+CD25+FOXP3+ T-cells was observed in RRMS patients at 1.69% versus in remitting patients at 2.78%.

In the CNS, it is thought that the CSF is the primary entry route for T-cells [48], though they can be granted passage through the blood-brain barrier (BBB) as well. MS can be attributed to autoimmune T-cell responses in the CNS, which can initiate inflammation by activating myelin-specific T-cells in the periphery in response to antigen-presenting cells (APC) presenting a self-antigen [49]. Moreover, CD4+ T-cells secreting IL-17 were found in abundance in active lesions of MS patients, indicating that a pathological immune response develops when inflammatory cells become dysregulated [50]. McGeachy and colleagues [51] investigated autoimmune pathology within the CNS using experimental autoimmune encephalomyelitis (EAE), an animal model of brain inflammation. Their results showed that depletion of CD25+ T-cells not only resulted in the inhibition of natural EAE recovery but also identified that these cells control inflammatory lesions at effector sites. Haas *et al* [52] also detailed how the impaired suppressive ability of CD4+ CD25+ Tregs was present in MS patients even though they possessed similar amounts of Tregs in the blood and CSF. These results implicate CD4+CD25+ Tregs in the pathogenesis of MS.

Demyelination events are hypothesized to be mainly mediated by CD4+ T-cells of the Th1 and Th17 [36]. Specifically, IL-17 producing Th17 regulates autoimmune diseases due to its control of inflammatory responses [53] (refer to Figure 1). Notably, IL-17A was observed in elevated levels in MS plaques compared to healthy participants in a study by Lock and colleagues [54]. In EAE, large amounts of autoreactive Th17 cells were present in the CNS, and after EAE recovery, high levels of Th17 cells were still present in the immune periphery [55]. RRMS patients display greater numbers of Th17 cells in the CSF after relapse as opposed to RRMS patients in remission [56]. Accordingly, when matched CSF and blood samples from multiple sclerosis patients were analyzed, the frequency of Th17 cells in the CSF was two times greater than in the peripheral blood in both relapse and remission individuals. What's more, is the finding that patients with inflammatory diseases other than MS had a higher frequency of Th17 cells. Taken together, their data proposed that Th17 cells could be a relevant pathogenic contributor in MS. Additionally, the implication of CNS MHC class II expression in demyelination was explained when, for the first time, *in vivo* results presented that it may worsen CNS demyelination [57]. However, they found that T-cells do not play a role in remyelination. Nevertheless, after transferring Tregs into immunodeficient mice (RAG1 -/-), Tregs were not detected in the CNS but did dampen inflammatory responses by decreasing T-cell proliferation, dendritic cell activation, and proinflammatory cytokine and chemokine production [58]. Since the autoimmune T-cells that regulate antigen-specific immune responses against rhMOG, a GTP-binding protein, are impaired MS patients exhibit lower CD4+CD25+ T-cell binding, impacting their ability to inhibit rhMOG-specific effectorT-cell immunological responses when compared to healthy adults. [52]. These findings allude to an indirect regulatory function of Tregs in inflammation that serves to exacerbate the process of demyelination, rather than a direct association.

CD4+ T-cells

Naturally occurring CD4+CD25+ T-cells are produced by the thymus as a separate subpopulation of T-cells [59] and are derived from naïve CD4+ T-cells in the periphery [60]. These naturally occurring Tregs, which account for 5–10% of peripheral CD4+ T-cells in circulation, have significant immunosuppressive properties [61]. Similar to all CD4+ T-cells, Tregs possess T-cell cross-reactivity that allows for the recognition of MHC class II molecules [17], implying that they may be antigen-specific. Self-reactive T-cells are destroyed via apoptosis or removed by phagocytes in the thymus during development to prevent autoimmune reactions to self-antigens [62]. In 1995, Sakaguchi *et al* [63] uncovered the importance of CD25+CD4+ cells in the maintenance of self-tolerance by means of the downregulation of immune responses to both self and non-

self-antigens. Likewise, the discovery that genetic defectiveness of the FOXP3 was associated with autoimmune and inflammatory syndrome in humans and mice advanced our knowledge of the role of CD4+ T-cells in self-tolerance [64]. Localized on the X chromosome [65], FOXP3 is a transcription factor necessary for the formation and activity of CD4+ CD25+ regulatory T-cells. It also aids in the suppression of IL-2 and effector T cytokines [66]. Recent work also documents that the loss-of-function of the FOXP3 gene manifests as terminal and systemic inflammatory lesions in mouse models and human patients [67]. In addition, a mutation in the FOXP3 gene as a transcription factor for Tregs plays a vital role in the emergence of autoimmune diseases [68]. Diseases include rheumatoid arthritis (RA), diabetes mellitus type I, celiac disease, and MS. Hence, there is evidence of the importance of CD4+CD2+ T-cells in regulating self-tolerance and inflammatory responses.

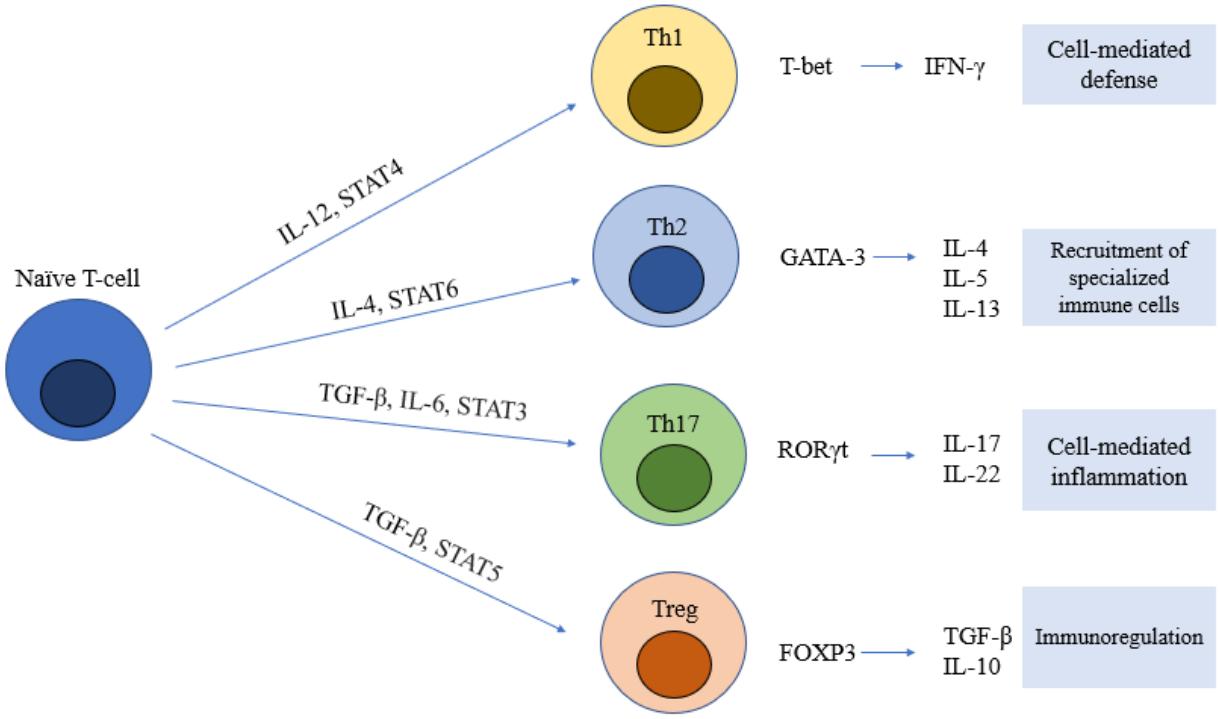

Figure 1. Naive T-cells undergo differentiation into specialized effector cells in the thymus (Created using Microsoft PowerPoint).

Aging and its Implications in MS

It is widely accepted that aging is associated with both an increase in the number of Tregs and Treg function [69]. Since it is the responsibility of Tregs to attenuate immunological responses, their upregulation is correlated with a disability in controlling autoimmunity. Using BALB/c mice, Sharma *et al* [70] demonstrated that there were more CD4+CD25+ Tregs in the spleen and lymph nodes of older BALB/c mice compared to younger mice when they tested aged mice's ability to reject transplanted tumours. Moreover, they reported that CD4+ and CD8+ Tregs contribute to immune suppression in older mice and restoring immune responses in these mice may require depletion of CD25+ cells. Zhao and colleagues [71] discussed the accumulation of FOXP3 cells in older mice and reported that they are able to maintain functionality. As previously found in old BALB/c mice, elderly C57BL/6 mice had a much higher proportion of FoxP3+CD4+ T-cells in several lymphoid organs than young mice [71]. Taken together, these data suggest a change in T-cell levels as a result of aging. With respect to the consequences of increased Treg numbers, it is thought to result in weaker antipathogen responses, which may explain the elevated risk of disease recurrence as it may lead to disease reactivation in adults 60 years and older because there are more dysregulated T-cells present [16].

Uncontrolled inflammation may aggravate the aging process and induce age-related chronic illnesses [72]. Immunosenescence is defined by a reduction in cell-mediated immune activity as well as humoral immunological responses [73]. The buildup of cell debris and self-antigens resulting from cellular stress or viral infections is the primary trigger engaged in the advancement of inflammaging [74]. Changes in Treg cell activity appear to play a vital role in immunological senescence and help in increasing vulnerability to immune-

mediated illnesses as people get older [69]. In healthy people, the proportion of CD4+CD25+ Tregs has been found to range from 0.6 to 8.7% of CD4+T-cells and appears to be age-dependent [65]. Newborns typically show high amounts of CD4+ CD25+ T-cells and that number steadily declines from ages 2 to 3 due to T-cell production [75]. Moreover, a lack of T-cell creation is common in older age, but there is an increase in CD4+CD25+ Tregs [76]. Given this, an asymmetry in Treg homeostasis predisposes older adults to immunological dysfunction, explaining their increased risk of immune-mediated illnesses [77]. CD4+ cells are more resistant to apoptosis, and Treg suppression shows that immunosenescence in MS matches age-related dysfunctions [6].

Certainly, as people become older, senescent neurons and glial cells amass in the nervous system, predisposing them to the onset and progression of neurodegenerative diseases [78]. Using the EAE model to confirm whether a link between age and axonal vulnerability existed, Hampton and Chandran [79] discovered that, compared to younger animals, older animals were more vulnerable to axonal damage and had lower remyelination rates. Remyelination in older animals was primarily mediated by Schwann cells, as opposed to oligodendrocyte-driven remyelination in younger animals. Both cell types were compared since oligodendrocytes and Schwann cells mediate CNS remyelination. The change to the secondary progressive phase of MS may be determined by the rapid accumulation of senescent cells over a particular threshold, and neurodegeneration in progressive MS may be driven by a senescence-associated loss of function [78].

Discussion

There has been strong evidence to suggest that CD4+ T-cells are crucial in mediating autoimmune diseases like MS. Various studies have outlined that diminished Treg activity is associated with immunological responses that lead to the demyelination of axons and that they are markedly lower in older adults. This has led to the investigation of whether the interplay between aging and T-cells has contributed to the pathology of MS. These findings implicate chronic inflammation as a symptom of aging whilst also coining it as a major contributor to neurodegenerative diseases like MS. This implication is critical for the preservation of immunosuppressive activity in such conditions, which, as has been shown, relies on the functionality of CD4+ T-cells that falter with age. A lack of homeostasis in Treg activity implies a heightened risk of immunosenescence. In both the white and grey matter of the brain and the spinal cord, these immunological processes cause astrocyte and microglia activation, oligodendrocyte death, and axonal loss. Infiltrating the CNS, activated autoreactive CD4+ T-cells are reactivated by myelin antigens delivered by microglial cells, triggering a cascade of immunological responses that lead to demyelination and tissue destruction [80]. Novel therapies are taking the approach to target biological systems involved in immunosuppression to modulate the activity of CD4+ and CD8+ T-cells and Th17 cells. However, many of these treatments are undergoing clinical phase II and III trials. Nonetheless, they have shown promising results in targeting the immunological pathologies fundamental to chronic inflammation and immunosenescence.

Conclusions

Tregs are crucial for maintaining proper immunotolerance. In conjunction with dysfunctional Tregs, data suggests that aging may affect immunomodulatory elements of the immune system, such as reduced suppressor function, which is exacerbated in older adults. In MS, both an impairment of Treg function and old age are major contributors to its pathology. Various therapies are being studied to aid in the treatment and management of MS, most of which are showing promising results for the future. For the treatment of MS, researchers are looking for ways to either produce Treg cells in vivo or grow them ex vivo in addition to interferon-β, natalizumab, cladribine, and immunosuppressive drugs. There is still much to be gleaned about T-cells and MS treatments, and further research may provide newer insights into potential mechanisms through which interactions of cells of the immune system and age influence the progression of MS.

List of Abbreviations Used

APC: antigen-presenting cells
BBB: blood brain barrier
CNS: central nervous system
EAE: experimental autoimmune encephalomyelitis
FOXP3: transcription factor forkhead box P3
MS: multiple sclerosis
Tregs: regulatory T-cells
RRMS: relapsing-remitting multiple sclerosis
SPMS: secondary progressive phase
CSF: cerebrospinal fluid

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This was a literature review and did not require any ethical approval or participant consent.

Authors' Contributions

JZ: made substantial contributions to review planning, assisted with the collection and organization of primary data, and drafted the manuscript.
BZ: aided in the interpretation of the data and revised the manuscript.

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