Autoimmunity Reviews 20 (2021) 102893

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Immunosenescence in multiple sclerosis: the identification of new therapeutic targets

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ARTICLE INFO

*Keywords:*
Immunosenescence
Ageing
Autoimmunity
Multiple sclerosis

ABSTRACT

The number of elderly multiple sclerosis (MS) patients is growing, mainly due to the increase in the life expectancy of the general population and the availability of effective disease-modifying treatments. However, current treatments reduce the frequency of relapses and slow the progression of the disease, but they cannot stop the disability accumulation associated with disease progression. One possible explanation is the impact of immunosenescence, which is associated with the accumulation of unusual immune cell subsets that are thought to have a role in the development of an early ageing process in autoimmunity. Here, we provide a recent overview of how senescence affects immune cell function and how it is involved in the pathogenesis of autoimmune diseases, particularly MS. Numerous studies have demonstrated age-related immune changes in experimental autoimmune encephalomyelitis models, and the premature onset of immunosenescence has been demonstrated in MS patients. Therefore, potential therapeutic strategies based on rejuvenating the immune system have been proposed. Senolytics and regenerative strategies using haematopoietic stem cells, therapies based on rejuvenating oligodendrocyte precursor cells, microglia and monocytes, thymus cells and senescent B and T cells are capable of reversing the process of immunosenescence and could have a beneficial impact on the progression of MS.

## 1. Introduction

The world's population is rapidly ageing. By 2050, it is estimated that 22% of people will be over 60 years old [1]. Ageing is broadly defined as a progressive functional decline that leads to impaired biological functions, which are the main cause of multiple human pathologies, such as cancer, diabetes, cardiovascular disorders and neurodegenerative diseases. Several hallmarks define the process of ageing, including genomic instability, telomere attrition, epigenetic alterations, the loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, stem cell exhaustion, altered intercellular communication and cellular senescence [2]. The age-related changes that take place in the immune system, a process known as immunosenescence, generally result in a higher susceptibility to infections, a reduced response to vaccines [3] and a higher prevalence of autoimmunity [4] and neurodegenerative disorders [5]. The immunosenescence process is the consequence of a series of events that affect the differentiation and maturation processes of different immune cell subtypes as well as their functionality.

Immunosenescence is defined by a set of immune markers known as the immune risk phenotype, which includes the inversion of the CD4: CD8 ratio, the expansion of $CD8^{+}CD28^{-}$ T cells, the presence of cytomegalovirus (CMV) seropositivity, poor T cell proliferation and low B cell numbers. In fact, immune risk phenotype features are associated with increased morbidity and mortality in elderly individuals [6]. In addition, recent studies have revealed that the ageing process is also

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https://doi.org/10.1016/j.autrev.2021.102893
Received 25 April 2021; Accepted 2 May 2021
Available online 5 July 2021

associated with an increased activity of immunosuppressive cells such as regulatory T (Treg) cells, regulatory B (Breg) cells and myeloid-derived suppressor cells (MDSCs) [7]. Numerous changes have already been described to occur in the adaptive immune system during immunosenescence; however, fewer studies have been performed to determine the impact of immunosenescence on innate immunity. Innate immunity seems to be more preserved with age, although recent reports point to age-associated impaired functionality of innate immune cells [8].

Multiple sclerosis (MS) is a chronic neurodegenerative, inflammatory and demyelinating disease of the central nervous system (CNS) characterized by the formation of demyelinating lesions. Although the immunopathological events occurring in the initial stages of the disease are not yet well understood, it is clear that the immune system is involved in the destruction of myelin sheaths that ultimately leads to neurological disability in patients. Taking this into account, many experts point to an autoimmune origin of MS [9]. Several studies suggest that autoimmunity itself as well as MS progression could be associated with premature immunosenescence. Thus, an understanding of the mechanisms underlying immunosenescence is a challenging objective in the field of MS to determine the possible efficacy of already approved therapies that have the capacity to reverse the process of immunosenescence. This review gives an overview of recent research findings on immunosenescence features and links the events that cause immunosenescence with MS immunopathogenesis. Finally, the possible beneficial impact of currently approved therapies aiming to rejuvenate the immune system on MS progression is discussed.

**Table 1**
Age-related alterations in innate and adaptive immunity.

| Immune cell type | Age-related alterations | References |
|---|---|---|
| T cells | ↓ naïve cells, ↑ memory cells | [14–17] |
| | ↓ TCR repertoire diversity, ↓ TRECs | [11–13] |
| | ↓ CD28 co-stimulatory receptor, ↓ CD40L, ↓ helper ability | [19,23,24] |
| | ↑ TIGIT and PD1 inhibitory receptors | [20] |
| | ↑ CD57 and KLRG-1 senescent markers | [17] |
| | ↑ SASP cytokines | [21] |
| | ↑ NK receptors, ↑ cytotoxic response | [28–30] |
| | ↑ autoreactivity | [22,23] |
| B cells | ↓ naïve cells, ↑ memory cells | [34] |
| | ↓ BCR repertoire diversity | [33] |
| | ↓ class switch, ↓ AID enzyme | [37,38] |
| | ↑ autoantibodies | [40] |
| | ↑ ABCs | [39,40] |
| | ↑ inflammation recruitment | [36] |
| Monocytes/ macrophages | ↑ M2 macrophages | [45] |
| | ↓ MHC-II receptor, ↓ TLR receptors, ↑ TAM receptors | [44,46,47] |
| | ↓ antiviral response, ↓ inflammation recruitment | [43] |
| DCs | ↓ DC responsiveness | [50] |
| | ↑ ROS, ↓ phagocytosis, ↓ cross-presentation | [48] |
| | ↓ stimulation of CD8+ T cells, ↓ IFN-γ | [49] |
| NK cells | ↓ $CD56^{bright}$ immunoregulatory cells, ↑ $CD56^{dim}$ cytotoxic cells | [51,52] |
| | ↓ mature NK cells in periphery | [53] |
| | ↓ degranulation capacity | [52] |
| Neutrophils | ↓ ROS, ↓ NETs | [54] |
| | ↓ phagocytosis | [55,56] |
| | ↓ inflammation recruitment | [56] |

*Abbreviations*: T cell receptor (TCR); T cell receptor excision circle (TREC); Tyrosine-based inhibitory motif domain (TIGIT); Senescence-associated secretory profile (SASP); B cell receptor (BCR); Activation-induced cytidine deaminase (AID); Age-associated B cell (ABC); Major histocompatibility complex (MHC); Toll-like receptor (TLR); Tyro3, Axl, and Mer (TAM); Dendritic cell (DC); Reactive oxygen species (ROS); Natural killer (NK); Neutrophil extracellular trap (NET).

## 2. Ageing of the immune system: immunosenescence

The events that take place in the aged immune system result in poor immune responses in older adults (Table 1). Indeed, these events affect not only the functionality of immune cells but also the number and frequency of certain immune cells due to decreased haematopoiesis and progressive atrophy of the thymus. Immune cells are generated in the bone marrow from haematopoietic stem cells (HSCs), which are able to self-renew and differentiate into any of the lineages of the immune system. The ageing of HSCs is characterized by impaired telomerase activity, which leads to telomere shortening with each division; as a consequence, the pool of HSCs is progressively reduced due to decreased self-renewal capacity. Moreover, immunosenescence bears other consequences involving the commitment of progenitors, since myeloid differentiation is potentiated over lymphoid differentiation [10].

### 2.1. Adaptive immunity

T cell changes are the most described in the immunosenescence process. One of the main consequences of ageing is the progressive involution of the thymus, which deeply affects the maturation of naïve T cells and the diversity of the T cell receptor (TCR) repertoire [11,12]. These two features bear important consequences in T cell-mediated immunity. Moreover, the involution of the thymus also involves a decrease in the detection of T cell receptor excision circles (TRECs), which are circular DNA products generated from the rearrangement of TCR genes in the thymus. TRECs are detected only in naïve T cells, so their content has been suggested as a biomarker of the naïve T cell pool state and thymic function in immune ageing [13]. Although the overall T cell population is maintained in older adults, the number of naïve T cells in the periphery is reduced (especially the number of $CD8^+$ T cells) [14,15]. Terminally differentiated memory T cells (especially $CD8^+$ T cells) are expanded and accumulate due to persistent infections, most commonly with CMV [16,17]. As a consequence of the lower number of naïve T cells and their decreased diversity in the TCR repertoire, the normal function of the T cell-mediated immune response is also impaired, presenting a decreased ability to respond properly to infections and vaccination [18]. Senescent cells lack the CD28 co-stimulatory molecule and express CD57 and KLRG1 senescence markers. This phenotype is commonly associated with terminally differentiated memory $CD8^+$ T cells in elderly individuals [17]. Terminally differentiated memory $CD8^+$ T cells that tend to accumulate with age present an impaired capacity to proliferate, more resistance to undergo apoptosis and shortened telomeres, which are typical features of cellular senescence [19]. There is evidence that senescent $CD8^+$ T cells also express inhibitory receptors such as T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and PD1, which are characteristic of not only senescent T cells but also exhausted T cells [20]. Although these terminally differentiated memory $CD8^+$ T cells could fight against persistent infections in older adults [17], senescent T cells are also characterized by the secretion of a determinate cytokine profile termed the senescence-associated secretory profile (SASP) [21], which could contribute to tissue damage.

Although major changes are observed in the $CD8^+$ T cell compartment, $CD4^+$ T cells also experience modifications with age, but to a lesser extent. Terminally differentiated $CD4^+$ T cells present senescence features that are similar to those of terminally differentiated $CD8^+$ T cells, since they also accumulate with age due to persistent antigen stimulation with pathogens or self-antigens, present shortened telomeres, produce a high number of pro-inflammatory cytokines, express CD57 and KLRG1 senescence markers and lose CD28 co-stimulatory molecule. Particularly, in senescent $CD4^+$ T cells, there is an increased number of autoreactive cells [19,22,23]. Furthermore, the loss of CD28 leads to a deficiency in the induced expression of CD40L, impeding $CD4^+$ T cells from interacting with CD40 molecules present on the surface of B cells; consequently, $CD4^+$ T cells lose their helper ability to

induce B cell proliferation and the production of antibodies. Moreover, senescent $CD4^+$ T cells lose their helper ability to induce somatic hypermutation on B cells and the formation of germinal centres, which is a T cell-dependent process that negatively interferes with the humoral immune response in older adults [23,24].

It is well reported that a subset of $CD8^+$ T cells constitutively express the NK-associated receptor NKG2D in humans and upon stimulation in mice, as NKG2D serves as an activating receptor in cytotoxic cells [25]. However, $CD8^+$ T cells with a senescent-like phenotype, lacking CD28 expression, accumulate NK receptors with age [26]. Despite their inability to respond to TCR-mediated signals, $CD8^+$ senescent T cells mediate cytotoxic immune responses through NKG2D and other NK receptors instead. The switch from TCR- to NK-receptor-mediated cytotoxicity probably increases their capacity for immune surveillance and the elimination of senescent cells in aged tissues as well as tumour cells [27]. In contrast, $CD4^+$ $CD28^-$ T cells express NK receptors de novo, and these cells are expanded in certain pathological conditions, including acute coronary syndrome [28] and rheumatoid arthritis [29]. In aged individuals, $CD4^+CD28^-$ T cells with senescent features that specifically express the NKG2D receptor are expanded and, moreover, have been suggested as a differentiation marker in the $CD4^+$ T cell compartment in elderly individuals [30]. Innate-like properties in senescent T cells confer beneficial adaptation mechanisms to mediate faster effector functions, suggesting that the limits between the innate and adaptive immune systems may not be as distinct as was first thought [31].

Numbers of peripheral B cells are not deemed with age, but many changes are observed in the composition of the different compartments and in the functional features of B cell subtypes, mainly due to a deficit in $CD4^+$ T helper cells, as mentioned above. The production of B cells in the bone marrow is decreased in elderly individuals [32], as well as the diversity of the B cell receptor (BCR) repertoire in the bone marrow, lymph nodes and peripheral blood [33]. Moreover, a shift from naïve to memory B cells has been described, which is consistent with the decrease in IgD levels observed [34]. Late memory B cell numbers are increased in older people and express markers associated with migration to sites of inflammation [35,36]. Another age-associated feature is the decreased isotype switch from IgM to IgG, IgE or IgA [37], possibly due to a decrease in the expression of activation-induced cytidine deaminase (AID) [38]. Age-associated B cells (ABCs) are antigen-experienced B cells with features of memory B cells that are activated through Toll-like receptor (TLR) 7 and TLR9 and not by BCR stimulation alone [39,40]. ABCs continuously expand with age and are hardly detectable in youth. However, ABCs are particularly expanded at earlier ages in individuals with autoimmune diseases, and ABCs often produce antibodies recognizing self-antigens [41].

### 2.2. Innate immunity

Although alterations induced by age in the adaptive response are well established, changes in the innate immune response in human ageing are not well understood. Most studies suggest that the total numbers of different innate immune cell populations do not change dramatically; however, recent findings support that many of their functions, such as cytotoxicity, phagocytosis, antigen presentation and the secretion of inflammatory cytokines, are altered.

Monocytes play an important role as starters of the inflammatory response, as they are circulating cells that are recruited to the site of inflammation, where they can differentiate into macrophages or into DCs in certain inflammatory situations [42]. Aged monocytes stimulated with agonists of pattern recognition receptors show differences at the transcriptional and functional levels, resulting in reduced production of IFN-α, IFN-γ, IL-1β, CCL20 and CCL8, which participate in antiviral responses and in the recruitment of monocytes to the sites of inflammation [43]. Monocytes in elderly individuals also express more TAM (Tyro3, Axl and Mer) tyrosine kinase receptors, a family of receptors that negatively regulate the immune responses mediated by TLRs and, in turn, inhibit inflammation [44]. Macrophages are considered the main phagocytes of potential pathogens and are capable of initializing and regulating inflammation. Polarization to alternatively activated anti-inflammatory M2 macrophages, rather than pro-inflammatory M1 macrophages, is predominant in the tissues of older mice [45]. Moreover, age negatively impacts the expression of TLRs and major histocompatibility complex II (MHC-II), which probably contributes to impaired antigen presentation and the activation of $CD4^+$ T cells [46,47].

DCs are the most important antigen-presenting cells, thereby acting as a link between innate and adaptive immunity. Age-related alterations in DCs, such as mitochondrial dysfunction and increased reactive oxygen species (ROS) production, have specific deleterious effects on the phagocytosis and cross-presenting capacity of DCs [48]. The alteration of the antigen processing and presentation machinery specifically contributes to an impaired stimulation and cytotoxic response of $CD8^+$ T cells, together with lower secretion of IFN-γ [49]. Moreover, circulating plasmacytoids (pDCs) and myeloid DCs (mDCs) are less represented and less responsive to TLR stimulation in elderly women [50].

NK cells are the main innate cell subtype responsible for killing cells infected by viruses, which have altered self or missing self-antigens. Unlike T and B cells, the absolute number of NK cells is slightly increased in elderly individuals, which could be associated with a redistribution of NK cell subtypes. There is a decrease in $CD56^{bright}$ immunoregulatory cells and an increase in $CD56^{dim}$ cytotoxic cells; however, older subjects show a defective degranulation capacity [51,52]. In contrast, the maturation of NK cells in the bone marrow of mice was shown to be impaired with age and is associated with reduced proliferation, resulting in reduced numbers of mature circulating cells in peripheral tissues [53]. Taken together, these data highlight the need for more studies on how ageing affects NK cells.

Neutrophils are the first cells recruited against bacterial and fungal infections and they produce many degradative enzymes, antimicrobial peptides and ROS for their activity. Aged neutrophils display a reduced ability to target infected tissue, as these cells present a lower capacity to generate ROS and neutrophil extracellular traps (NETs) [54]. In elderly individuals, alterations in surface molecules of neutrophils, such as CD11b or CD16, have been reported, affecting phagocytosis and intravascular adhesion to the endothelium and, consequently, the recruitment of immune cells to the infected tissue [55,56].

## 3. Age-related autoimmunity

One of the most important features of immunosenescence is inflammaging, a chronic low-grade inflammation characterized by a gradual increase in pro-inflammatory mediators, including TNF-α, IL-6 and IL-1β, which results from an imbalance between pro-inflammatory and anti-inflammatory networks during ageing [57]. Pro-inflammatory responses can confer not only a high resistance to infectious diseases but also an increased susceptibility to inflammatory-based diseases. On the other hand, anti-inflammatory responses not only can increase susceptibility to infectious diseases but also can provide a survival advantage in older individuals. In fact, centenarians seem to deal with this chronic low-grade inflammation through an anti-inflammatory response called anti-inflammaging, which may be one of the secrets of longevity [58]. The principal stimulus involved in the progression of inflammaging is the accumulation of cell debris and self-antigens derived from cellular stress or viral infections. The mechanisms devoted to cleaning cell debris and misfolded self-antigens become defective with age, leading to an overexposure of the immune system to these products and sustained low-grade inflammation, which favours autoimmunity [59].

Immune tolerance is a mechanism of the unresponsiveness of the immune system to antigens and is aimed at discriminating self from non-self-antigens. However, some autoreactive lymphocytes escape all tolerance mechanisms, leading to the expansion of autoreactive T cells

and the production of autoantibodies. Most likely related to a higher exposure to exogenous factors, elderly people show an increased prevalence of autoantibodies such as rheumatoid factor, anti-neutrophil cytoplasm and anti-nuclear antibodies, among others [60,61].

Ageing is associated with the emergence of unusual cell subsets that are thought to have a role in the development of autoimmunity. Senescent $CD4^+CD28^-$ T cells were originally isolated in the context of an autoimmune disease and were found to be outgrowths and autoreactive to self-antigens [22]. Their autoreactive properties and inability to serve as helpers in B cell responses are very similar to the deficiencies found in senescent $CD4^+$ T cells from aged individuals [23]. Furthermore, senescent $CD8^+CD28^-$ T cells expressing NK receptors can be found not only in elderly individuals but also in patients suffering from autoimmune diseases, who present alterations in the number and function of these cells [26]. ABCs continuously expand with age and are hardly detectable in youth; however, they are particularly expanded at earlier ages in people with autoimmune diseases presenting enriched autoantibody production [40]. There are other factors that might accelerate immunosenescence and contribute to the onset of autoimmune diseases, like genetic factors such as the human leucocyte antigen (HLA) haplotype and environmental factors such as persistent viral infections and high consumption of different medications in elderly individuals [62].

Systemic lupus erythematosus (SLE) has immune features that overlap with features of ageing, suggesting the presence of premature immunosenescence, such as telomere attrition and a generally lower phagocytic capacity [63,64]. The clearance of apoptotic bodies is mediated by macrophages and its deregulation could generate danger signals and the exposure of self-antigens to DCs [65], which present an affected tolerance and a greater autoreactivity with age [66]. In addition, ABCs are significantly increased in these patients and positively correlate with high anti-chromatin antibody production [67]. Moreover, ABCs are B cell activating factor (BAFF)-dependent, and the blockade of this cytokine has been proven to be effective in SLE patients, which confirms the implication of ABCs in the disease [68]. Furthermore, autoreactive B and T cells are thought to be activated after infection by CMV or Epstein-Barr virus (EBV) with pathogen antigens that share structural similarities with self-antigens. This cross-recognition mechanism principally provokes the production of anti-nuclear autoantibodies, which are also found in healthy elderly individuals [69].

As in ageing, in rheumatoid arthritis (RA), it is well established that $CD4^+CD28^-$ T cells accumulate and show signs of senescence; in fact, this population of cells was first identified in RA patients [22]. Senescent T cells no longer require a CD28 co-stimulatory signal for complete activation, and at the same time, they acquire cytotoxic properties [62]. In addition, a novel $CD4^+$ $CD28^-$ T cell subset has been described in RA patients, revealing features of both Treg cells and senescent T cells. These $CD4^+CD28^-FoxP3^+$ Treg-like cells insufficiently suppress the proliferation of effector T cells and induce a pro-inflammatory cytokine profile [70].

It is known that age-related gene expression profiles overlap with gene expression profiles in tissues affected by autoimmune thyroid disease (AITD), suggesting that there is also a relation between premature immunosenescence and autoimmunity in the thyroid gland. These changes include the downregulation of genes related to mitochondrial and proteasomal functions and the upregulation of genes related to the immune response [71]. AITD patients present a peripheral T cell phenotype reminiscent of findings in elderly patients and patients with other autoimmune diseases. There is a significant increase in $CD4^+CD28^-$ T cells associated with CMV seropositivity in individuals with Hashimoto's disease [72] and an increase in $CD4^+CD28^-$ T cells producing IFN-γ in individuals with Graves' disease [73], which might drive the destruction of thyroid tissue.

The most frequent causes of Sjögren syndrome (SjS) are the chronic use of medications and viral infections [74], which are both common features in elderly individuals, suggesting a relationship between premature ageing of the immune system and the developmentof the disease. ABCs are also implicated in the pathogenesis of this syndrome, as they are elevated in the blood of SjS patients. ABCs remain unresponsive in peripheral blood and are probably activated through TLRs, breaking tolerance and leading to B cell lymphoproliferation [75].

## 4. Immunosenescence in MS

MS is a chronic neurodegenerative, inflammatory and demyelinating disease of the CNS that is probably of autoimmune origin. MS affects approximately 2.5 million people worldwide, and MS is the primary cause of non-traumatic disability in young adults [76]. MS typically initiates between 20 and 40 years of age, with a higher prevalence in women than men (2.3–3.5:1), a ratio that is increasing over time [77]. Clinically isolated syndrome (CIS) is the first clinical acute episode that shows inflammatory demyelination; however, CIS does not fulfil clinical and radiological criteria to be considered definite MS, and not all patients with CIS necessarily develop MS. Most patients present a relapsing-remitting (RR) form of MS, the most frequent form of the disease (80%), characterized by episodes of neurological dysfunction, and the majority of these patients (65%) progressively accumulate disability with time, developing secondary progressive (SP) forms of MS. A minority of patients (20%) present a progressive disease course from the onset, known as primary progressive (PP) MS [78].

Although the aetiology of MS remains unknown, MS is known to result from an interplay between genetic and environmental risk factors. Genome-wide association studies have identified 233 independent associations that are significantly linked to MS susceptibility, the majority of which were found in the autosomal non-MHC genome [79–81]. Nonetheless, the main genetic risk factors are related to HLA genes, with the variants DRB1*15:01, DRB5*01:01 and DQA1*01:02 being associated with an increased risk of developing MS, while HLA-A*02 is associated with protection from the disease [82]. Sex, living in high-latitude areas, smoking, low vitamin D levels caused by insufficient sun exposure or dietary intake, obesity during adolescence, commensal microbiota composition and EBV infection have been identified as possible environmental risk factors related to MS development, whereas the use of oral nicotine or alcohol, seropositivity to CMV and high coffee consumption are related to a reduced risk [83,84]. Among these risk factors, EBV is strongly associated with the development of MS. Several myelin antigens, including myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP), have been proposed as the principal candidate autoantigens involved in the development of MS [85]; however, other non-myelin antigens have been identified to trigger immune attack on myelin components [86]. The most accepted hypothesis to explain the immunopathogenesis of MS involves an initial immune activation in the periphery of $CD4^+$ T cells reactive to myelin antigens. Then, activated autoreactive $CD4^+$ T cells infiltrate the CNS, where they are reactivated by the recognition of myelin antigens presented by microglial cells, initiating a series of immune events that contribute to demyelination and tissue damage. These immune events provoke the activation of astrocytes and microglia, the apoptosis of oligodendrocytes and axonal loss in both the white matter and the grey matter of the brain and the spinal cord. In addition, the release of pro-inflammatory mediators facilitates the permeabilization of the blood-brain barrier (BBB), attracting monocytes and additional lymphocytes, thus sustaining the inflammatory process that leads to progressive tissue degeneration [87]. The analysis of the autoimmune response showed structural homology between MBP and EBV peptides presented by HLA-DRB1*15:01, as well as the presence of T cells with specificity for both antigens. Altogether, molecular mimicry with EBV antigens is one of the main mechanisms involved in MS pathogenesis [88].

The prevalence of MS and the age of affected patients are increasing due to the increasing longevity of the general population and the availability of effective disease-modifying treatments. Patients with PPMS normally have a later disease onset than those with RRMS, the majority of whom develop SPMS over time. However, current

treatments reduce the frequency of relapses and slow the progression of the disease, but they cannot stop the disability accumulation associated with disease progression [89]. These facts support the idea that there are differences between the processes driving relapses and those driving chronic progression commonly in elderly individuals, which could be due to the impact of age on the immune system. Indeed, there are numerous studies in the animal model of MS experimental autoimmune encephalomyelitis (EAE) and in MS patients that demonstrate the impact of immunosenescence on the disease [90].

### 4.1. Age-related immune changes in EAE

EAE is a well-established animal model used for the study of MS that has provided helpful information about various pathological processes, including inflammation, demyelination, axonopathy and neuron loss mediated by immune cells [91]. However, there are some differences in immunopathology between EAE and MS, since $CD4^+$ T cells predominate in the inflammatory infiltrate in EAE, while in MS lesions, $CD4^+$ T cells are much less frequent, with $CD8^+$ T cells and macrophages being the predominant infiltrating cells [92,93].

A key mediator in central tolerance is the autoimmune regulator (Aire), a transcription factor highly expressed in medullary thymic epithelial cells (TECs) that promotes ectopic expression of peripheral-tissue-specific self-antigens, leading to central tolerance. Some autoreactive T cells escape this process, but they are regulated by peripheral tolerance mechanisms, including immune regulation by Treg cells. There is an age-related association between Aire and Treg cells in susceptibility to EAE. The resistance of young Aire-knockout (KO) mice to EAE correlated with an elevated percentage of peripheral Treg cells, whereas older Aire-KO mice presented more severe disease and no differences in the frequency of Treg cells in the periphery, demonstrating age-related impaired peripheral tolerance [94]. A spontaneous EAE mouse model also showed a decrease in intrinsic regulatory mechanisms involved in the maintenance of self-tolerance and Treg cell suppressive function with age [95]. EAE rats show an age-associated alteration in the autoimmune response, while young rats show an anti-MBP antibody response during the acute period, no epitope dominance was detected in the older rats [96].

Little is known about the age effect on BBB disruption in EAE, a critical step in the development of the disease, as myelin-specific T cells infiltrate the CNS by crossing the BBB. Several molecules are altered in response to BBB disruption, such as nicotinamide adenine dinucleotide phosphate oxidase, matrix metalloproteinases and cell adhesion molecules. These molecules were elevated with age in a non-relapse EAE mouse model, suggesting that they play a role in BBB disruption and the subsequent autoreactive T cell infiltration that leads to neurodegeneration [97]. However, age not only is a risk factor for neurodegeneration but also influences neuroregeneration. Using a focal EAE rat model, immunization with MOG followed by localized injections of cytokines in the spinal cord to generate focal demyelinating injury increased vulnerability to axonal injury and reduced the efficiency of remyelination in older animals compared with young animals. Moreover, remyelination in aged rats was mediated by Schwann cells, while in younger rats, oligodendrocytes mediated the regeneration process [98].

### 4.2. Age-related immune changes in MS

Age, sex and viral infections are known to influence the phenotype and function of the immune system. The frequencies of immune cells depend on lifetime exposure to pathogens such as CMV, which leads to late differentiation and the accumulation of senescent immune cells with age [99]. Indeed, senescent neurons and glial cells also accumulate in the nervous system with age, predisposing individuals to the appearance and aggravation of neurodegenerative events [100]. Furthermore, the evolution from RRMS to SPMS normally occurs over time at older ages, and this transition is dependent on age rather than disease duration [101]. Neuroinflammation mechanisms such as synaptopathy and synaptic plasticity impairments are exacerbated and accelerate with age in MS patients [102]. In particular, disease progression is characterized by a marked decrease with age in the $CD8^+$ T cell response to EBV-infected B cells, which may result from the deletion of EBV-specific T cells through exhaustion mechanisms that occur during chronic viral infections [103].

### 4.3. Premature ageing of the immune system in MS

Patients suffering from MS are also characterized by premature immunosenescence [104] and reduced immune function that resembles that of healthy elderly individuals. The reduced immune function can be a consequence of the diminished proliferative capacity of bone-marrow-derived cells and the shortening of telomeres, which are both observed in MS patients [105]. Telomere length reduction and increased oxidative stress have been suggested as premature ageing markers in many autoimmune diseases, including MS. The shortened telomeres and oxidative stress found in PPMS patients may reflect the most severe state of the disease and may also be associated with greater disability and brain atrophy [106,107]. Furthermore, RRMS and PPMS patients also present prematurely reduced immune functions related to thymic dysfunction, including a contraction of naïve T cells, Treg cell dysfunction and decreased signal joint TRECs [108]. Similar alterations in T cell homeostasis are observed in paediatric MS patients, confirming the presence of an early thymic involution [109]. The main common characteristic between ageing and MS is the accumulation of $CD4^+CD28^-$ T cells. These effector memory T cells result from repeated viral antigenic stimulation, typically CMV and EBV, before migrating to the CNS, which contributes to tissue damage, thereby causing the release of self-antigens. IL-15 produced by peripheral B cells, astrocytes and infiltrating macrophages in CNS inflammatory lesions is known to enhance the cytotoxic properties of $CD4^+CD28^-$ T cells [110]. Alterations in B cell subsets are also found in the cerebrospinal fluid of MS patients with acute relapse, as there is a higher frequency of non-switched memory B cells in paediatric patients and class-switched memory B cells in adults [111]. However, B cell participation in MS goes beyond the production of antibodies. ABCs are increased in MS patients as well, corroborating the presence of early ageing [112].

MS is primarily mediated by adaptive immune responses, while chronic stages are believed to be mediated by compartmentalized innate immune responses in the CNS [9]. Therefore, a complete understanding of the impact of age on the immune system and disease progression, as well as the premature immune ageing observed in MS patients, needs to be achieved to develop effective immunotherapies against immunosenescence in MS.

## 5. Rejuvenation of the immune system as a therapy for MS

Currently, there is no cure for MS and no effective therapy options available that can stop disability accumulation in individuals with progressive forms of the disease, who represent the majority of patients over 65 years of age. Food and Drug Administration (FDA)-approved therapies for RRMS have failed to demonstrate efficacy as a treatment for PPMS, and there are few disease-modifying therapy options for SPMS [113,114]. In addition, emerging data suggest that premature immunosenescence strongly influences MS progression; thus, several therapeutic strategies based on rejuvenating the immune system have been proposed to reverse this phenomenon (Fig. 1).

### 5.1. Senolytics and HSC regenerative strategies

Senescent cells accumulate with age in the CNS and contribute to disease progression. Senolytic drugs have been developed to selectively remove senescent cells by targeting anti-apoptotic pathways, and

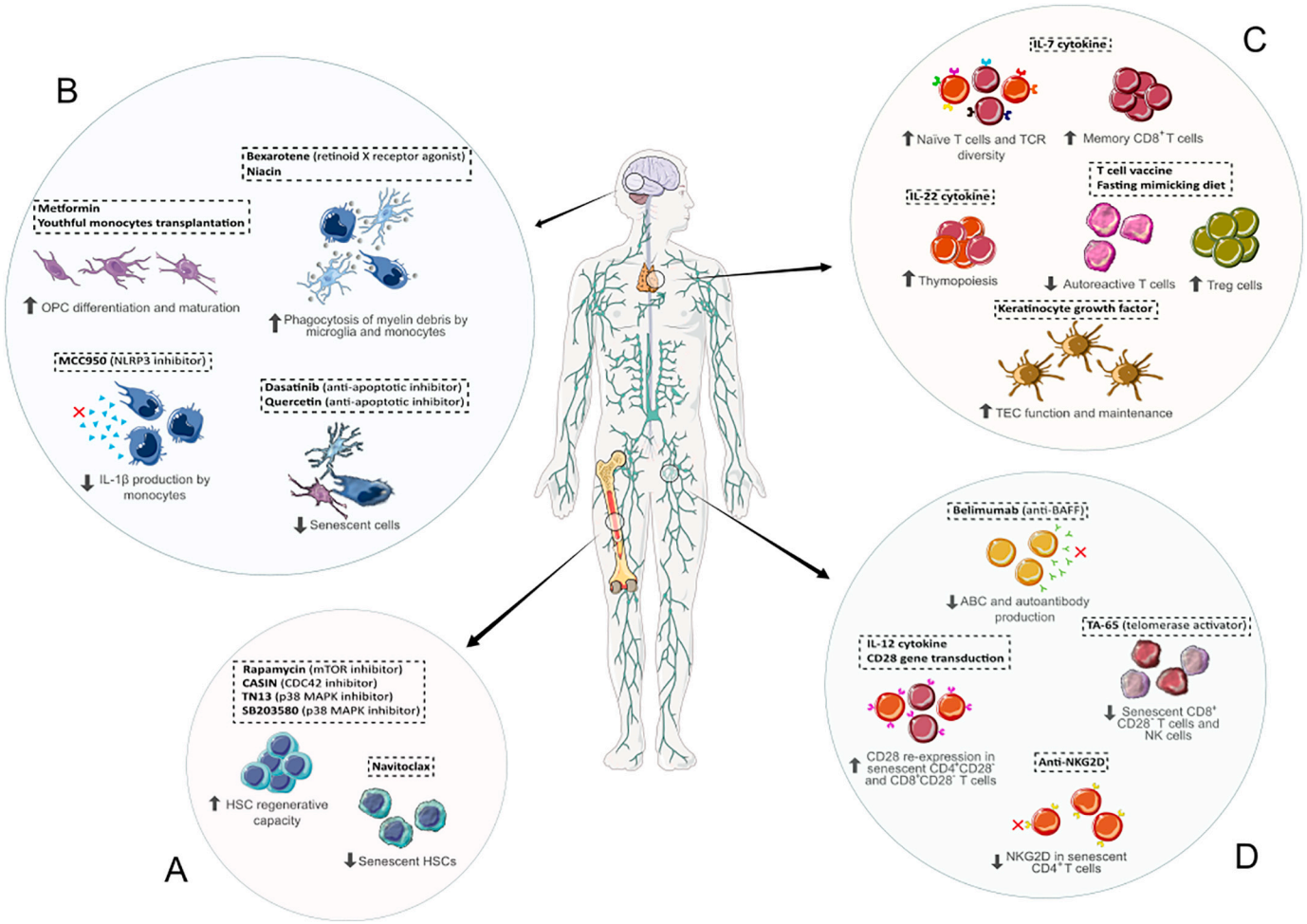


**Fig. 1.** Senolytics and regenerative strategies using haematopoietic stem cells (A), therapies based on rejuvenating oligodendrocyte precursor cells, microglia and monocytes (B), thymus cells (C) and senescent B and T cells (D) are capable of reversing the process of immunosenescence and could have a beneficial impact on the progression of MS. *Abbreviations*: Oligodendrocyte precursor cell (OPC); Haematopoietic stem cell (HSC); T cell receptor (TCR); Regulatory T cell (Treg); Thymic epithelial cell (TEC); Age-associated B cell (ABC); Natural killer (NK).

senolytics have recently been suggested as potential rejuvenation strategies against progressive MS [115]. The use of the tyrosine kinase inhibitor **dasatinib** and **quercetin** in combination decreased the accumulation of senescent cells and increased survival in older mice. Moreover, these drugs showed immunomodulatory effects on MS when used separately [116–118]. Another important senolytic drug is **navitoclax**, or ABT263, which is able to induce apoptosis in senescent bone marrow HSCs, reduce myeloid bias and improve haematopoietic functionality [119]. In fact, HSC ageing is related to reduced self-renewal capacity, which leads to altered immune cell numbers and functions. The ageing of the HSC compartment was initially considered to be irreversible; however, recent findings show rejuvenating strategies that are capable of reversing HSC dysfunctions related to ageing, including prolonged fasting and pharmacological targeting to inhibit molecules such as mTOR (**rapamycin**) [120], CDC42 (**CASIN**) [121] and p38 MAPK (**TN13 and SB203580**) [122,123]. These strategies are capable of enhancing the regenerative capacity of HSCs, reducing ROS levels and re-establishing an immune system similar to that of young organisms (Fig. 1A).

### *5.2. Rejuvenation of oligodendrocyte precursor cells (OPCs), microglia and monocytes*

MS progressive forms are characterized by accumulative neurodegeneration due to persistent demyelination of axons. Although the CNS has the capacity to remyelinate axons and, thus, prevent neurodegeneration, the efficiency of CNS remyelination declines with age, and age-related failure of OPCs to differentiate into myelinating oligodendrocytes is particularly involved. The fasting mimetic drug **metformin** reverses the poor differentiation and maturation of OPCs and restores remyelination and neuroregeneration in aged rodents [124]. Furthermore, older mice with a focal demyelination exposed to a youthful systemic milieu through heterochronic parabiosis (a young mouse surgically joined to an aged partner) could recruit young macrophages and rejuvenate OPCs, suggesting that **youthful monocyte transplantation** could be considered a remyelination therapy [125]. Microglia and macrophages are essential for remyelination, as both are responsible for the phagocytosis of myelin debris that inhibits remyelination and for the release of growth factors necessary for OPC maturation. With age, a decline in the phagocytic clearance of myelin debris occurs, a phenomenon that has also been observed in MS patients. Given that retinoid X receptor activation in monocytes enhances myelin debris clearance in MS, the agonist **bexarotene** was found to reverse phagocytosis defects and lead to a younger state of these cells [126]. In addition, with age, a decrease in the expression of CD36 by microglia occurs, which is also involved in myelin debris clearance by phagocytosis. Daily treatment of old microglia with **niacin** or vitamin B3 upregulates CD36 expression and enhances phagocytosis, which leads to remyelination. Thus, niacin can stimulate innate immunity and represents a regenerative therapy for chronic demyelination, which is an interesting therapeutic strategy for

MS [127]. **MCC950** regulates innate immunity by specifically inhibiting the NLRP3 inflammasome and subsequently reducing IL-1β production. MCC950 attenuated the severity of EAE, improved the histopathology of the CNS and protected against axonal damage in organotypic cerebellar cultures. Therefore, MCC950 could be considered an anti-inflammaging therapy for MS [128,129] (Fig. 1B).

### 5.3. Rejuvenation of the thymus

Recently, many potential rejuvenation therapeutic strategies have been developed to restore aged thymic function and, consequently, defects in negative selection and in the generation of Treg cells. As the FOXN1 transcription factor is strongly implicated in the differentiation of TECs cells and is responsible for the ectopic expression of peripheral-tissue-specific self-antigens that lead to tolerance, it has been proposed as a target for several rejuvenation strategies against thymic involution [130]. Because thymic atrophy is related to a failure in the thymic microenvironment and consequently in thymopoiesis, targeting this process could also reverse the observed thymus dysfunction in MS patients. There is evidence that an age-related decrease in the expression of IL-7 is involved in thymus involution. Treatment with **IL-7** promotes the maturation of thymocytes to naïve T cells, enhances TCR diversity and results in higher numbers of memory $CD8^+$ T cells [131]. Another cytokine involved in thymopoiesis is **IL-22**, which was shown to enhance thymic recovery after the depletion of $CD4^+CD8^+$ double-positive thymocytes [132]. **Keratinocyte growth factor** is important for the maintenance of TECs and has been proven to increase thymopoietic capacity in aged mice by restoring the function of TECs [133]. However, thymic involution results in not only decreased numbers of naïve T cells but also increased output of potential autoreactive T cells to the periphery and consequently to higher susceptibility to developing autoimmune diseases such as MS. The most promising rejuvenation immunotherapies focused on targeting these autoreactive T cells are therapeutic vaccinations that include TCR peptides, MBP-based DNA, altered peptide ligands and attenuated autoreactive T cells [134]. Among them, **T cell vaccines** have shown clinical efficacy in clinical trials, as they induce an anti-idiotypic response against MBP-reactive T cells and restore Treg cell function in MS patients, making them a potential strategy against MS [135]. Additionally, a **fasting-mimicking diet**, a very low-calorie and low-protein diet, prevents autoimmunity in an EAE model by reducing the levels of autoreactive T cells and increasing the production of Treg cells, which are both cell subsets that are altered with immunosenescence [136]. Another strategy to counteract immunosenescence is to reduce as much as possible the antigenic load represented by common infectious agents such as influenza virus and CMV to avoid inflammaging. Strategies of specific vaccination should be applied to prevent not only morbidity and mortality but also any additional persistent stimulation of the immune system and, thus, reduce the impact of inflammaging in elderly individuals and in the context of autoimmune diseases (Fig. 1C).

### 5.4. Rejuvenation of senescent B and T cells

Different cell types that become senescent during MS could be interesting targets of rejuvenation. Anti-BAFF treatment with **belimumab** decreases the proliferation of ABCs and, consequently, the production of autoantibodies [68]. As in MS, chronic viral infections such as CMV promote telomere shortening and premature ageing of the immune system, particularly of cytotoxic T cells. These T cells also lack the expression of the co-stimulatory receptor CD28, and hence, their capacity to respond to infections is diminished. **TA-65** is a purified telomerase activator that, when given orally to aged subjects, can lengthen short leucocyte telomeres and decrease the percentage of senescent cytotoxic $CD8^+CD28^-$ T cells as well as NK cells. This effect has been observed mostly in CMV-seropositive subjects, whose leukocytes switch towards a younger profile [137]. The re-expression of CD28 and the restoration of helper function in senescent $CD4^+$ T cells can be partially achieved when $CD4^+$ T cells are exposed to the cytokine **IL-12** [138]. A similar functional restoration and production of IL-2 was shown in senescent $CD8^+$ T cells by **CD28 gene transduction** [139]. Both strategies can delay or reverse the ageing effects of the loss of the CD28 co-stimulatory molecule. In addition, the expression of innate receptors such as NKG2D on $CD4^+$ T cells is characteristic of ageing and regulates the cytotoxic functions of these cells by promoting pro-inflammatory cytokine production. Treatment with a blocking **anti-NKG2D** antibody ameliorates EAE inflammation, making this receptor a promising therapeutic target for MS treatment [140] (Fig. 1D).

## 6. Conclusions

Overall, the evidence presented here demonstrates that age-related immune changes are observed in EAE and MS patients, as well as premature ageing of the immune system in MS patients. Therefore, we propose different therapeutic strategies based on rejuvenating the immune system, which could reverse the process of immunosenescence and have a beneficial impact on the treatment of MS, as potential add-on treatments to current FDA-approved therapies. Moreover, therapies focused on the rejuvenation of the immune system could provide new therapeutic opportunities for the PP form of the disease. A broad knowledge of the impact of age on the immune system and disease progression in MS patients would facilitate the development of new effective immunotherapies against immunosenescence in MS.

## Funding

This work was supported by the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, and co-funded by the European Union (European Regional Development Fund/European Social Fund), "A way to build Europe", under Grant PI18/01146 and RD16/0015/004 and the "Agència de Gestió d'Ajuts Universitaris i de Recerca" (AGAUR; Generalitat de Catalunya) under Grant 2017SGR527.

## Declaration of Competing Interest

MD, HE, LMV and CE: None.

XM has received speaking honoraria and travel expenses for participation in scientific meetings and has been a steering committee member of clinical trials or has participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, MedDay, Merck KGaA, Darmstadt Germany, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

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