Immunity & Ageing

REVIEW

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Review of evidence linking exposure to environmental stressors and associated alterations in the dynamics of immunosenescence (ISC) with the global increase in multiple sclerosis (MS)

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Abstract

Historical survey confirms that, over the latter part of the 20th century, autoimmune-based diseases, including multiple sclerosis (MS), have shown a worldwide increase in incidence and prevalence. Analytical population studies have established that the exponential rise in MS is not solely due to improvements in diagnosis and healthcare but relates to an increase in autoimmune risk factors. Harmful environmental exposures, including non-communicable social determinants of health, anthropogens and indigenous or transmissible microbes, constitute a group of causal determinants that have been closely linked with the global rise in MS cases. Exposure to environmental stressors has profound effects on the adaptive arm of the immune system and, in particular, the associated intrinsic process of immune ageing or immunosenescence (ISC). Stressor-related disturbances to the dynamics of ISC include immune cell-linked untimely or premature (p) alterations and an accelerated replicative (ar) change. A recognised immune-associated feature of MS is pISC and current evidence supports the presence of an arISC during the disease. Moreover, collated data illustrates the immune-associated alterations that characterise pISC and arISC are inducible by environmental stressors strongly implicated in causing duplicate changes in adaptive immune cells during MS. The close relationship between exposure to environmental risk factors and the induction of pISC and arISC during MS offers a valid mechanism through which pro-immunosenescent stressors may act and contribute to the recorded increase in the global rate and number of new cases of the disease. Confirmation of alterations to the dynamics of ISC during MS provides a rational and valuable therapeutic target for the use of senolytic drugs to either prevent accumulation and enhance ablation of less efficient untimely senescent adaptive immune cells or decelerate the dysregulated process of replicative proliferation. A range of senotherapeutics are available including kinase and transcriptase inhibitors, rapalogs, flavanols and genetically-engineered T cells and the use of selective treatments to control emerging and unspecified aspects of pISC and arISC are discussed.

Keywords Multiple sclerosis, Immunosenescence, Replicative immunosenescence, Premature immunosenescence, Environmental stressors, Senotherapy

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Introduction

Background to epidemiological variation in autoimmune-based diseases including MS

Global demographic analysis, that encompasses population

growth and ageing, has revealed and clarified the dramatic societal changes witnessed over the current and previous centuries. However, the perceived improvements that have materialised as a result of communal expansion, especially in the Western world, are counterbalanced by unforeseen challenges to nations' health which includes a dramatic increase in non-communicable diseases. In particular, epidemiological studies over the previous half-century, to date, have established an unequivocal worldwide growth in the number of individuals identified with a disease of autoimmune aetiology that includes chronic conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [1–4]. Moreover, investigations have revealed the increase is greater in women than men leading to speculation over the reasons for the gender bias including genetic variations and hormonal status [5].

Also contained within the date-related epidemiological rise in disorders closely linked to maladaptive autoantigenic responses are patients diagnosed with the demyelinating disease multiple sclerosis (MS) [6–13]. Data from global studies presented in Atlas of MS 3rd edition [14], and as detailed, more recently, by Walton et al. [15], estimates 2.8 million people have diagnosed MS which represents a concerning 30% upturn since 2013. In addition, there is recognition that the condition has developed worldwide with an increased rate of diagnosis in previously low-risk populations. Moreover, examination of collated data from 5 continents indicates striking alterations to the profile of incidence and prevalence of the disease [16–18]. Also, numerous studies have provided detailed analysis of epidemiological data from a large number of geographical areas indisputably demonstrating higher absolute figures of patients and a preferential rise in the incidence of MS in women compared with only a modest increase in men [19–26]. Indeed, there has been a reported 3- to 6-fold escalation of the disease in females over the last 50–70 years suggesting exposure to an increasing number of communicable and non-communicable external factors that impact immunological determinants during gestation, childhood and adulthood effect a gender bias [27]. Incorporated into the expanding figures and in parallel with dramatic environmental change is an alarming increase in confirmed cases of MS during childhood and adolescence which contrasts with the infrequency of the disorder in the young before and after the second half of the twentieth century [28–32]. Hence, there is a real concern that exposure of susceptible individuals to an antagonistic environment that includes infectious agents and chemical pollutants or causes psychological disturbances may impact on the epidemiology of autoimmune diseases including MS [32, 33].

The history and pathology of juvenile and adult MS phenotypes

Historical background

There is compelling evidence that MS in adults existed well before any impact from environmental influences and much in advance of the clinical characteristics described, in the 19th century, by Augustus d'Este, and the comprehensive histological examination of post-mortem central nervous tissue by Leopold Ordenstein and Jean-Martin Charcot. Incidentally, contemporary diagnostic databases have been employed to append historical medical information and the neurodiagnostic programme, SimulConsult, was applied to the clinical description of the condition described by d'Este and an alternative objective diagnosis of neuromyelitis optica, rather than MS, was made [34]. Interestingly, there is mention of a condition, retrospectively and plausibly diagnosed as MS, in the 14th century by the Dutch Saint, Lidwina of Schiedam, who described disturbed vision, limb paralysis and other neurologically recurrent symptoms over almost 4 decades [35–37]. Eventually, through the documented accounts and additional nosological considerations, MS, originally referred to as disseminated sclerosis, became a separate, classifiable neurological disease second only to syphilis as the most frequent disorder of the nervous system [38].

The initial appearance of MS in adults has a defined age span between the 3rd and 4th decade with a peak onset at 30 years old [39, 40]. Early symptoms include visual disturbances, linked to optic nerve dysfunction, plus muscle and limb impairments, due to defective motor neuron conduction, following resident and migratory immune, inflammatory cell-mediated damage within central nervous system (CNS) white matter. The acute pathology develops into a more chronic profile with the formation of perivascular lesions that coalesce to create plaques and an inflammatory milieu that causes the characteristic loss of myelin from axons and impedes the remyelination process by effecting oligodendrocyte necrosis. The clinical progression of MS is, for the majority of adult patients, a series of relapses and remissions of neurological symptoms that develop into a secondary progressive condition with increasing disability or, for a minority, an unremitting primary progressive disorder that causes an irreversible and accumulative incapacity [41–43]. Immunologically-directed neuroinflammation is prevalent in brain and spinal tissues during relapsing–remitting (RR) MS while neurodegeneration is the prominent trait in the more chronic forms of the disease. Interestingly, whereas segregated T- and B-cell-directed involvement appears a force for clinical progression there is an important contribution to the pathology and neurological outcome via the CNS response to the chronic inflammation [44, 45].

An increasing array of treatments is available to the therapist for RRMS such as the injectables interferon-beta (IFN-β) and glatiramer acetate, the oral immunomodulators fingolimod and teriflunomide and infusion therapy with the monoclonal antibodies natalizumab and ocrelizumab [46]. However, the choice of drugs for the management of progressive MS phenotypes is more limited. There are disease-modifying therapies (DMTs) that act either by immune modulation, cellular depletion or the inhibition of immune cell proliferation or migration and include the oral compound siponimod and, for more extreme cases, the chemotherapeutic mitoxantrone. For more contemporary information on the use of DMTs in MS there is a comprehensive list of compounds under present use, classified according to effectiveness and as continuous medications or pulsed doses, in a recent review by Lee and Chan [47]. Also, there is the potential for treatment through stem cell intervention with the capacity for regeneration, immunomodulation and trophic effects established through clinical studies that quantify any benefits [48, 49].

Interestingly, it was not until the early half of the 20th century and the incidental possibility of environmental influences that MS was recognised in children when nosology again facilitated distinctions between the demyelinating condition and a group of hereditary hypomyelinating leukodystrophies [50]. Paediatric patients diagnosed with MS, as defined by onset at eighteen years of age or below, present with distinct clinical differences compared to adults with the condition [51–53]. Reasons for the variations in disease presentation are uncertain but may be age-related and associated with immunological dissimilarities and physiological distinctions within the CNS. Indeed, paediatric MS occurs at a time of active immune development typified by prolific thymic output of naïve lymphocyte populations offering a potential response to a wide variety of antigens [54, 55].

In general, clinical MS begins in the young with a shorter pre-clinical latent phase, compared to adult disease, followed by acute and severe disabling neurological symptoms [31, 53, 56–59]. Almost all patients experience a RR course with a CNS pathology of inflammatory demyelinating lesions that feature distinct acute axonal damage. The condition in early years is also characterised by a higher relapse rate, compared to adult cases, but with less development of primary and secondary progressive disease. Notably, there is significant data showing a high level of cognitive impairment in young people with MS that is comparable to adults and includes deficiencies in information processing, verbal memory and fluency with detrimental effects on daily activities and quality of life [60, 61]. Indeed, the often-unappreciated psychological consequences and neurobehavioral effects of the disease include a range of cognitive difficulties [62, 63]. Encouragingly, the emergence of digital technologies, such as e-training, have generated positive results for managing and recording cognitive and motor irregularities [64]. Treatment options have increased, over the past decade, to include first-line medication with IFN-β or glatiramer acetate for reducing relapse rate and teriflunomide for decreasing lesion activity plus the use of natalizumab, fingolimod or mitoxantrone to control breakthrough disease during initial therapy [53, 65–67].

Aim of the review

The aim is to examine evidence that exposure to environmental stressors causes the age-related dynamic changes to the immune system in MS which contribute to the global increase in the disease. The review is comprised of sections under five general headings that consider:

1. Factors affecting the global increase in MS.
2. Environmental stressors and aberrant immune ageing.
3. The ageing immune system, cellular senescence and immunosenescence.
4. Dynamic changes to immunosenescence in MS.
5. Senotherapy.

Factors affecting the global increase in MS

Diagnostic improvements and epidemiological consequences

The British neurologist RW Brain recorded, over the last century, the changing epidemiology of MS and, through a growing number of related surveys, recognised the disease featured unpredictable clinical development, a variable time course amongst populations and, to this day, an indeterminate latitudinal difference in occurrence despite recent detailed genetic ancestry studies [38, 68]. Explanations for the documented rise in adult MS, the expanding female to male ratio and the upturn in juvenile cases of the disease are, at present, unforthcoming but, and as previously suggested, may be associated with exposure to or interaction with an established and burgeoning array of environmental factors [69, 70].

Although a diagnostic test for MS is, to date, not available advances in detection methods, including improved scanning techniques and amendments to disease evaluation that has allowed the development and revision of scoring systems have assisted confirmation of the condition in young and older patient groups. For example, the McDonald criteria, first detailed in 2001 and twice updated, in 2010 and 2017 with proposals for additional categorisations, has been used with increasing confidence, to diagnose MS in adults and adolescents above 11 years of age [71, 72]. However,

the system is not as useful for confirming the disease in children where magnetic resonance imaging (MRI), first used in the 1980s, is a more favoured diagnostic technique [66]. Indeed, amended measures for MRI and revisions by the International Pediatric MS Group of diagnostic standards account, at least in part, for the increase of recorded MS in the young [51, 73].

Noteworthy, the development and refinement of analytical methods to confirm MS have provided the means to determine the effectiveness of treatments. In particular, there has been detailed scrutiny of the procedures and criteria used to evaluate drug efficacy on the course of disease. For example, quantitative systems such as the Expanding Disability Status Scale and the Modified Rio score have been employed, either individually or in combination, to monitor therapeutic effects [74, 75]. Furthermore, MRI has been used to observe the results of treatment and guidelines have been developed, via the MRI in MS (MAGNIMS) group, for joint use of the descriptive data with the approved scoring systems [76]. Also, there has been an international effort by medical societies who have worked towards the creation and use of worldwide registries and patient databanks to improve prompter case detection which has contributed to charting the raised frequency of MS [77]. However, and despite the advances, there remains worldwide restrictions on early diagnosis largely due to a lack of resources in regional health care systems [78].

In summary, and an essential premise of the Review, is confirmation that, since the first half of the last century, a real global increase in the incidence of MS has occurred which, in turn, has altered the prevalence of disease. The recorded rise in new cases plus the percentage affected in a population is not merely due to better use of updated diagnostic techniques or a positive response to improved treatments. Undoubtedly, advances in analytical methods have substantially improved the diagnosis of MS which, together with an increased number of neurologists trained to identify and report the disease, has contributed to the documented epidemiological increase [79]. Enhanced investigative methods, upgraded health facilities, better identification and amended assessment criteria would help eliminate incorrect or missed diagnoses and generate a maximum value for the number of new cases in a population over a period of time. Therefore, any increase in numbers, relative to previous values, would indicate a valid rise in new patients and the cumulative incidence of disease defined as the number of new cases over a specified time ÷ size of population at beginning of time period. Indeed, and as with other autoimmune-type disorders, the incidence of MS in adult and younger populations is not evolving at a steady rate but exponentially and suggests unidentified intervening factors are contributing to disease pathogenesis.

Overview of causal links to the global growth in MS

The acknowledged rise in adult and paediatric cases of MS is, as reasoned above, unlikely to result solely from improvements in detection and diagnosis. The disease falls into the category of complex genetic disorders and therefore, by definition, is partly influenced by contact between specific genes that regulate susceptibility and responses to the external environment [80]. A joint association between the International Multiple Sclerosis Genetics Consortium and The Welcome Trust Case Control Consortium [81] concluded that the principal genetic risk factors are linked to human leukocyte antigen genes with the variants DRB1*15:01, DRB5*01:01 and DQA1*01:02 being related to an increased risk of developing MS. Also, a recent study by Jokubaitis et al. [82], using data from the international MS registry MSBase, discovered sex dimorphism but no significant genetic variations and, employing machine learning techniques, forecast disease severity to improve prognostic capabilities at diagnosis [83].

Therefore, a rise in MS due to genetic anomalies would presume and require *de novo* gene modification through either hereditary or acquired mutation. However, a genomic aberration targeting predisposition would be unlikely to operate exclusively to trigger disease and account for the upturn in cases over an acknowledged age range. Also, and as noted in a recent article by Matzinger [84], the global frequency of autoimmune disease is rising faster than human genetic variations. Indeed, the relatively brief time scale over which the changes have occurred diminishes the effects that might be conveyed through genomic interference. Nonetheless, individuals with genetic variations linked to disease susceptibility may be rendered more prone to the detrimental effects of environmental factors on immunity [85]. In fact, the aetiology of MS is regarded as multifactorial which has prompted several theorised origins including the recent multiple hit hypothesis that suggests a collection of putative causative agents interact to manifest disease plus data indicating the acquisition of a genetic risk several thousand years ago in Europe and promoted by pathogenic exposure and environmental change [68, 86]. Current risk factors include a deficiency in vitamin D and environmental exposure to gut bacteria, such as *Akkermansia*, or viral pathogens including Epstein-Barr virus (EBV) with associated pathological variations in microRNA expression and myelin component cross-reactivity [87–90]. Indeed, the importance of vitamin D and, in particular, receptor binding and receptor-mediated susceptibility to autoimmune diseases has been previously

highlighted [91] and recently documented in a study by Adams et al. [92]. Moreover, a prominent role for EBV in MS is well- documented and current work indicates infection predicts and dramatically increases the risk of disease [93].

The chronology and corollaries of a world-wide increase in MS and other age-related conditions

The temporally-associated development of MS symptoms and pathology classifies the disorder as age-related which contrasts with age-dependent conditions, such as coronary heart disease and hypertension that occur as part of the ageing process [40]. Interestingly, the characteristic unimodal appearance of clinical MS is typical of other illnesses, such as RA and SLE, with an age-related onset and an autoimmune-based aetiology [94–97]. Intriguingly, chronologically delayed and defined onset of disease in a distinct population with autoimmune-linked conditions, such as RA and SLE, was not, until recently, an obvious feature of MS. Indeed, the emergence of MS symptoms noticeably fell in the over-50 s age group and the clinical profile assumed a more progressive phenotype. In fact, the condition was once exceptionally rare in the older age-set which contrasts with an increasing prevalence due to improvements in therapy, health and social care, that extends life expectancy of MS patients [98–100]. However, in a recent article by Capasso et al. [101] demographic analysis, suggests the incidence of late onset MS, with a progressive phenotype and low relapse rate, has risen over the latter 20th century and the influence of deleterious environmental exposure and immune-associated changes in the aged group of patients may be a major determinant in delayed disease.

The pattern of MS distribution will undeniably be altered by the documented increased incidence of the disease in adults and, in particular, juveniles. Indeed, previous age-specific incidence curves [102] now tend towards a negative skew, with a longer and steeper rise, before a peak and unaltered decline. Also, the illustrative profile is expected to persist as the incidence of MS has recently been predicted, by global MS market analysis, to increase between 1 and 2% over the next 5 years [103]. In addition, the probability of developing MS before a given age, defined as the age-specific cumulative incidence, will change as a consequence of the increased occurrence of the disease in the young with symptom onset emerging over a broadening timescale [104, 105]. Clearly, variation in the epidemiology of MS has important socioeconomic implications for the provision of health care, the allocation of research funds and the development of new therapies that ultimately relies on revised recognition that the disease is a coexistence of pathologies over a variable age range [106, 107]. Hence, there are compelling reasons to investigate a basis for the increase and identify putative effector mechanisms that may ultimately aid discovery of new methods of control.

Environmental stressors, aberrant immune ageing and rising autoimmune disease

The review thus far leaves little doubt that the demographic and global profile of autoimmune-based conditions, including MS, has changed over recent decades but what are the reasons for the upsurge in cases? An earlier review by us collated information that showed the inherent process of immune ageing, or immunosenescence (ISC), is prematurely altered during MS and hinted that the untimely changes may contribute to the recorded increase [40]. In particular, we suggested chronic exposure to antigenic risk factors cause exhaustive long-term activation of adaptive immunity which hastens intrinsic immune cell-dependent changes, including ISC, that contribute to the upturn in the disease. Interestingly, in an earlier review by Martin [108], environmental stressors were classified as age-enhancing risk factors, or gerontogens, that may regulate the appearance and dynamics of precise features of the senescent phenotype. Later work by Sorrentino et al. [109] developed the concept by suggesting that repeated contact with gerontogens expediates physiological aspects of senescence and, moreover, accelerates the rate of molecular ageing *in vivo*.

Since publication a number of commentaries support our suggestions by acknowledging the continuing global increase in many autoimmune disorders, such as MS, may be due, in part, to environmentally-derived stressors that disturb the performance and inherent age-related remodelling of the immune system. Indeed, contemporary observations indicate that, over a wide demographic boundary, the onset of MS is accompanied by early alterations to the dynamics of ISC which are precipitated through exposure to environmental risk factors in genetically susceptible individuals [101, 110, 111]. Further endorsement of our proposal is provided through recent studies in SLE [102] and previous related work by Bauer and colleagues [113–115] who implicate chronic stressors as causative of untimely immune ageing and hence a risk factor in RA. Importantly, the current view considers the early alterations in ISC, which occur in the absence of chronic inflammation, are a primary rather than secondary cause of RA and, via environmental stimuli, contribute to the documented rise in cases of the disease. Similarly, harmful exposures may act as a trigger for the premature age-related immune changes detected in MS that begin a chain of events which eventually impact the rate of disease.

The putative and established risk factors implicated in the aetiology of and, in particular, the increase in

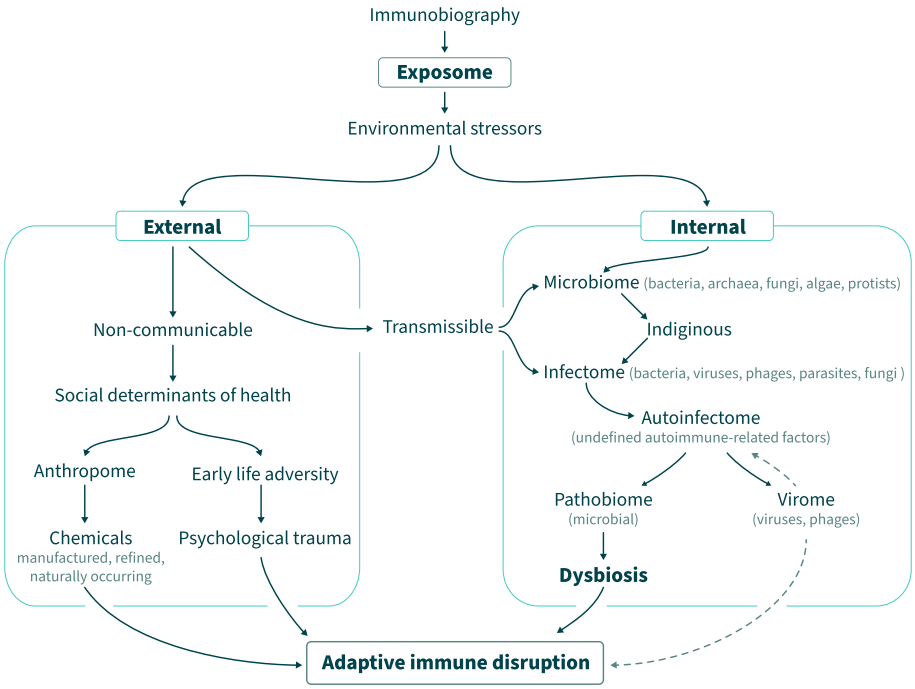

Fig. 1 Determinants and locations of environmental stressors that comprise the exposome. The immunobiography is determined by the exposome which comprises several categories of environmental stressors. Internal stressors are contained within the microbiome which also accommodates externally-derived transmissible agents that together create the infectome and sub-infectomes. The anthropome and social determinants of health constitute the non-communicable arm of the external stressors. Adaptive immune disruption includes alterations to the dynamics of immune ageing

represents the contents of each biome and infectome

signifies changes associated with the virome that may proceed independently of dysbiosis

autoimmune diseases, such as MS, are extensive and generally categorised as either non-communicable or transmissible (Fig. 1). Included in the non-communicable stressors are subjection to psychological trauma, due to incidental early life adversity (ELA), and exposure to chemical entities collectively classified as anthropogens [116–119]. Transmissible risk factors comprise non-pathological microbes and opportunistic pathobionts that have accessed and colonised the environment of a healthy human microbiome. The stressors are capable of variable and dynamic interplay between biological systems and, specifically, immune reactions that, if recurrent over a lifetime, will accumulate to generate a totality of exposures, or exposome, that creates an immunobiography of personal antigenic encounters [120–122].

Non-communicable psychological and chemical stressors

Psychosocial trauma during childhood and adolescence is grouped as episodes of ELA that are known to impact on immune effectiveness which predisposes young adults, from late second decade to mid-third decade of life, to the onset of chronic inflammatory disorders and the development of autoimmune disease [118, 123–129]. In particular, there is mounting evidence that exposure to ELA augments ageing of the immune system that features dynamic alterations to ISC including changes to T cell-related biomarkers such as telomere length, variable receptor expression and quantitative alterations to lymphocyte populations [127–132].

Recent investigations have also been directed towards the consequences of ELA on the emergence and course of MS during young adulthood that begins post-teenage years and continues to the mid-forties and throughout the following duration of middle adulthood. Initial illustrative studies by Spitzer et al. [133] and later work by Shaw et al. [134] found adult MS patients who experienced ELA subsequently developed an advanced onset of disease and increased relapse rates compared to controls. Also, specific stressful life events during childhood, including an experience of lower socioeconomic status, were found to raise the risk and speedier progression of MS in adulthood although supplementary investigations were contraindicative [135–142].

The vast majority of chemical risks have evolved from industrial concepts, techniques and manufacture which has prompted classification under the collective heading of anthropome (Fig. 1) that, in particular, directly challenges and antagonises the immune system [143–145]. Arguably, the types of anthropogens have not varied substantially with time but, undeniably, there is currently a greater variety of stressors, at concentrated levels, within the groupings. Examples of anthropogens include nutritional factors, small particle pollutants and a wide range of chemicals including toxic elements, pesticides and volatile organic compounds [144, 146]. Over recent years, an awareness has developed of the serious harmful influence anthropogens have on human health, the impact on chronic disease and, in particular, the effects on immune function and the frequency of autoimmune disease. Indeed, there is a growing belief that long-term interaction with certain environmental stressors, and in particular, anthropogens contributes to the worldwide escalation in autoimmune diseases [3, 147]. For example, a recent short paper by Bertucci [148] has discussed the ability of various anthropogens to induce a dysbiosis, or microbial imbalance, in the gastrointestinal (GI) tract and, consequently, an unfavourable environment that facilitates disruption of inherent ISC. Moreover, anthropogens have been acknowledged by the World Health Organisation International Programme on Chemical Safety [149] and considered, more recently, in The Lancet Commission [160] as globally and profoundly damaging to human health and especially disruptive to immune system performance.

There is mounting proof and a growing acceptance that exposure to and absorption plus accumulation of anthropogens via routes including inhalation and topical contact increases the propensity and incidence of MS. For example, there is substantial combined evidence indicating a strong association between a range of chemicals, including neurotoxic metals and organic solvents, and the augmentative effects on the epidemiological profile of juvenile and adult MS [151–156]. In addition, there is increasing confirmation that anthropogens disturb the control systems that maintain adaptive immune integrity and especially the processes which regulate immune ageing [143, 157–160]. Moreover, there are definite indications that chronic exposure to or repeated interaction with anthropogens promotes a change in the momentum of immune ageing that supports an accelerated state of ISC [143, 157].

Indigenous and transmissible microbes

A second category of risk factors involves a whole-body community of intrinsic and acquired microbes, or microbiota, contained within either a single microbiome or constituent microbiomes unified on the epithelial cells of mucosal and non-mucosal body surfaces of the oral and nasal cavities and the respiratory, urogenital and GI tracts. The indigenous bacteria and other native microorganisms of the microbiota within each microbiome have co-evolved with the host. In contrast, there resides another population of externally-derived and transmissible, non-pathological and pathological microbes, within a sub-biome referred to as the infectome, that encompasses the designated sectors of the autoinfectome, pathobiome and virome (Fig. 1) [161, 162]. Interestingly, an efficient immune system is dependent upon good cooperation between the host and the microbiota which, if disturbed by exposure to environmental risk factors, may cause dysbiosis and impact on the augmented increase in autoimmune-type diseases [163].

The most abundant microflora is within the microbiome of the GI tract that creates a mutualistic rather than, as originally thought, a commensal, one-way relationship with the host [161]. However, and despite defensive mechanisms, the constitution of the gut microbiota is not static and, with time, also becomes populated by environmentally-derived symbionts and transmissible pathobionts that inhabit the constituent sectors of the infectome which creates a dysbiosis [164–167]. Essentially, the assimilated presence of transmissible microbial stressors shifts the gut flora from a eubiotic to a dysbiotic state and a considered driving force for altered ISC together with a loss of immune tolerance in autoimmune-based diseases [168–170].

Reasons to explain the unequivocal global increase in autoimmune diseases, such as MS, prompted studies of the GI microbiome, using genetic-based sequencing, that confirmed compositional and functional changes in patients, compared to healthy controls, and speculated environmental factors to be instrumental in the discrepancies [171]. Specifically, a growing number of recent studies found that, compared to controls, the gut microbiome of MS patients shifts from a well-controlled eubiosis to a distinctive dysbiosis between organism types [172–184]. Moreover, recent comprehensive investigations on the gut microbiome in MS and findings recently reported by the International Multiple Sclerosis Microbiome Study (iMSMS) Consortium indicate dissimilar microbial systems in MS and reveal specific GI microbial associations with the development and course of disease [185, 186].

In summary, aberrant age-related changes to the adaptive immune system, whether elicited by exposure to psychosocial, anthropogenic or transmissible pathobiont-related stressors, in susceptible individuals may be an impetus for the worldwide increase in autoimmune

disorders that includes MS. A definitive link between environmental-induced effects, abnormal alterations to intrinsic ISC and a global increase in autoimmune-based conditions, such as MS, is difficult to unequivocally establish. However, one strategy to explore a relationship is to examine, more precisely, the senescence-related constituents of an aged immune system and establish which elements of each category are susceptible to disturbed alterations mediated by exposure to environmental stressors.

The ageing immune system and the global increase in autoimmune-based disease

Age-related remodelling of adaptive immunity within a framework of cellular senescence

In order to understand the operating framework on which age-associated anomalies to adaptive immune performance are built and exposome-induced malfunctions occur there is a need to appreciate the scheduled but indeterminant effects of ageing that selectively involve immunological processes which form part of the larger network of cellular senescence [187, 188]. There has been confusion surrounding the definition of cellular senescence, originally applied to *in vitro* preparations attaining maximum replication, which has hampered understanding and, in turn, impeded a clear interpretation of immune cell ageing [189, 190]. Therefore, a brief discussion on the complex and overall process of cellular senescence is worthwhile to differentiate and understand the mechanisms governing constitutive ISC and the consequences of senescent immune cell interaction with non-immune cells in ageing tissues and for age-related diseases such as MS.

Age-dependent cellular senescence, first observed in primary cell cultures over half a century ago, was originally described as a permanent state of mitogen-resistant cell-cycle arrest of diploid cell division that, more recently, has been defined mathematically, by the International Cell Senescence Association (ICSA), as a non-linear multivariable function $F(x,y)=z$ where outcome, (z), depends on stimulus, (x) and environment (y) [191, 192]. Subsequent *in vitro* studies distinguished two major cell phenotypes that age either prematurely, before the expected time, or at a replicative-dependent rate that has also been described as accelerated which, after reviewing current findings, may only apply to cells subjected to stressful conditions that generates a proposed augmented state of maximum proliferation and permanent arrest. Additional work has highlighted other distinct differences between the two processes and classified an aberrantly-activated, developmentally programmed third state of oncogene-induced senescence [193, 194].

Premature senescence is stress-induced, often referred to as SIPS, independent of telomere shortening and triggered by damage signals such as mitochondrial dysfunction, persistent deoxyribonucleic acid (DNA) disruption and oxidative stress. In contrast, and with the appearance of telomere attrition, a loss of protective telomere function, plus a decrease in activity of the ribonucleoprotein telomerase enzyme complex, a replicative or apparently atypically accelerated senescence programmes a limited number of cell divisions but leaves a state of residual biochemical activation [195–197]. Senescent cell production following stress exposure is a chronic primary response, unlike the normal acute embryonic-linked counterpart, and capable of inducing non-senescent cells to undergo a secondary paracrine-based senescence, via extracellular modulators that constitute the senescence-associated secretory phenotype (SASP), or a juxtacrine senescence through cell-to-cell contact. Hence, a preliminary small collection of distressed, non-replicative senescent cells has the potential to increase and propagate phenotype numbers and effects [198]. Also, an additional point to acknowledge is that age-related diseases like MS often present within an environment of acquired senescent cells, referred to as primary, which have accumulated as a result of normal tissue atrophy. Tissue resilience to stressful insults from an ongoing condition is reduced by the presence of primary senescent cells and, over time, a secondary population of aged cells is generated that, in combination, power, enhance and perpetuate disease [199]

In summary, the continuously expanding, multifaceted process of cellular senescence, is time-dependent and age-linked and has either long-term chronic and often inflammatory-associated implications or immediate and potentially beneficial consequences for age-related diseases such as MS [200]. Moreover, the events which culminate in cell-cycle arrest occupy key *in vivo* positions in maintaining physiological equilibrium or homeostasis, age-related morbidity including cancers, chronic pulmonary and kidney disease and age-associated effects in various tissues involving lung, liver and bone which may be referred to as pulmono-, hepato- and osteosenescence, respectively [199].

Transformative ageing of the immune system within an environment of cellular senescence

Reconfiguring the immune system: a 20th century phenomenon?

The framework of cellular senescence includes the construct of ISC that features an inherent progressive decline in immune integrity over the infant-to-adult human lifespan [201]. An increase in lifespan, together with

life expectancy, reflects the health of a nation which, paradoxically, challenges inherent survival mechanisms and compromises defence networks, including the immune system, that are designed to protect against disease. Enhanced life expectancy, and prospective ISC, becomes noticeable during the 20th century, mainly due to improved health care and chiefly in the developed countries of Europe and North America, rising to almost 90%, or 75 years from an average of 40 years, during the early 19th century [202]. Immunological restructuring consistent with ISC and increased longevity was considered undesirable but recent opinion incorporates a view of essential adaptation to previous and, in particular, current harmful exposures [203, 204].

Immune ageing is regarded as the accumulated molecular injury, plus phenotypic changes associated with biological ageing, that propagates a lasting, but not complete, inability of a selective population of viable cells, comprising the innate and adaptive immune systems, to propagate beyond a certain point [205, 206]. Normal pressure on the triggers that launch ISC appears inherent and gradual over a defined period. Current sociological and scientific opinion considers ISC to begin, in healthy aged individuals with a 20th century enhanced life expectancy, between the sixth and seventh decades [207–209]. Therefore, the probability of detecting ISC, which appears chronologically-dependent rather than biologically-reliant, in early middle-aged healthy persons during the 19th century would be minimal. Indeed, the occurrence of ISC is viewed as evolutionary restricted and also closely linked to an age-associated and cumulative antigenic exposure that would have been considerably less for a population prior to the 20th century [210]. Notably, the degree of immune deterioration or ISC is characterised by historic antigen exposure and a declining response to novel antigens resulting from a decrease in peripheral naive B-cells and T-cells with a concomitant rise in memory T lymphocytes and a gradual state of adaptive immune cell fatigue [176, 177, 211, 212].

The origins of cellular senescence and ISC are closely interwoven and, specifically, *in vitro* cell-based studies indicate, as confirmed features of aged immune cells, a dynamically-distinct, dual phenotype that is either replicative telomere-dependent or premature telomere-independent [179, 180, 213, 214]. Ongoing *in vivo* adaptations that typify ISC, are general features of cellular senescence and vulnerable to dynamic transformations would include either augmented [accelerated], telomere-dependent and telomerase-limited or untimely [advanced], telomere-independent alterations to the immune system [215]. A contemporised view, based on current discussion, considers replicative, or accelerated, and premature, or advanced, ISC to be relatively new phenomena that have slowly developed and become either primary causes or consequences of autoimmune-associated disease. Alternatively, and before the 20th century, the absence of ISC in a healthy population may have been altered by diseases which provoked accelerated or untimely remodelling of an uncompromised and naturally ageing immune system. However, the origins, timing and identity of the stressors that activate the mechanisms which disrupt the schedule and disturb immune aging within a pathological setting are not understood. In addition, the corroborated evidence of active changes to the immune system in autoimmune-based and non-autoimmune-related conditions, together with the consequences of age-related immune alterations on clinical and epidemiological outcomes, are speculative.

Adaptive immunity and ISC in MS

Innate immunity governs the initial response to pathogens via a variety of blood-derived cells and related inflammatory mediators including neutrophils, macrophages, natural killer lymphocytes and cytokines plus chemokines. Intrinsic immunity is susceptible to age-related changes but appears less sensitive to ISC, compared to the adaptive system, which exhibits quantitative and functional alterations to various T cell and B lymphocyte subsets [216]. However, ISC, with often negative connotations linked to increased disease susceptibility and not to be confused with immune exhaustion, or immune cell quiescence, exerts more complex changes to adaptive immunity. Indeed, interest has grown in the relationship between immune ageing and the adaptive arm of the immune system that has examined the impact on age-related disease pathogenesis, such as occurs during MS, and considered the interaction from a mechanistic and therapeutic perspective [217–220].

Research into immune ageing has developed, from the latter half of the last century and over the intervening years, to provide several theories that attempt to explain ISC by considering autoimmunity and T and B cell behaviour, immunodeficiency and impaired defences, deregulation and abnormal immune activation and a viral concept that highlights altered adaptive mechanisms [205, 221, 222]. Moreover, ISC has been defined through the damage theory of ageing that incorporates either an overall systemic or site-specific deterioration which may alter the susceptibility to or profile of autoimmune-related diseases with potential repercussions for worldwide epidemiology [223–227]. Indeed, our collective studies considered the consequences of ISC on the course of MS and especially adaptive immunity which, despite conjecture, substantially contributes to the aetiology and pathogenesis of the condition [228]. Detailed evidence verified, as anticipated, ongoing ISC during MS

that would gradually remodel the immune system and, together with a recently confirmed age-linked inflammation, termed inflammageing, expose patients with typical chronic, progressive and neurological disabling disease to the uncertain effects of immune ageing in peripheral and central tissues [40, 229–232].

Evidence for premature and accelerated replicative ISC in MS

Premature ISC (pISC)

Clearly, age-related remodelling of immune mechanisms occurs irrespective of health status but the presence of disease, particularly of autoimmune origin, will bias alterations, predominantly to the adaptive rather than the innate arm of the system, and therefore the control of immune tolerance [187, 238]. Our work assembled evidence of age-related, untimely immune cell-associated alterations during MS which were specifically referred to as occurring prematurely. For example, involution of the thymus is a major characteristic of ISC and several studies have observed similar advanced physiological changes to thymic tissue in the disease. Also, supplementary markers of pISC have been detected in MS patients including the enhanced presence of cluster of differentiation (CD) $CD4^{+}CD28^{null}$ cells in the circulation and CNS tissues together with decreased levels of T-cell receptor excision circles which represent a bi-product of immune cell maturation.

Since publication of our review additional investigations support age-linked, immune cell-associated alterations during MS that may occur via an untimely activated route. For instance, controlled studies by Zuroff et al. [213] in adults showed MS-associated, abnormal age-related changes in activated and cytotoxic $CD4^{+}$ T-cell levels. Also, results revealed an inverse relationship between cytotoxic T-lymphocyte associated protein-4 (CTLA-4) expression and the enhanced appearance of a costimulatory B-cell molecule which may advance quantitative alterations in the subsets of $CD4^{+}$ T-lymphocytes. In addition, earlier investigations in samples from MS patients confirmed pISC through analysis of biomarker protein ligand levels and $CD8^{+}$ T-cell populations [189, 190, 211, 214]. Interestingly, with increasing age, the profile of ISC in patients was similar to matched controls indicating that, with the chronological and clinical progression of disease, the untimely immune changes either decelerate to the estimated norm or maximise earlier to eventual values of healthy aged subjects. Furthermore, a recent review by Thakolwibbon et al. [212] suggests that ISC-associated changes to adaptive immunity affect the profile of RR disease and active demyelination whereas ageing of the innate immune system, that targets resident CNS cells and occurs during the progressive course of MS, has important consequences for the accompanying levels of neurodegeneration and physical disability.

Accelerated replicative ISC (arISC)

Another valuable and distinct observation to subsequently emerge from the current review is that not all age-related modifications to the adaptive immune system in MS patients are premature. Indeed, and by definition, those ISC-associated changes which are dependent on telomere attrition and related telomerase activity occur via replicative (r) or an accelerated replicative (ar) senescence. Moreover, direct and indirect proof, via predictive analysis, of an arISC in MS patients is provided by an increasing number of carefully controlled investigations that confirm an augmented presence of the replicative senescence biomarker, altered telomere length, in leukocyte populations and bone marrow-derived stem cells at clinically defined, often chronic, stages of the disease [215, 239–243]. Also, and using predictive Mendelian randomisation studies that estimate exposure-linked outcomes, there appears an association between telomere length and the increased risk of MS which implies the involvement of an arISC at an undefined stage in the disease process [244–247]. The degree of disability in RRMS may also be predicted by leukocyte telomere length which, when reduced, is a general defining feature of primary and secondary progressive disease allied to increasing debility and brain atrophy. Also, the telomere-dependent changes closely associated with the progressive MS phenotype invariably follow immune age-related modifications that are telomere-independent which provides further dual biomarker-related evidence of a defined combination of pISC and arISC operating across the disease process [248].

A correlation between the dual phenotypes of ISC and induction by environmental factors linked to MS pathology

Table 1 shows the features of a SIPS or, more specifically, pISC that, as expected but with the exception of morphological changes and activation of the TGF-β pathway, appear as a consequence of immune cell-dependent exposure to environmental stressors. In particular, the table lists the pISC-related traits verified in MS and reveals compelling evidence of an association between the disorder and extrinsic risk factors that mediate untimely stress-induced immune cell changes which may occur either prior to or immediately before the initial appearance of clinical disease. Interestingly, putative stress-induced activation of the SASP and, in particular, the p53-p21 signalling pathway that, when triggered, down regulates cell cycle events are not exclusive to

Table 1 The occurrence of immune cell-related features of pISC following exposure to environmental stressors and during MS

Feature	Reference	Environmental stressor	Reference	MS	Reference
Thymic involution	[197]	V	[249]	V	[40]
Morphological changes*	[250]	NV		NV	
Epigenetic changes	[251]	V	[252, 253]	V	[254]
DNA damage response/activation pathway	[255, 256]	V	[254]	V	[254, 257]
Oxidative stress	[263]	V	[264]	V	[239, 265]
Mitochondrial dysfunction	[258, 259]	V	[260, 261]	V	[262]
Disordered proteostasis	[266]	V	[267]	NV	
SASP activation*	[268]	V	[253]	V	[229, 269]
p53-p21 pathway*	[256]	V	[252]	V	[272]
TGF-β pathway	[273]	NV		NV	
$p38^{MAPK}$pathway	[228]	V	[275]	V	[276]
SA-β-gal*	[270, 271]	V	[252]	NV	

There is no single biomarker with absolute specificity for cellular or immune cell senescence [188] and a multi-marker approach to detection and identification, in non-MS and MS-based studies, has been applied in the compilation of Tables 1 and 2. Furthermore, the biomarkers, some of which are, to date, not verified (NV) or verified (V) and common to pISC and arISC (*) following exposure to environmental stressors or during MS, and confirmed in immune cell populations as previously detailed [309–311]. Verification of MS-associated or environmental risk factor-related hallmarks of immune cell-related senescence indicates a close inter-relationship. There is also an inter-connection provided by the comprehensive picture of a relationship with pISC and arISC despite conjecture over biomarker expression in MS (†) [312–317]

Table 2 The occurrence of immune cell-related features of arISC following exposure to environmental stressors and during MS

Feature	Reference	Environmental stressor	Reference	MS	Reference
Morphological changes*	[277]	V	[252]	NV	
Telomere attrition	[278]	V	[124, 279]	V	[231, 239, 242, 243]
Restricted ribonuclease telomerase	[278]	V	[280]	NV	
SASP activation*	[285]	V	[286]	V	[222, 229]
Downregulated CD27†	[281, 282]	NV		V	[283]
Downregulated CD28	[278, 284]	NV		V	[283]
Upregulated CD45RA/TEMRA	[216, 219]	NV		V	[283, 289, 290]
Upregulated CD57	[216, 284, 287]	NV		V	[288]
Upregulated TIM-3	[216]	NV		V	[211]
Upregulated KLRG-1	[219, 284]	NV		NV	
Reduced perforin/granzyme B	[219]	NV		V	[298]
Increased $p16^{INK4a}$	[291, 292]	V	[108, 252]	V	[297]
Increased p21 CIP1/WAF1/SD11	[293, 294]	V	[252]	NV	
Increased p53	[295, 296]	V	[252]	V	[299]
Activated p53-p21 pathway*	[249]	V	[252]	V	[272]
SA-β-gal*	[223]	NV		NV	
DNA damage	[255]	NV		NV	
Lipofuscin	[300]	V	[301, 302]	NV	

There is no single biomarker with absolute specificity for cellular or immune cell senescence [188] and a multi-marker approach to detection and identification, in non-MS and MS-based studies, has been applied in the compilation of Tables 1 and 2. Furthermore, the biomarkers, some of which are, to date, not verified (NV) or verified (V) and common to pISC and arISC (*) following exposure to environmental stressors or during MS, and confirmed in immune cell populations as previously detailed [309–311]. Verification of MS-associated or environmental risk factor-related hallmarks of immune cell-related senescence indicates a close inter-relationship. There is also an inter-connection provided by the comprehensive picture of a relationship with pISC and arISC despite conjecture over biomarker expression in MS (†) [312–317]

pISC. Indeed, p53 and p21, together with the cyclin-dependent kinase inhibitor $p16^{INK4a}$, are involved in arISC and appear sensitive to induction following contact with external stressors (Table 2). However, many of the features related to arISC, other than those shared with pISC and associated with telomere attrition and cell cycle events, appear unreactive to harmful exposures. For example, each of the T cell surface CD molecules that define arISC and are upregulated in MS appear unaffected by environmental exposure. In contrast, and independent of risk factors, expression of the majority of the T cell receptors are altered and protein regulators central to the cell cycle events are activated during disease.

In conclusion, a collective appraisal of data relating to the components of ISC reveals two dynamically-distinct cell-dependent processes but also common proliferative stressor-sensitive pathways, as previously suggested [312] and a heterogenous secretory phenotype which supports intercellular signalling mechanisms. Specifically, pISC is initiated and appears almost entirely driven by stress-related exposures that are potentially harmful through altered adaptive immune cell functions at molecular and physiological levels. In comparison, the immune cell senescence associated with arISC is intrinsically programmed but may be more precisely augmented by extrinsic risk factors that essentially promote a protective growth arrest and consequently curb proliferation through upregulation of restrictive molecular signalling pathways. Therefore, under stressful conditions and irrespective of chronological age, cells of the adaptive immune system, in prospective or early onset MS, may be subject to a bilateral influence that restricts proliferative events and promotes untimely senescence beginning in advance of or immediately prior to clinical disease. Importantly, and supporting our original suggestion linking immunogenic risk factors, altered immune ageing and the shifting epidemiology of MS, there is further evidence of pISC over the course of disease and, notably, data to support the presence of an arISC during the condition that correlate with immune cell-dependent changes found inducible by exposure to environmental stressors.

Reciprocal involvement of the periphery and CNS with pISC and arISC in MS

Cellular senescence and specifically ISC is not confined to the tissues of peripheral organs. Indeed, and of particular relevance to the pathogenesis of MS, there are age-linked alterations in recognised immune cells of the CNS, via a reciprocal relationship with systemic immunity that crucially governs central immune responses [114, 313]. A bilateral profile of pISC and arISC changes are present in astrocytes and augmented telomere-dependent features of immune ageing, with SASP involvement, become evident in vulnerable innate mononuclear phagocytic microglia that also includes morphological changes and disruption of immunological function via probable interaction with an aged and reconfigured peripheral immune system [229, 314, 315]. Also, the interconnection between peripheral and central immune systems may promote the observed changes to biomarker expression on primed and activated microglia that provide resident cell immunity and endorse an inflammatory environment with neuronal disturbances characteristic of neurodegenerative diseases including MS.

Therefore, the remodelled profile of an inherently or inappropriately aged systemic immune system would directly influence immune function in the CNS and shape the progression of neurodegenerative diseases such as MS [315, 316]. Indeed, peripheral interaction between ISC and the inflammageing process influences CNS immune cell behaviour and generates a neuroinflammation capable of effecting the neurodegenerative process characterised in MS [316–322]. In fact, microglial senescence has been linked to malfunction through, in particular, an increase in neuroinflammatory responses that target neurons and therefore drive the neurodegenerative process characteristic of MS [323]. Moreover, the apparent intensification of systemic ISC by harmful exposures may, indirectly and through joint exchange, accelerate and promote inherent rISC and pISC respectively in the CNS of MS patients.

Explanation on the scheduling of pISC and arISC in MS from other autoimmune-based diseases

Contemporary research into geroscience, defined as biological ageing and the relationship with disease, together with the construction of a knowledge-based Aging Chart, has revealed a spectrum of variations and pathways including personalised changes to the immune system that are immune cell-selective and, consequently, fundamental for an aged immune response to antigenic challenge [118, 324–326]. Similarly, ISC is individually unique to patients with MS and, as now verified, includes the presence of accelerated and untimely phenotypes which may challenge immune function, including self-tolerance to neoantigens, predispose to illness and modify the progression of disease. Also, and as originally proposed [40] and now verified, the induction of indeterminate mechanisms that adjust the pace of ISC, via a valid link with harmful environmental exposures, may contribute to the recognised global rise in MS.

The possibility that susceptibility to and occurrence of MS is changed by induced or non-induced dynamic

variations in immune ageing is a relatively new concept but one that has been considered in other human conditions and, initially, in experimental models with ISC-linked transformation of immunity that encompass a decline in efficiency with a reduced self-tolerance [327]. For example, a similar pattern of immune cell-related factors, including SASP release and telomere attrition suggesting pISC and arISC, have been recorded in and allied to the progression of autoimmune-associated diseases such as RA and SLE [114, 328]. Incidentally, altered immune ageing in disorders such as RA have often been categorised as premature but, and as highlighted in the current article, are more accurately defined as a replicative phenotype that participates in disturbed immune stability [329–332].

The development of a bilateral ISC, under an age-related backdrop, appears to be operating in MS, and possibly other autoimmune conditions, where inappropriate immune ageing occurs more gradually and, crucially, must manifest either during the typical pre-clinical latent phase or over the course of symptoms with onset during young adulthood or later when inherent immune ageing has begun [333]. Also, and to reiterate, if environmental stressor-influenced untimely or accelerated immune alterations are to disadvantage the long-term epidemiological profile of autoimmune disorders, then disturbances to inherent immune ageing must be activated prior to diagnosis. Information to determine, more precisely, the scheduling of early immune changes during the pre-clinical and clinical course of MS, and other autoimmune disorders, such as RA, is offered through paediatric studies. Indeed, the disorders in the young suggest a putative predisposition in an immature immune system governed by genetic bias or relatively brief but chronic exposure to suspected environmental risk factors [54, 334–338]. Moreover, untimely immunological variations in populations of memory, regulatory and effector T-cells have been verified in young MS patients which may relate to symptoms and explain the clinical variance between age groups [31, 339].

Therefore, identification of causative influences, through genomic analysis and retrospective examination of environmental exposures, becomes more focused within a defined timeline that also enables an investigation of the triggers for an aberrant bilateral ISC. Indeed, initial reports have presented and considered evidence that supports a distinct pISC during paediatric MS, and also RA, through detection of early thymic involution and proportional alterations in T cell subsets, particularly in demyelinating disease, that are advanced, by 2 to 3 decades, to resemble variations assigned to adulthood [340, 341]. In fact, the prematurely aged immune cells in paediatric cases occur in ratios similar to older patients with early MS and also express adult phenotypes that govern susceptibility to the disease.

The prospect of senotherapy to alter divergent dynamics of ISC associated with MS

The documented global increase in MS, via a proposed long-term exposure to environmental stressors, may be, as has been suggested, the outcome of cellular senescence-based activity which directly promotes neurodegeneration through interplay between constituent ageing mechanisms [342] that include the combined replicative and premature changes now shown to be associated with ISC. Also, the established occurrence of premature and accelerated alterations to the intrinsic process of ISC in MS and, indeed, other conditions with an autoimmune aetiology, will have noticeable consequences on the incidence of disease in susceptible individuals but without precise knowledge on the specific changes to immune components. In addition, the development of an excessively aged immune system composed of increasingly senescent cells, due to dual dynamic effects, presents unknown long-term consequences for disease prognosis including the suspected build-up of debilitating symptoms [232]. Moreover, the influence of ISC and consequences for the MS patient, which should also be appreciated by the therapist, are age-related with the possibility that wide-ranging changes to the immune system predispose to co-morbidities including infections, neoplasms and cardiovascular disease [99]. Other major concerns that may be elicited as a result of the altered dynamics of ISC are an intolerance to treatment and changes to drug efficacy.

Restricting chronic contact with resident or non-resident stressors to reconfigure the cellular senescence associated with atypical ISC and potentially improve the outcome for disorders like MS may not be entirely feasible. Also, there is a need for greater understanding of the age-related immune cell-dependent systemic and CNS-associated interactions and changes over the course of disease. One approach to limit the detrimental impact of pro-immunosenescent risk factors and study aged-related immunity is to counteract untimely or accelerated modification of immune cell function through the use of geroprotectors that represent a class of over 200 compounds designed to target mechanisms involved in the ageing process. Generally, the use of geroprotectors decelerates aspects of ageing and, more specifically, includes senotherapeutics that are either senolytic and hinder build-up or enhance ablation of viable senescent apoptosis-resistant immune cells or senomorphic and senostatic which reduce the inflammatory effects of SASP-related factors and development of inflammageing [343–345]. Interestingly, there have been proposals, by us and others, to

employ established forms of experimental autoimmune encephalomyelitis that model the clinical and histopathological aspects of MS and, practically, show elements of immune cell ageing during disease that may be modified by senolytics and tissue-related rejuvenating therapies prior to evaluation in MS-centred clinical trials [40, 232].

The immune system is considered a key force that steers cellular senescence and guides the essential clearance of aged cells [346]. Therefore, if immune surveillance is compromised by ISC then non-immune senescent cells may collect in tissues with increasing age and pathological consequences [347]. Senotherapeutics are potentially useful in the regulation of inherent or disordered ISC and, ultimately, the restoration of an efficient immune system particularly for the management of autoimmune disease. Indeed, a restriction on ISC to reduce senescent cell accumulation and target depletion may allow regeneration and recuperation of new and existing cells. However, current senolytics appear to have only some degree of effect on immune cells [348]. Moreover, and despite continuing clinical research and subjective discussion there is an absence of therapies with proven efficacy in rejuvenating an ageing immune system and, in particular, redressing the aberrant components of stress-induced ISC [328, 349]. A more targeted approach has been to use senolytic immune-associated treatments through which genetically engineered T lymphocytes recognise cell surface receptors on senescent immune cells. For example, chimeric antigen receptor (CAR) T cells have been artificially created that recognise the natural killer cell receptor NKG2D on immune cells, including CD4 and CD8 lymphocytes, to elicit selective elimination and restriction of cellular senescence [350, 351]. Senolytic drugs are often repurposed and include the multityrosine kinase inhibitor dasatinib and the flavanol quercetin, frequently used in combination, and the B-cell lymphoma 2 (Bcl-2) inhibitor navitoclax that selectively target pro-survival mechanisms via induced apoptosis [352, 353]. Senomorphics comprise nucleoside reverse transcriptase inhibitors like lamivudine, the Janus kinase (JAK) 1/2 inhibitor ruxolitinib, the antidiabetic metformin and glucocorticoids plus mechanistic target of rapamycin (mTOR) inhibitors or rapalogs [354].

Tailored management and measured use of senotherapeutics to counteract a persistent threat from prosenescent risk factors that may undesirably bias the epidemiology of MS could benefit from the increasing array of screening techniques, including mathematical and computational modelling plus image-based phenotypic profiling, to improve drug selection [355–357]. Indeed, targeting specifics of cellular senescence, and especially a bilateral ISC, would affect replicative and premature components that have now been shown to operate in MS, with potentially disparate effects and, therefore, essential distinctions that would require selective therapy [358]. For instance, the replicative pathway of ISC is considered protective, despite a conflicting link with chronicity in MS [229], whereas pISC is deemed harmful because of a close association with the development of inflammageing. Support for cautious selective senotherapy is also provided by evidence that cells entering senescence, via contrasting routes, are distinctly susceptible to different senolytic drugs [359].

However, and regardless of some success in the senotherapy of neurodegenerative conditions, such as Alzheimer's disease, there is a lack of clinical data concerning efficacy in MS [360–362]. Nevertheless, there is understanding of the role systemic and CNS cellular senescence plays in the development of relapsing disease and how conventional therapy may be affected by age-related immune changes in patients with late-onset symptoms and co-morbidities [363–366]. There is, as a result, awareness of an unmet need for immune redress and rejuvenation in MS through the use of senotherapy but, to date, only proposals have been offered [229, 232, 366, 367].

Recognition that ISC is composed of an untimely and accelerated senescence adds value to accumulating evidence that any rate change in ISC during phases of MS impacts on the pharmacokinetics, therapeutic index and effect of DMTs administered to patients both young and old[368–370]**.** Indeed, the documented efficacy of DMTs, such as cladribine (Mavenclad), fingolimod (Gilenya) and natalizumab (Tysiabri), and the pattern of side-effects may be altered by the time-dependent, immune-linked changes that occur systemically and within the CNS particularly during late-onset MS and very late onset disease [371–373]. In fact, the current evidence of a dual dynamic change in ISC ongoing during MS may, and as proposed in a recent study by Manouchehri et al. [370] and reinforced through current work by Gelibter et al. [374] help to explain the failure of DMTs, plus high efficacy therapies, to modify the more progressive forms of MS. Furthermore, the realisation of efficacy differences in older patients had led to predictive Delphi-based studies that have reinforced the need for age-associated tailored therapy [375]. Mention should also be made of vitamin D therapy as an inexpensive, readily-available and easily-administered supplement that has been demonstrated to improve immune protection in age-related diseases, such as MS. In particular, vitamin D has been recognised as an immunomodulator which regulates ISC and, as a consequence, inflammageing via various mechanisms including altered T cell ratios and cytokine levels [376, 377].

Conclusions

Reasons for the documented rise in the incidence and prevalence of MS, from the latter half of the twentieth century to date, are unclear but may include a response to repeated and prolonged contact with a variety of transmissible or non-transmissible risk factors believed to alter immunological function and, in particular, change the dynamics of immune ageing. In particular, the review has provided a valuable perspective on the potential for critical environmentally-influenced alterations to the immune system that may have serious repercussions for the epidemiological of MS and, indeed, other conditions with an autoimmune aetiology. The adaptive immune system is especially prone to disruption by exposure to environmental stressors which have been verified to provoke features of untimely or pISC and encourage an augmented or arISC. Collated evidence confirms many of the immune cell-dependent changes that typify stressor-induced pISC and arISC are replicated in duplicate cell populations during MS which corroborates evidence of a dysregulated ISC during the disease. The discovery of a close link between the effects of environmental stressors on specific aspects of age-related acquired immunity and the untimely and augmented changes to ISC during MS suggests a mechanism through which pro-immunosenescent risk factors operate to shift the global epidemiology of MS.

The disordered ISC-related pathways to early immune ageing or an accelerated proliferative decline that appear triggered by harmful environmental risks may impact not only the epidemiological profile but also the pathogenesis of MS in ways that, along with other factors, either enhance susceptibility to and onset of disease or contribute to prognosis. The incidence and prevalence of MS are metric targets for adverse and persistent environmental threats that alter the dynamics of ISC. However, blanket restrictions to limit exposures are not feasible to counter the untimely or accelerated ISC-related disruptions. However, the use of selective senolytic drugs to curtail or reverse pISC or prevent and eliminate arISC-mediated senescent immune cell accumulation offers a promising therapeutic alternative. Unfortunately, and despite availability, the use of senotherapy for the management of MS has not, to date, been sufficiently assessed to conclude on the specific effectiveness to taper the onset, progression and acquired disabilities associated with the disease.

Abbreviations

arISC	Accelerated replicative immunosenescence
B cell	Bone marrow-derived cell
Bcl-2	B-cell lymphoma 2
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CNS	Central nervous system
CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
DMTs	Disease modifying therapies
DNA	Deoxyribonucleic acid
D	Antigen region-related beta
DQA	D antigen region Q-related alpha
EBV	Epstein-Barr virus
ELA	Early life adversity
GI	Gastrointestinal
HIV	Human immunodeficiency virus
ICSA	International Cell Science Association
ISC	Immunosenescence
IFN-β	Interferon-β
JAK	Janus kinase
MRI	Magnetic resonance imaging
MAGNIMS	MRI in MS
mTOR	Mechanistic target of rapamycin
MS	Multiple sclerosis
OAR	Office of AIDS Research
p53	Protein 53
$p16^{ink4a}$	Protein $16^{\text{inhibitor of cyclin—dependent kinase4a}}$
pISC	Premature immunosenescence
RR	Relapsing–remitting
rISC	Replicative immunosenescence
RA	Rheumatoid arthritis
SASP	Senescence associated secretory protein
SIPS	Stress-induced premature senescence
SLE	Systemic lupus erythematous
T-cell	Thymus-derived cell; TGF-β: transforming growth factor- β

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Author's contributions

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