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Immunosenescence and multiple sclerosis

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ABSTRACT

Changes in the immune system associated with ageing are known as immunosenescence. This is characterised by a decline in immune response, chronic inflammation and an increased risk of autoimmune diseases. A chronic inflammatory process with persistent production of proinflammatory mediators increases the risk for morbidity and mortality related to age, and has been dubbed 'inflamm-ageing'.

Immunosenescence is associated with a decrease in the number of naive T and B cells, NK cells and disruption of the pro- and anti-inflammatory balance by changes in the production of cytokines. In fact, ageing of the immune system has a complex network of underlying causes which include not only natural mechanisms of senescence but also chronic disorders, lifestyle, environmental and epigenetic factors, and infections. Moreover, immunosenescence has an influence on the course of chronic diseases which have an onset in young adults, such as multiple sclerosis (MS).

Current disease modifying therapies (DMTs) in MS aim to reduce the frequency of relapses and to slow disease progression, but they do not necessarily stop the accumulation of disability related to disease progression. Some features of immunosenescence found in aged healthy controls are already observed in MS patients at a younger age.

The older population is characterised by an increased susceptibility to infections, a poor response to vaccinations, and a higher risk of developing cancer, vascular diseases and neurodegeneration. Immunosenescence is an important factor influencing the course of MS, and the safety and effectiveness of DMTs. The relationship between the pathogenic process underlying the development of MS and immunosenescence requires further investigation.

Key words: immunosenescence, multiple sclerosis, DMTs, inflamm-ageing

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Introduction

Ageing is a progressive process of changes in the living organism that leads to a gradual decline of bodily functions. The progressive and general deterioration of these functions results in a lower ability to react to changes and preserve homeostasis adaptively [1]. This process is inevitable for every living organism. However, it represents a mystery in the evolution of higher organisms and is not well understood [2]. Changes in the immune system associated with ageing are known as immunosenescence [3]. This is characterised by a decline in immune response, chronic inflammation and an increased risk of autoimmune diseases [4]. A chronic inflammatory process with persistent production of proinflammatory mediators increases the risk for morbidity and mortality related to age and has been called 'inflamm-ageing' [5]. It seems that lifestyle factors as well as age-related intrinsic factors contribute to inflamm-ageing.

Immunosenescence is associated with a decrease in the number of naive T and B cells, NK cells and disruption of the pro- and anti-inflammatory balance by changes in the production of cytokines [3]. Crucial processes that occur over

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the human lifespan include involution of thymus, decreasing output of naive T-cells, skewing of haematopoietic stem cells towards the production of myeloid cells, loss of function of various cell lines including innate cells and B lymphocytes, and the accumulation of terminally differentiated T-cells. Furthermore, two additional mechanisms are of the utmost importance: oligoclonal expansion of T-cells specific for common persistent pathogens, including cytomegalovirus (CMV) and Epstein-Barr virus (EBV); and tissue accumulation of senescence-associated secretory phenotype (SASP) cells, which results in low-grade inflammation [6]. These alterations play important roles in morbidity and the course of neurological diseases.

This review aims to discuss immunosenescence in the context of neurological disorders, especially multiple sclerosis (MS).

Immunosenescence and inflamm-ageing

Immunosenescence is described as age-associated changes within the immune system [7]. Inflamm-ageing plays an important role in immunosenescence. The mechanism of inflamm-ageing is far from completely understood. According to Kirkwood [8], the primary feature of inflamm-ageing is an increase in the proinflammatory status with advancing age. According to Franceschi et al. [9], inflamm-ageing is connected with an interplay between genetic and environmental components. Chronic inflammation is related to an imbalance between proinflammatory and anti-inflammatory mediators, which leads to cellular damage [2].

Cellular senescence is a phenomenon of cessation of cell division and terminal exit from the cell cycle by the senescent cells [4]. Senescent cells accumulate in ageing tissues and produce cytokines, chemokines, growth factors, proteases and angiogenic factors [4, 5]. This secretory activity is termed SASP. Age-dependent accumulation of senescent cells in tissues contributes to the development of age-related diseases [10]. These cells produce IL-6 and IL-8, which have been implicated in age-related diseases [4]. Serum IL-6 has been found to be a reliable marker of inflamm-ageing [11].

Excessive stress response and increasingly high proinflammatory response contribute to inflamm-ageing [11]. Stress stimuli such as active oncogenes, DNA damage, telomere dysfunction and oxidative stress lead to senescence [10]. Chronic stress has been found to be linked to shorter telomere length [12]. Some studies have reported a suppressive effect of chronic stress on basal telomerase activity, and this phenomenon is probably due to the increase in oxidative stress levels induced by stress [12]. Oxidative stress has an impact on homeostasis and influences both speed of ageing and lifespan [11]. It contributes to immunosenescence by causing oxidative damage to proteins, lipids and carbohydrates, which results in a decrease in cellular functions and cellular apoptosis due to the accumulation of oxidised molecular aggregates [13]. It is thought that antioxidant intake may contribute to improved immune function and lifespan [11].

Exo- and endogenous factors cause DNA damage, which can induce errors in replication and translation [11]. An increase in DNA damage with age has been reported in human lymphocytes, and the accumulation of these genetic abnormalities can lead to cell cycle arrest or even apoptosis [14].

Another potential mechanism of immunosenescence is connected to epigenetic changes i.e. changes in DNA methylation and hydroxymethylation due to its contribution to the regulation of levels of immune-related factors as well as to the proportions of immune cell types [7].

Autophagy plays an important role in maintaining cellular homeostasis [15]. This ability enables the clearance of nonfunctional proteins, intracellular pathogens and damaged organelles [15]. Autophagy transfers the abnormal substances of the cell to lysosomes for degradation [11]. Cleansing capacity declines gradually with age, leading to an accumulation of proteins in cells, which causes cellular senescence [11].

Clinical characteristics of elderly in context of immunosenescence

Immunosenescence is connected to changes in innate and adaptive immunity. The total amount of haematopoietic tissue in the bone marrow decreases with age [16]. These changes involve also thymus involution, which results in the reduction of naive T cells [17]. Involution of thymus leads to a decreased output of regulatory T cells, and regulatory T cell-mediated suppression is reported to decline after the age of 50, which seems to contribute to increased inflammation and autoimmunity in that population [16]. Ageing of the immune system is also related to reduction and functional alterations of naive B-cells [17]. In older people, these cells are characterised by a decreased capacity of antibody production, which results in a reduced ability to respond to infections and impaired formation of antibodies in response to vaccination [18].

Ageing of the innate immune system is associated with decreased function of epithelial barriers, which enables pathogenic organisms to invade tissues [16]. NK cells have a decreased cytotoxic capacity and secrete a lower amount of IFN-γ [18]. Macrophages may maintain inflammation when they differentiate into the proinflammatory phenotype [17]. Microglia are associated with the production of proinflammatory cytokines [17]. In neutrophils, the ability for migration and phagocytosis is impaired and an alteration has been reported in pathogen destruction mechanism mediated by neutrophil extracellular traps [18].

Immunosenescence is related to increased morbidity and mortality in the older population [1]. Although ageing itself should not be considered a disease, it is the main risk factor for the occurrence of chronic age-related diseases [1]. According to Goronzy et al. [19], the main features of immunosenescence

include persistent low-grade inflammation, decreased ability to respond to new antigens, increased incidence of autoimmunity, and unsustained memory responses. Ageing is an important risk factor for diseases such as diabetes, cancer, cardiovascular and neurodegenerative diseases, the development of which is related to low-grade inflammation [15]. In the elderly, the benefits of vaccination to prevent infectious disease are limited due to an insufficient ability to generate protective immunity [19].

Ageing of the immune system is part of a larger group of natural processes in various organs of the body. Regardless of the specific tissue or organ, common aspects of ageing include a decrease in cell number, cell function and integrity of organs (e.g. a reduction in the number of cardiomyocytes and pacemaker cells and decreased myocardial strength). In the gastrointestinal tract, the decrease in cell number and function results in a reduction in gut motility and the integrity of the gut-blood barrier [20].

Neurodegenerative diseases are age-related neurological disorders. However, immunosenescence has an influence on the course of chronic diseases with onset in young adults, such as multiple sclerosis (MS). Alzheimer's Disease (AD) and Parkinson's Disease (PD) are the most common age-related neurodegenerative diseases [5]. Inflamm-ageing has been found to have an impact on the deterioration of cognitive functions and the development of dementia [5]. In AD, microglia-mediated inflammation contributes to the degenerative process [21]. Microglia secrete pro-inflammatory cytokines, and their capacity for phagocytosis of amyloid beta peptide is impaired [21]. Changes in the immune system may also contribute to the pathogenesis of PD [22]. Williams-Gray et al. [22] found that the peripheral immune profile in patients with PD was atypical for an older population due to a lack of the CD8+ T cell replicative senescence that characterises normal ageing, which may suggest the 'abnormal' process of immunosenescence [22].

It has been found that patients diagnosed with HIV were at risk of experiencing the cumulative effects of HIV infection and ageing on brain functions [23]. It seems that a synergy between these factors leads to brain injury and degradation similar to that seen in PD [23]. The elderly are also more prone to develop paraproteinemic, vasculitic and inflammatory demyelinating neuropathies, which could be related to immunosenescence [24]. Age is an important risk factor in stroke and its outcomes [25]. Engler-Chiurazzi et al. [26] found that the activation of brain-resident immune cells and peripheral immune infiltration played an important role in the post-stroke acute injury phase and in the long-term recovery period. Age-related changes in leukocyte gene expression in patients with ischaemic stroke have been confirmed, and may have an influence on the risk of stroke and its outcome [25]. The risk of cancer is increased by long-lasting inflammation [27]. The impact of immunosenescence in tumours is complex and includes oncogenic stress in the tumour microenvironment, which can induce the senescence of T cells, macrophages, NK cells, and dendritic cells. Accordingly, these senescent cells could influence tumour progression [28].

Epidemiological studies on some infectious diseases provide the best evidence of the deleterious effects of ageing of the immune system. In some acute infectious diseases, such as influenza, smallpox and measles, the highest mortality is reported in the neonatal period or in infancy, while the lowest is in school-age children. On the other hand, in their recent analysis, Glynn et al. [29] showed that a marked increase in mortality of most acute and persistent infections (e.g. tuberculosis, HIV, *Salmonella spp.,* Ebola) could be observed after the age of 15–20, and increased over a lifespan. These authors provided clinical proof of immunosenescence, and concluded that immune senescence could begin much earlier than has been previously believed.

During the COVID-19 pandemic, the individuals with the most severe symptoms and the highest risk of death were the elderly and those with a chronic illness [30]. The following risk factors were reported: hypertension, diabetes and chronic respiratory disease [31]. The SARS-CoV-2 virus can worsen symptoms from pre-existing conditions and diseases [30]. Regardless of the fact that age and multimorbidity overlap, most studies have demonstrated the predominance of age as a risk factor for death in COVID-19. Docherty et al. [32] showed a hazard ratio of 2.5 for death in patients aged below 50, dramatically increasing to 11 at the age of 80 and older. Even when age and multimorbidity were analysed separately, age was the leading risk factor for death or a severe course in most diseases except for some types of cancer [33, 34]. In the elderly with SARS-CoV-2 infection, changes in the immune response had an impact on the acceleration of disease progression [31]. An age-related decline in the clearance of inhaled particles in the small airway region has been reported, and this phenomenon could be responsible for the high prevalence of respiratory symptoms in the elderly [35]. Chronic low-grade inflammation can be a predisposing factor for aberrant inflammation that increases the severity and risk of death [30]. Cytomegalovirus (CMV) seroprevalence approaches 80% in adults aged over 70 and causes clonal T cell proliferation and reduction in naive T cell diversity, which may lead to reduced capacity for immune responses to novel viral infections [31].

In fact, ageing of the immune system has a complex network of underlying causes which include not only natural mechanisms of senescence but also chronic disorders, lifestyle, environmental and epigenetic factors, and infections [36]. Many studies have confirmed that chronic stimulation of the immune system with high concentrations of viral antigens in HIV, HBV or HCV infections has a deleterious effect on specific CD8 and CD4 T cell function. Functional anergy of effector cells is a progressive phenomenon that results in decreased cytotoxicity, cytokine synthesis and proliferative potential of T cells [37]. For many viruses, overproduction of antigens is a mode of persistence by inducing immune dysfunction. For example, the synthesis of HBsAg in chronic hepatitis B can exceed the number of virions by more than

3,000 times [38]. According to many researchers, persistent infections with CMV and EBV have the largest effect on immunosenescence [39]. Both pathogens are members of the herpes virus family. These are latent and incurable infections with a potential for reactivation in immunodeficiency. Their clinical impact is further enhanced by their high prevalence, reaching 90% for EBV and 50% for CMV [40, 41]. Both infections have a high ability to induce transformation of T-cells to terminally differentiated effector memory (TEMRA) cells expressing CD45RA [42]. A higher threshold of terminally differentiated T-cells reduces immune reserve, especially of naive T cells, but also decreases diversity and plasticity of the immune system [39]. Interestingly, in their recent study, Gate et al. [43] discovered an immune signature of AD that consisted of increased numbers of TEMRA cells. These cells were also negatively associated with cognition [43].

The age-related decline of homeostatic systems does not occur at the same rate in all individuals of the same species and chronological age [1]. Biological age is the concept of using biophysiological measures to more accurately determine an individual's age-related risk of adverse outcomes [44]. Great efforts have been made to identify ageing biomarkers, which were described by Baker and Sprott as "biological parameters of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age" [45, 46]. Molecular and phenotypic biomarkers of ageing have been considered (e.g. telomere length or epigenetic clock) [46].

The process of ageing is multifactorial. A lack of physical activity, poor nutrition, smoking and excessive alcohol consumption are the most common causes of age-associated chronic diseases [2]. Nutrition is an important factor because diets including a large amount of fat are associated with obesity, and proinflammatory signals released from adipocytes lead to oxidative and inflammatory stress [1]. The consumption of natural products such as vegetables, fruit, cereals and legumes is associated with a decreased risk of many diseases [2]. Nutritional interventions such as caloric restrictions, variations in macronutrient ratios, supplementation with probiotics, vitamins and antioxidants may have a positive impact by slowing down oxi-inflamm-ageing [1]. A sufficient amount of antioxidants in the diet reduces oxidative stress and may prolong lifespan [11]. Martinez de Toda et al. [1] suggested that an adequate social environment could be an effective strategy to delay oxi-inflamm-ageing by increasing social communication, strengthening social bonds, and reducing the stress associated with loneliness and social distancing.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that affects c.2.5 million people worldwide [47]. Due to ever-improving healthcare management, the life expectancy of MS patients has increased, meaning that elderly patients with MS are growing in number. Most patients present with relapsing-remitting MS (RRMS), characterised by at least partly reversible episodes of neurological deficits [47]. In the past, most (untreated) patients with RRMS experienced conversion to secondary progressive MS (SPMS) within 10–15 years of disease onset, characterised by a chronic progression of disabilities with or without superimposed relapses [47]. Patients with primary progressive MS (PPMS) normally have a later disease onset than those with RRMS [48]. PPMS affects c.5–10% of MS patients [47]. Current disease modifying therapies (DMTs) aim to reduce the frequency of relapses and to slow disease progression, but do not necessarily stop the accumulation of disability related to disease progression [47]. One possible explanation is the impact of immunosenescence which is associated with the accumulation of unusual immune cell subsets that may play a role in the development of an early ageing process in autoimmunity [48]. Some features of immunosenescence found in aged healthy controls have already been observed in MS patients at a younger age [49].

Patients with MS present with the signs of early thymic involution and reduced immune functions [48]. Involution of thymus results in a decline in the production of naive T cells and reduced T cell activity [50]. Eschborn et al. [51] suggested that ageing in MS was associated with a loss of balance between costimulatory and immunoregulatory signals provided by CD8 T cells, favouring a proinflammatory phenotype.

In MS patients, next to changes related to the natural process of ageing, the accumulation of iron in the central nervous system has also been reported [50]. Iron is released by oligodendrocytes damaged by the disease process and its extracellular accumulation increases oxidative stress, leading to further neurodegeneration [50]. Patients with MS present with diminished proliferative capacity of the bone marrow-derived cells and the shortening of telomeres [48]. Premature cellular senescence is associated with accelerated telomere shortening [52]. Shortened telomere length is related to the pathogenesis of some chronic neurological diseases [52]. Analysis of telomere length in leukocytes in MS patients showed that patients with RRMS had significantly shorter telomeres compared to patients with primary progressive multiple sclerosis (PPMS) and the control group [53, 54]. In patients with MS, shorter telomere length has been connected to a greater degree of disability, a lower brain volume, an increased relapse rate, and a quicker conversion from relapsing to progressive MS [52].

The process of autophagy becomes less efficient with age, which leads to cellular senescence. In active RRMS patients, this capacity is increased [49]. In progressive MS, the signs of neurodegeneration are present despite increased autophagy in the brain tissue [50]. It seems that sustained autophagy related to damage could lead to the dysregulation of this process, and paradoxical inflammasome activation and apoptosis [49].

The pathology of MS changes with age, with predominant inflammation, demyelination, and remyelination in RRMS,

and axonal damage with astrogliosis and lack of remyelination in the progressive phase [55]. In patients with relapsing-onset MS, the annualised relapse rate (ARR) decreases with advancing age [56]. The capacity of recovery from relapse also declines with age [57]. The probability of detecting Gd-enhancing lesions in MRI decreases with age [58, 59]. Typical MRI features of elderly patients with MS include the accumulation of lesions, brain atrophy, spinal cord pathology and the identification of comorbidities [50]. In patients with MS, comorbidities are found more commonly than would be expected [60]. The most common comorbidities in MS patients include hypertension, hyperlipidemia and thyroid disease, which is one of the most prevalent comorbid autoimmune diseases [61]. All types of psychiatric comorbidities have been found to be more likely in MS patients [60]. In some pathological conditions such as cognitive decline, it is difficult to determine whether they are related to ageing or are due to the pathological process in MS [50]. Vascular comorbidities are of great importance as they have been shown to be associated with increased disability progression in MS [61].

There is a lack of data on safety and efficiency of DMTs in older people with MS [50]. Patients over the age of 55 are usually excluded from clinical trials. Therefore, the safety and efficacy of DMTs in this group of patients is not confirmed [49]. Schweitzer et al. [17] suggested that the benefits of high efficacy DMTs could decrease with age. Weideman et al. [62] found that the efficacy of DMTs was negatively correlated with age, and predicted no efficacy of DMTs in patients after the age of 53 [49]. In MS patients over 40, natalizumab, dimethyl fumarate and fingolimod have failed to significantly reduce the risk of disability progression. Furthermore, fingolimod has failed to significantly reduce ARR [63]. Dimethyl fumarate and peginterferon-β-1a reduced significantly ARR in MS patients older than 40 [63]. Kallman et al. [64] found that teriflunomide reduced relapse rates also in older groups of MS patients. In patients over 40, high-efficacy drugs seem to lose their proven higher efficacy compared to low-efficacy drugs [17]. In older patients, ocrelizumab and ozanimod could not significantly reduce ARR compared to interferon-β [63]. Siponimod was found to reduce ARR and 3-month disability progression in SPMS patients aged over 41 years compared to a placebo [63].

The risk of adverse events associated with DMT, including the risk of infection and cancer, may increase with age [17]. DMTs have an impact on the distribution and function of immune cell populations, which may promote certain immunosenescence features in addition to MS-related premature immunosenescence [49]. Ocrelizumab has been associated with depletion in IgM and IgG, which is related to a higher risk of severe infection. In the elderly, this is a risk factor of increased mortality [63]. Similar changes in IgG, IgM and IgA were observed after therapy with alemtuzumab and they contributed to an increased risk of infection up to three years after treatment [63]. One of the infectious complications is JC polyomavirus-associated progressive multifocal leukoencephalopathy (PML): older age may be a risk factor for its development, severity and outcome [17]. This is of particular concern in patients treated with natalizumab [65]. However, this has also been reported in MS patients treated with dimethyl fumarate and fingolimod [17].

Older age is related to an increased risk of many types of cancer. A shorter lifespan is probably the cause of a lower risk of cancer in patients with MS [63]. As the lifespan of patients increases, an increase in the prevalence of cancers has been observed [63]. Some DMTs, including mitoxantrone, fingolimod, cladribine may increase the risk of malignancies [17]. However, this has not been confirmed in elderly populations with MS. Therefore, further studies are warranted in this respect.

The problem of treatment discontinuation requires discussion in light of the decreased efficiency and increased risk related to DMT in the elderly. Bsteh et al. [66] demonstrated that age (≥ 45 years) and DMT intake ≥ 4 years without evidence of clinical or radiological disease activity were factors associated with remaining relapse-free after DMT discontinuation. On the other hand, older age and a greater degree of disability at discontinuation of treatment were related to further disability progression after DMT discontinuation [66, 63]. Kister et al. [67] showed that MS patients who discontinued injectable DMT after a prolonged relapse-free period had a similar relapse rate to that of score-matched patients who continued on DMT, but they had a higher risk for disability progression. Hua et al. [68] analysed discontinuation of treatment in patients aged over 60, and their results suggest that drug cessation seems to be safe in these patients [63]. According to their analysis, patients over 60 in whom DMT discontinuation was considered could be divided into two groups: patients with stable disease where inflammation had 'burnt out' and progressive patients who had significant disability as they were likely to be poor responders to treatment with marginal benefits of treatment [68].

Conclusions

Immunosenescence is an important process in the context of neurological disorders. Many mechanisms are involved in this complex phenomenon.

The older population is characterised by an increased susceptibility to infections, a poorer response to vaccinations, and a higher risk of developing cancer, vascular diseases and neurodegeneration. Immunosenescence is an important factor influencing the course of MS, as well as the safety and effectiveness of DMTs. The relationship between the pathogenic process underlying the development of MS and immunosenescence requires further investigation.

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