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The ageing immune system and its clinical implications

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Summary

Ageing is associated with multiple changes in many different components of the immune system. A healthy immune system exists in a state of balance between efficient effector responses against pathogens and tolerance to self antigens. This balance is changed with age; functions such as antigen recognition, phagocytosis, antigen presentation, chemotaxis, cytokine secretion and killing ability are all compromised. Aberrant cellular responses lead to an altered cytokine network with increases in inflammatory cytokines and decreases in anti-inflammatory cytokines leading to a pro-inflammatory state. Consequently older patients require extra care in diagnosis of infections as symptoms may be perturbed, resulting in unusual presentations of common conditions. The defects in immunity due to immunosenescence also mean that older patients require more care and screening than other patients in the same disease cohort. Though it is generally understood by clinicians that older patients are more at risk from multiple infections, the wider clinical effects of immunosenescence are less understood. The immune system is involved in several neurodegenerative conditions and the inflammatory conditions of immunosenescence may be a key factor in pathogenesis. Similarly, there is reason to believe that immunosenescence might be a key factor explaining the increased incidence of cancer in older age. With increasing understanding of the immune system's involvement in many of these pathological processes, and the contribution that immunosenescence makes to these, more efficient vaccines and novel therapies may be developed to prevent/treat these conditions.

Key words: immunosenescence, infection, immunology, vaccination.

Introduction

The immune system is composed of a complex web of interacting factors that together determine the host response against pathogenic invasion. It is the balance between the activation and suppression of the immune system that prevents pathological autoimmune conditions whilst maintaining appropriate immune responses to pathogens. Much of the developed world is experiencing a shift in demographics towards increased populations of older people, with the UK population of over-65s expected to rise from 16% in 2008 to nearly a quarter by 2033.[1] Therefore an understanding of age-related immunological changes and their clinical effects are becoming increasingly important for clinicians.

Immunosenescence is defined as the gradual deterioration of the immune system that occurs with age and involves alterations in many components of the immune system. Its effects are mainly recognized as an increasing susceptibility to infection in old age, which occurs across a wide spectrum of pathogens. Furthermore, while the older population is in most need of protection, vaccinations are less effective in older patients. Chronic inflammation in old age is a feature of immunosenescence that may also play a wider role in several conditions including autoimmunity, cancer, neurodegenerative disease and cardiovascular disorders. The importance of the immune system is illustrated by the fact that biomarkers of immunosenescence can strongly predict survival in older people.[2] In this review we briefly outline the various changes in the senescent immune system and discuss the clinical consequences of these changes.

Innate immunity

The innate immune system includes cells such as neutrophils, macrophages and dendritic cells (DCs) that are capable of recognizing common pathogen-associated molecular patterns (PAMPS) in order to phagocytose and destroy the pathogen. Key to pathogen recognition is the expression of toll like

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receptors (TLRs) on their surface, which recognize PAMPS such as lipopolysaccharide (LPS), bacterial DNA, flagellin, etc. Antibody opsonization is also important in pathogen recognition, enabling cells of the innate system to recognize opsonized pathogen via their receptors for antibody Fc regions.

Macrophages and dendritic cells are antigen-presenting cells (APCs) that process the ingested pathogens in order to present pathogen-associated antigens to the adaptive immune system. Macrophages, derived from monocytes, are tissue-resident phagocytes that are the first cells at sites of infection. After they phagocytose and kill the pathogen, they process it into antigens and present these on their cell surface using major histocompatibillity complex II (MHC II) molecules. They also secrete cytokines to attract other cells of the immune system to the area. Tumour necrosis factor-alpha (TNF-α) and other cytokines alter the vascular endothelial cells allowing greater ease of neutrophil extravasation from the blood, whilst the chemokine interleukin 8 (IL8) causes neutrophils to migrate to the source of infection.[3,4] Macrophages also secrete granulocyte macrophage-colony stimulating factor (GM-CSF), which acts on bone marrow to increase the quantity of neutrophils being produced.[5]

Aged macrophages display reduced responses following stimulation with both LPS and GM-CSF.[6,7] Not only are their cytokine secretion responses reduced, but the ability of monocytes to display the key co-stimulatory molecules CD80 and CD86 is impaired.[8] The primary role of macrophages in pathogen detection and neutrophil recruitment means that any age-related changes in macrophage function will have important consequences for the remainder of the immune system.

The chief function of neutrophils is the phagocytosis and digestion of invading pathogens.[9] They are short-lived, having a lifespan of several hours following their exit from the bone marrow as new cells. However, they can be rescued from apoptosis in conditions of challenge if stimulatory signals such as GM-CSF and bacterial LPS are received.[10,11] They have a high replicative turnover and migrate through the body following chemical gradients of chemokines released by other immune cells.[12]

Several alterations in neutrophil activity are observed in immunosenescence. Neutrophil migration is impaired in old age, partly due to a decreased up-regulation of the chemotactic receptors required for relocation to areas of infection.[13] They are also more prone to apoptosis, as intracellular signalling defects lead to decreased responsiveness to anti-apoptotic signals such as GM-CSF.[14,15] SHP-1, an inhibitor of the GM-CSF response, is also constantly up-regulated on the cell surface, which further reduces the likelihood of rescue from apoptosis.[16] Immunosenescent neutrophils show a decreased respiratory burst, possibly due to an alteration in membrane distribution of the receptors responsible for triggering the burst.[17] They also have reduced expression of TLRs,[18] lower levels of CD16 (receptor for IgG) on their surface and are less able to ingest pathogens.[19] Altogether these defects result in neutrophils being less likely to migrate to sources of infections with a reduced ability to ingest and destroy pathogens and less likelihood of survival upon pathogen encounter.

Dendritic cells are professional APCs that ingest and process antigen for display on MHC II molecules. They transport antigen from the periphery to lymph nodes where they can activate B and T lymphocytes that have specificity for the displayed antigen. They have been shown to respond poorly to TLR ligation and vaccination in older age, secreting lower levels of cytokines TNF-α, interferon-gamma (IFN-γ), IL6 and IL12.[20–22] Their ability to stimulate T lymphocytes is decreased, leading to decreased T lymphocyte proliferation and muted T cell responses.[23] Since APCs represent one of the main bridges between the innate and adaptive immune systems, age-related defects in APCs are especially important. If APCs are less able to display antigen to the adaptive immune system then lymphocytes cannot be efficiently activated.

Adaptive immunity

The adaptive immune system is composed of antigen-specific B and T lymphocytes that can adapt to encountered antigen, 'remembering' previous exposure in order to respond in a quantitatively and qualitatively enhanced way upon re-challenge with the same antigen. Lymphocytes encounter antigen displayed by APCs of the innate system and, if provided with co-stimulation, are activated and proliferate to effect a response. CD4+ T helper cells release cytokines

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to modulate the immune system and can stimulate other cells through cell-to-cell contact, whilst CD8+ cytotoxic T lymphocytes (CTL) induce apoptosis in target cells. The chief function of B cells is to provide good quality antigen-specific antibodies, but they can also secrete regulatory cytokines and express co-stimulatory molecules.

Most studies have focused on cell populations in the peripheral blood, although there are a few studies in lymphoid tissue that indicate an altered organization of cells with age.[24–26] Total numbers of blood lymphocytes decline slightly with age. This is most likely due to the decreased production of mature naïve lymphocytes.[27,28] Reduced replenishment of lymphocytes may be partially due to progenitor cell-intrinsic defects, such as accumulation of DNA damage, although other cell-extrinsic circulatory factors (as yet uncharacterized) are also involved.[29,30] While the overall numbers of lymphocytes do not change drastically there are substantial alterations in the proportions of different lymphocyte subsets since some populations appear to be more susceptible to age-related depletion than others.[31] The CD4+ T helper cell population contracts less with age compared with CD8+ cytotoxic T cells[32] and there is a significant decrease in the output of naive T cells. Since the overall numbers of T cells do not change much then the immunological niche that is not taken up by new cells is filled with memory T cells. The overall consequence of this is an older population of T cells containing more memory cells than naïve cells and having less T cell receptor (TCR) diversity than in a younger population.[33] This reduces the ability of the T cell population to launch a response against novel antigen.

Older CD4+ T cells also have decreased functional ability. Cognate interaction with B cells is impaired, causing a reduction in the expansion of antigen-specific B cells. They also release less cytokines in response to stimulation, thus reducing the possibility of activating other immune cells.[34] CD8+ CTL show multiple age-related defects, having decreased expansion, decreased receptor diversity and impaired release of apoptotic effectors when stimulated.[35–37] Another cell type of the adaptive immune system is T regulatory cells (Tregs), which are potent immune inhibitors able to suppress other T lymphocytes.[38] They have been shown to be increased with age in humans, potentially contributing to the immunodeficiency seen in old age.[39]

B cells produce antibodies and, whilst total antibody levels do not decrease with age, there are some reports of altered proportions of the different isotypes; a decrease in IgM and IgD and increase in IgG and IgA levels. There are also reports that memory B cells are increased at the expense of naïve B cells due to a decreased production of naïve B cells in the same way as happens for T cells in ageing.[24,40,41] We have shown that B cell diversity is also decreased with age and this loss of diversity is associated with increased frailty and decreased survival in later life.[42]

Cytokine environment

Cytokines are chemical messengers released by a range of cells in the immune system, plus others such as platelets, endothelial cells and keratinocytes, that can alter the behaviour, migration and responses of immune cells.[43,44] As such they play a pivotal role in co-ordinating leucocyte behaviour and communication between different types of cell. Small changes in cytokine levels can have large effects on the immune system.

A large contributor to immunosenescence, and potentially to many age-related pathologies, is the phenomenon termed 'inflammageing', where it has been shown that a number of key pro-inflammatory cytokines increase with age.[45] Most noteable are IL6 and TNF-α, although increases in IL1, Il2, IL12, IL18 and IFN-γ have also been reported.[46–49] Higher levels of IL6 in ageing have been associated with a sedentary lifestyle, higher leucocyte counts and an increased disease burden.[50] The increases in IL6 may be, in part, influenced by genetics since polymorphisms of the IL6 gene are associated with longevity.[51] TNF-α levels have been reported to correlate with IL6, sTNFR and C-reactive protein (CRP) levels and, although TNF-α polymorphisms have not been associated with longevity, they have been associated with age-related diseases such as Alzheimer's disease (AD) and cardiovascular disease (CVD).[52,53] IL10 is an anti-inflammatory cytokine and it was found that the increase in plasma inflammatory cytokines such as IL6 was not accompanied by any compensating change in IL10 levels.[54]

An increase in inflammatory phenotype, defined by IL6 levels, is part of an 'Immune Risk Phenotype' (together with changes in CD4+/CD8+ T cell ratios) that can be used to predict 2-year

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mortality rates in older people, predicting 97% of survival cases and 57% of mortality cases.[55] Elevated levels of IL6 can cause increases in levels of other serum protein inflammatory biomarkers such as the acute phase protein YKL-40 secreted by neutrophils and macrophages. YKL-40 is raised in half of healthy older people compared with younger controls.[56] The numbers of different cells involved in cytokine production has meant that the exact cause of dysregulated cytokines in old age has not yet been precisely determined.

Age-related alterations in cytokines and their receptors are found in tissues, for example an up-regulation of TGF-β1 and TNF R family in the skin.[57] TCR engagement in aged cells also showed increased secretion of IL6, which may be a significant source of the pro-inflammatory cytokines seen in older people.[58] Despite the generalized increase in serum pro-inflammatory cytokine levels, some immune cells secrete less cytokines with age. For example, specific stimulation of old DCs has been found to provoke a reduced inflammatory reaction with less TNF-α and IL6 compared with younger DCs.[20] Tregs are important in decreasing the immune system's response to infection, providing balance and preventing overwhelming activation. However, following chronic stimulation these cells have been shown to express a senescent surface phenotype and have a reduced ability to dampen the immune response. They secrete increased levels of IL 4 which would sustain inflammatory reactions.[59] Thus although they are increased in older people, they may be less effective at reducing inflammation.

Infection in older age

The main clinical effects of immunosenescence are associated with a decline in protection against external pathogens, resulting in a population that is increasingly susceptible to infection. A wide spectrum of pathogens are increased in infections in older individuals and infections are the most common discharge-limiting factors that result in increased length of hospitalization in older patients.[60] Infections in older people are more likely to have difficult presentations with absence of symptoms.[61,62] Patients may be afebrile despite infection, probably as a result of dysregulated cytokine responses.[63] This complicates the process of diagnosis and may contribute to the increased rates of mortality associated with elderly infection.[64]

Pneumonia is one of the most common infections affecting older people[65] and age is considered to be one of the strongest indicators of poor prognosis, as evaluated using the CURB-65 score. The CURB-65 score is recommended by the British Thoracic Society to evaluate the prognosis of patients with community-acquired pneumonia and is based on the variables of: confusion, serum urea, respiratory rate, blood pressure and age being greater than 65 years.[66,67] However, some authors have pointed out weaknesses in the CURB-65 model, recommending that immunosenescence and age require more weight in the model since more than 75% of pneumonia patients are over the age of 70.[68] The accuracy of CURB-65 has also been questioned since evidence indicates that it is adequate at predicting mortality under the age of 65 but that accuracy of prediction is inversely proportional to the patient's age above this.[69] This illustrates the importance of fully considering the clinical impact of immunosenescence, and shows that the immunological frailty and decreased resistance to infection accompanying old age should not be underestimated.

Other common infections in old age include urinary tract infections (UTI), which may be caused by a range of pathogens. The diagnosis of UTIs is complicated in old age as they can present solely with changes in mental status that mimic neurological problems or with symptoms suggesting respiratory infection. Diagnosis of UTIs can be achieved by reagent strips that can detect leucocytes and nitrites in urine. However, it has been suggested that reagent strips are inadequate for use in elderly UTI diagnosis.[70,71] The increase in susceptibility and alteration in symptoms in old age can make the differentiation between a UTI *versus* asymptomatic bacteriurea difficult, thus complicating treatment decisions. Infections such as UTIs can cause significant morbidity and result in increased hospital stays. They may also cause increased general frailty since it has been shown that there is a correlation between UTIs and an increased frequency of falls.[72–75]

Older people suffer increased morbidity and mortality from viral infections and the infections can result in lasting damage to the immune system. Most deaths associated with influenza infection are in the over-65 age group and reactivation of common latent viruses such as

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varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) occur in older age.[76] Viral infections may also play a causative role in the pathogenesis of immunosenescence, particularly in the case of CMV. CMV is a virus that establishes lifelong infection, having a high prevalence in the general population which increases to over 90% in old age.[77,78] Persistent CMV infection leads to an expansion of a range of CMV-specific T cells, which reduces the diversity of the remaining immune repertoire.[79–81] Higher quantities of CMV-specific IgG have been associated with increased mortality in older people, though the exact degree to which the chronic antigenic burden of infection contributes to immunosenescence has yet to be established.

Immunosenescence is of increased importance in human immunodeficiency virus (HIV) infections since there is an emerging population of HIV-positive older people. This population is composed of two groups of patients: those infected *de novo* in older age and those derived from younger HIV patients that have survived into old age. *De novo* infections in the over-65 HIV-positive group represent a minority of cases compared with other age groups and are probably a smaller population than HIV-positive patients that have survived into old age, though this may be an underestimate.[82,83] The second population, of long-term survivors, has emerged with the shift of HIV infection from being a rapidly lethal disease to being a chronic, treatable, disease state. HIV-positive older people are more likely to have multiple complications arising from infection and require more frequent screening than younger HIV-positive patients.[84] The clinical implications of HIV-infected older people are complex as the addition of antiretroviral treatment into old age polypharmacy can cause additional complications.[85] The issues arising from the interaction of HIV and immunosenescence represent a growing problem which will require new strategies and further research to improve the health of this vulnerable group of patients.

Efficacy of vaccination in older age

One of the most important effects of immunosenescence on clinical medicine is the decreased efficacy of vaccination.[86] A successful response to vaccination, in its simplest terms, first requires efficient antigen uptake by APCs. The APCs must then transport the antigen to secondary lymphoid tissue and successfully present it in order to stimulate lymphocytes. B and T cells undergo refinement and develop into memory cells so that future antigenic encounter will evoke a faster response with greater antigenic affinity. Given that immunosenescence has been shown to affect most of the different stages in this response it is perhaps not surprising that vaccines are less effective in older age.

There are arguments that we should routinely vaccinate older people against a much wider range of pathogens than the current programmes for pneumococcal and influenza vaccination of the over-65s.[87] However, in view of the data on efficacy of these vaccines compared with younger controls it would make sense to understand how to increase efficacy for older people. One meta-analysis has shown that the efficacy of influenza vaccination in old age is reduced by 40–50% compared with young controls.[88] Even more severe deficiencies in influenza vaccine efficacy are seen in older people with HIV infection due to their additional defects in both the T cell and B cell populations.[89]

Pneumococcal vaccines are polysaccharide vaccines used to prevent infection with *Streptococcus pneumonia,* which is the major cause of bacterial pneumonia cases. In the US, pneumonia caused by *S. pneumoniae* is a significant health care burden, costing an estimated $5 billion to treat.[90] In England pneumococcal vaccination has been shown to be a highly cost-effective intervention in older people.[91] Despite these benefits and UK guidelines recommending that all patients over 65 years of age should be vaccinated, uptake remains low at around 20–30%.[92,93] Although it is cost effective it has a lower efficacy in older patients, reducing the incidence of pneumonia by only 10% compared with 40–50% in younger patients.[94] The reasons for this are poorly understood but it is apparent that the poor quality of the antibody response is at least partially responsible.[95]

With an increased understanding of the effects that immunosenescence has on a vaccine response, we may be able to use biomarkers of immune function to predict the efficacy of vaccines in old age, thus identifying which older people are more at risk of infectious disease. To date it has been shown that the degree of CD80/CD86 up-regulation by monocytes in response to *ex vivo*

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TLR stimulation is predictive of influenza vaccine responses,[8] and rapid analysis of lymphocyte repertoire diversity from small blood samples may also prove to be a useful and practicable biomarker of immune function (authors' unpublished data). Better information on the immunodeficiencies of age may enable us to design vaccines tailored for efficacy in older patients and thereby reduce the healthcare burden of several common diseases. Several different delivery methods are being researched to improve vaccine response in older people including using higher antigenic doses, virus-like particles and virosomes (recombinant viral coats containing antigenic material).[96]

Non-immunological interventions are also showing promise in attempting to reverse the detrimental effects immunosenescence has on vaccine response. Dietary augmentation with whey protein has been reported to result in higher specific antibody levels.[97] Exercise may also increase the efficacy of vaccination, as several studies have shown increased seroprotection and decreased severity of infection with exercise.[98,99] The exact mechanisms are yet to be elucidated and there is disagreement on the best exercise protocol, with proponents of regimes varying between cardiovascular exercise to gentle stretching exercise.[98–101] It would appear that diet and exercise do have effects that can combat immunosenescence but further research is required to elucidate the mechanisms so that sound evidence-based lifestyle recommendations can be made.

Autoimmunity

Autoimmune disorders arise from an imbalance between activation and down-regulation of the immune system, leading to inappropriate immune stimulation in response to self components.

In general, the incidence of autoimmune conditions tends to increase with age.[102] Elderly patients with autoimmune conditions have shown greater declines in thymic output and greater disturbances in immune parameters compared with age-matched controls, suggesting a link between autoimmune conditions and increased immunosenescence.[103] One potential cause of autoimmunity may be the chronic inflammatory state observed in older people as evidenced by the alterations in the levels of cytokines, with increased quantities of inflammatory cytokines leading to an inappropriate activation of autoimmune cells. Changes in dendritic cells will also have an effect, since immunosenescent DCs show increased reactivity to self antigen such as intracellular DNA, and may cause increased stimulation and proliferation of auto-reactive lymphocytes.[104]

It has been shown that the serum level of auto-antibodies increases with age.[105] A chronic antigenic burden experienced by older people could lead to higher levels of auto-antibodies via a decrease in the inhibition of autoimmune B lymphocytes and increased stimulation of auto-reactive B lymphocytes to differentiate into plasma cells. However, increased auto-antibody levels do not always mean increased incidence of autoimmune pathology, therefore some other loss of balance in the immune system must be required to cause autoimmunity.

Changes in the relative numbers of different lymphocyte subsets will contribute to the loss of homeostatic control in the system. A novel population of CD27, IgD double negative memory B cells has been discovered and is associated with several autoimmune conditions such as systemic lupus erythematosus and juvenile idiopathic arthritis, having been shown to be expanded in these conditions and containing an activated phenotype.[106–108] This population is expanded in old age and so may also contribute to the pathogenesis of autoimmune conditions.[109]

The age-related changes in naïve/memory populations of both B and T cells, and changes in populations of T lymphocytes, may have consequences for autoimmunity. Although anti-inflammatory Tregs are slightly increased with age, which might lead us to expect better inflammatory control, it has also been shown that chronic TCR engagement in aged CD4+ T cells leads to production of twice as much IL 17 compared with young CD4+ T cells – suggesting larger increases in the pro-inflammatory Th17 subset.[58]

Cancer

The incidence of cancer increases with age alongside the development of immunosenescence.[110,111] This does not establish a causal link between immunosenescence and carcinogenesis, although it does suggest that there may be interplay between these processes. Immunosurveillance is the process by which cells of the immune system detect and kill cancerous cells.[112,113] Tumour-specific antigens

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are displayed via MHC I molecules on the cell surface and can be recognized by cytotoxic effector cells.[111]

Several immunosuppressed states have increased rates of malignancy. Post-transplant immunosuppression results in increased rates due to both virally mediated cancer and primary cancer arising from decreased immunosurveillance.[114] Acquired immunodeficiency syndrome (AIDS) results in increases in the rate of malignancy which are associated with a low CD4+ T cell count.[115] Primary immunodeficiency conditions also show similar increases in the rates of malignancy.[116] Since immunosenescence is a form of immunodeficiency, then it is likely that it will contribute in some way to tumour formation, particularly since a decrease in the number and diversity of CD8+ cytotoxic T cells is a clear feature of immunosenescence[117] and the function of these cells is decreased.[118,119] Tregs have also been shown to accumulate in old age, inversely correlating with the activity of cytotoxic T cells and potentially reducing their ability to destroy malignant cells.[120]

Older patients with cancer have T cells with decreased CD28 (a stimulatory molecule) and increased CD95 (an apoptosis-inducing receptor) compared with younger cancer patients. This accumulation of senescent T cells was closely correlated with increased numbers of lymph node metastasis and a worse clinical outcome.[121] Dysregulated function of APCs and cytokines with age may also contribute to decreased immunosurveillance and increased tumour progression. Dendritic cell antigen presentation is reduced with ageing, resulting in an impaired ability to stimulate tumour-specific CD8+ T killer lymphocytes.[23] It has been shown that tumour growth can be delayed in animals if DCs within tumours are stimulated via injected CpG, and this effect is diminished in aged animals.[122]

An inflammatory milieu is common in cancer and a range of cytokines have been shown to have pro- and anti-tumorigenesis effects.[123,124] For example, the senescence-associated cytokine IL6 has been implicated in the pathogenesis and progression of colon cancer[125] and prostate cancer.[126] Rescue of a senescent T cell population, resulting in increased diversity and numbers of naïve T cells, is possible by IL7 administration and is under investigation as a potential anti-cancer therapy.[127]

Neurodegeneration

Neurodegenerative disorders are associated with old age. The immune system has been shown to be involved in the most common disorder, Alzheimer's disease (AD), hence immunosenescence may play a role in the pathogenesis of the condition.[128,129] Immune system involvement in AD is indicated by the presence of central nervous system (CNS) inflammation and the activity of microglia and macrophages. Microglia are CNS-resident macrophages with highly motile processes which they use to continually survey the local environment.[130] They have been shown to be activated in AD, serving to ingest and degrade both soluble and insoluble amyloid beta (AB) plaques.[131–133] Their role in protection against AD is supported by evidence that AB toxicity can be reduced by inhibiting the macrophage migration inhibitory factor (MIF).[134] However, whilst microglia have protective effects by degrading AB plaques, they may also be neurotoxic in an inflammatory state.[135,136] An increase in the macrophage chemokine osteopontin has been reported to be correlated with cognitive decline in AD,[137] so a balance of microglial effector functions is key to preventing AD pathology. As with other cells of the immune system, microglia have been shown to have various defects in old age, producing lower quantities of AB plaque-degrading enzymes, which is correlated with an increased number of AB plaques.[138]

Parkinson's disease (PD) is another neurodegenerative disease that presents later in life.[139] Immune system involvement is evidenced by the fact that chronic expression of pro-inflammatory cytokines such as TNF-α is found in PD, and microglia in the substantia nigra are activated.[140,141] As with other conditions, the involvement of inflammation in PD pathology raises the question of whether the inflammatory milieu of immunosenescence contributes directly to pathogenesis, but a causal link has yet to be shown.

Cardiovascular

Stroke and myocardial infarctions (MI) are some of the serious disease sequelae that can arise from atherosclerosis. The immune system plays an important role in the pathogenesis of atherosclerosis and cardiovascular disease (CVD).[142] Atherosclerosis is an arterial lesion

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or thickening of vessel walls involving the deposition of plasma lipids, the proliferation of smooth muscle cells and immune cell migration into atherosclerotic plaques.[143] Macrophages (termed foam cells in this setting) migrate to the intima in coronary vessel walls and are activated, thus promoting inflammation.[144–146] DCs accumulate lipid and also display an activated phenotype within atherosclerotic plaques, adding to the release of pro-inflammatory cytokines.[147–149] T cells in atherosclerotic plaques have been implicated in the promotion and formation of atherosclerotic plaques. Inhibition of ApoB100 (a component of LDL) CD4+ T cell responses has been shown to reduce atherosclerosis.[150] An inflammatory and cytotoxic subset of CD4+ CD28– T cells develops due to replicative stress and accumulates in immunosenescence.[151] This population infiltrates atherosclerotic plaques and has been associated with recurrent cardiac events.[152–154]

Chronic CMV infection, which has been implicated as a cause of immunosenescence, has also been shown to correlate with the incidence of CVD. It has been hypothesized that the pro-inflammatory state induced by CMV contributes to CVD mortality.[155,156] Whether inflammation is a cause of CVD or vice versa is difficult to determine, although it has been shown that genetic polymorphisms of COX-2 and 5-LO enzymes (associated with pro-inflammatory phenotypes) are over-expressed in aged myocardial infarction patients compared with healthy age-matched controls,[157] implying that a genetic tendency towards an inflammatory phenotype may predispose towards CVD. Inflammageing in general will certainly contribute to the pathogenesis of CVD and it has been shown that a reduction in pro-inflammatory cytokines correlates with a reduction in atherosclerotic plaques.[158,159]

Conflicts of interest

The authors declare they have no conflicts of interest regarding this article.

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