AGE, AUTOIMMUNITY, AND INFLAMMATION: THE CURIOUS CASE OF IMMUNOSENESCENCE AND INFLAMM-AGING

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Submission date: May 5, 2022
Acceptance date: May 19, 2022

How to cite: Sundaram TG, Sakir A. Age, autoimmunity, and inflammation: the curious case of immunosenescence and inflamm-aging. Anti Aging East Eur 2022;1(1): 28-35. https://doi.org/10.56543/a aeeu.2022.1.1.04

Abstract

An ever-aging population has caused an increase in the prevalence of diseases which occur in the elderly like diabetes, cancer and autoimmune diseases like rheumatoid arthritis (RA). On the other hand, ageing also causes an increased susceptibility to infections, reactivation of latent infections and poorer vaccine response. Together, this ageing-related decline in immunity is called immunosenescence and the associated ageing-related inflammation is called inflamm-aging.

In this brief review, we describe the changes seen with ageing in innate and adaptive immunity and how these lead to the various peculiarities associated with ageing in the immune system. TEMRA cells, Senescence associated secretory phenotype (SASP) and exhausted T cells are the main changes that occur in ageing T cells. Age-associated B cells (ABCs) contribute to changes associated with autoimmunity in the elderly. In the innate arm, the macrophages-led inflamm-aging cause an overall net pro-inflammatory state. However, the macrophages have reduced phagocytosis leading to the accumulation of necrotic and apoptotic debris.

We also attempt to explain how immunosenescence and inflamm-aging cause defective vaccine responses and an increased predisposition to autoimmune diseases. As the average life expectancy of the world continues to increase, this is not just a curiosity to study at a whim, but an indispensable part of medicine in the near future.

Keywords: Aging; Immune paralysis; Age-related inflammation; Immunocompetence.

Introduction

Autoimmune diseases have a prevalence of about 3-5% in the western hemisphere [1,2]. In the Indian subcontinent, the prevalence of inflammatory rheumatic diseases has been estimated to be around 2%.[3] Autoimmune diseases have been shown to have a curious relationship with age, with some diseases like systemic lupus erythematosus (SLE) being more common in the younger age group. On the other hand, in diseases like rheumatoid arthritis (RA), incidence increases with age. Then there are diseases like giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) which are almost exclusively seen in age groups >50 [4]. With a fall in birth rate and increase in life expectancy, we are now faced with an ever-aging population, who are thus at higher risk of autoimmune diseases.

However, the relationship is not linear. Though there is a much-increased prevalence of autoimmunity in the elderly, this does not directly translate into an increase in autoimmune diseases [5]. Moreover, elderly patients of rheumatic diseases are more prone to have atypical insidious or explosive presentations. The elderly also have an increased susceptibility to infections, reduced vaccine efficacy and reactivation of latent infections, all signifying subnormal immunity. These peculiarities have piqued the interests of...
scientists and clinicians for long. Immunosenescence and inflamm-aging are concepts that attempt to explain these phenomena and an understanding of them is essential for the current-day rheumatologist, whose patients are expected to live longer and longer as medical sciences advance.

Search strategy
PubMed/MEDLINE, Scopus and WebofScience were queried using relevant search strings related to immunosenescence, inflamm-aging and immune-aging. The authors selected articles as per their experience and opinions to transcribe this review [6].

Immunosenescence vs inflamm-aging
The term ‘senescence’ literally means ageing. Ageing is often viewed as being associated with slowing down. In the content of the immune system, “immunosenesence” was initially considered an age-related decline of immune functions. But this was too simplified a theory. From an evolutionary perspective, a weak immune system would be at odds with prolonged survival. Moreover, it is a known fact that increased aging is associated with an increase in proinflammatory mediators, mainly from monocytes and macrophages. Franceschi et al named this phenomenon “inflamm-aging” and postulated that it is provoked by a continuous antigenic load and stress [7]. The network theory of ageing states that the stress associated with ageing (such as physical- UV radiation, heat, chemical- reactive oxygen species (ROS), biological- viruses, bacteria) are countered by various anti-ageing mechanisms (eg. antioxidants- superoxide dismutase, catalase, heat shock proteins) [8]. In the context of the immune system, these stressors exist in the form of antigens and they are counteracted by a progressive increase in pro-inflammatory factors; this phenomenon is called inflamm-aging. Inflamm-aging, thus increases the ability to cope with stressors and increases longevity.

Changes in innate immunity
Innate immunity is an evolutionarily primitive form of immunity compared to adaptive immunity. It responds to pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) through a limited repertoire of pattern recognition receptors (PRRs), with the net result being triggering of inflammation and a better adaptive immune response. It was initially believed that innate immunity is non-specific with no memory. Recent evidence has shown innate immunity has the ability to adapt, termed trained immunity and this provides a broad protection against infections [9]. Trained immunity causes an asymptomatic pro-inflammatory state and increased readiness of innate immunity and this explains many facets of immune ageing. Majority of changes in innate immunity occur in macrophages and they are underlined below.

Macrophages and inflamm-aging
Macrophages play a central role in innate immunity, stress response and inflammation. Studies have shown that there exists a direct relationship between ageing and macrophage inflammation [10]. This is also called macrophaging. By constantly tackling stressors with an inflammatory response, macrophages provide the elderly with a survival advantage [7]. But this is one of the mechanisms that are believed to increase the prevalence of metabolic diseases like hypertension and diabetes mellitus, and rheumatic diseases like RA and PMR, in which inflammation plays a central role. This theory is strengthened by the fact that the pro-inflammatory cytokine, IL-6 is undetectable in most individuals at a young age but is increased in even healthy adults above 60 years of age [11]. This increase continues steadily till the end of life and is present in equal measure in both the robust and frail. Other acute phase proteins like lipoprotein a [Lp(a)], and fibrinogen are also increased in the apparently healthy [12]. Even though this puts individuals at an increased risk of inflammatory disorders, this is probably a result of successful adaptation to stressors initially. Later, after the successful creation of progeny, there is an age that barely affects evolution. Then, inflamm-aging turns out to be detrimental.

Macrophages generally exist in a state of equilibrium between aerobic, oxidative phosphorylation and anaerobic glycolysis (Warburg effect) and this is maintained via various epigenetic changes [13]. The same difference in metabolic preferences exists between M1 and M2 macrophages. On subsequent stimulation of macrophages, a faster and stronger innate response is elicited.
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The best studied example of this phenomenon is how the Bacille Calmette-Guerin (BCG) vaccine confers immunity against a wide range of infections apart from tuberculosis [14]. With increasing age, this trained immunity most likely leads to a state of constant immune activation. The role of epigenetic control in ageing is underlined by a recent study by Lowe et al, which defines an ‘epigenetic clock’ that predicts age based on the linear combination of the DNA methylation levels of 353 CpG dinucleotides [15]. The methylated ELOVL2 gene (elongase of omega 3 and 6 fatty acids) has emerged as a new epigenetic marker of age [16]. Thus they may pave the way for epigenome and the metabolic pathways to be targeted to delay immune ageing in the elderly.

Apart from the constantly activated macrophages, a major source of inflammatory stimuli is the endogenous, dead, or damaged cell debris which is recognized by PRRs. This is called ‘Garb-aging’ [17]. Other factors that contribute to inflam-maging are mitochondrial dysfunction, ER stress, defective autophagy, misfolded/proteins, DNA damage response and age associated changes in gut microbiota [18, 19]. (Figure 1)

### Inflamm-aging to ‘Immune paralysis’ of the Innate arm

When on one hand, some components of innate immunity are hyperactivated through inflam-maging; on the other hand, it also undergoes a state of decline called immune paralysis [20]. This occurs through a reduced function of monocytes, an increase in suppressor cell populations, T-regulatory cells (Tregs) and myeloid derived suppressor cells and an increase in the anti-inflammatory cytokine, Interleukin-10 (IL-10) [21, 22]. An example of this is the increased incidence of bacterial infections post-hip fracture, likely due to a reduction in chemotaxis, phagocytosis, and ROS production [23]. The role of this immune decline in the background of inflam-maging is not very clear. It is hypothesized to be due to a “fatigue” of the immune system. It is not known whether intervening at the stage of supra-normal inflammation would be beneficial or would increase the prevalence of infections more than what is already seen [21]. Future research should aim to develop therapeutic targets, to achieve a balance between inflam-maging and immune paralysis.

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Figure 1. Factors contributing to inflam-maging.
**Changes in the adaptive immune system**

The adaptive immune system is made up of two main divisions, cellular immunity, and humoral immunity. Cellular immunity is conferred by T lymphocytes and humoral immunity by B lymphocytes. T lymphocytes include T helper cells (CD4+ T cells), which are the master regulators of the immune system and cytotoxic T cells (CD8+ T cells) which are effector cells against intracellular pathogens. T helper cells are further subdivided into Th1, Th2 and Th17 subpopulations. Further CD4+ T cells and CD8+ T cells are classified into naïve, effector, central memory, effector memory and TEMRA (T effector memory cells expressing CD45RA) cell populations, based on functions and surface markers [24].

**Changes in T lymphocytes**

Early in life, the major T cell population is of a naïve phenotype and as the immune system ages, memory T cells will tend to predominate [25]. This process and homeostatic proliferation sustain the number of peripheral T lymphocytes in an elderly individual. Because of the early involution of the thymus, T lymphocytes are more affected than any other immune cell by ageing [26].

Homeostatic proliferation is one of the key mechanisms by which T cell numbers are maintained in the elderly. This is done by weak T cell receptor (TCR) activation by self-peptide-major histocompatibility complex (MHC) expressed by stromal cells in secondary lymphoid tissues and by cytokines like IL-7 and IL-15 [27]. In the elderly, hematopoietic stem cells do not contribute much to peripheral T cell numbers. Homeostatic proliferation is efficient in maintaining the CD4+ T cell population but the same is not true for CD8+ T cells [28]. This decrease in CD8+ T cells is underestimated because a subset of CD8+ central memory cells lose CD45RO expression and regain CD45RA after viral infections, masquerading as naïve T cells! Such cells are called virtual memory cells in mice. It is not known whether such cells accumulate with age in humans [29]. With regards to cytokines, CD8+ T cells receive most survival signals from IL-15 and IL-7, while CD4+ T cells receive it from IL-7 and IL-2.

It is not only enough that T cell numbers are maintained; TCR diversities also need to be maintained. With the reduction in the number of naïve T cells, TCR diversity was expected to be compromised but practically that is not the case [30]. It has been estimated that ~10^6 unique TCR-beta chain sequences exist in young adults and this number decreases by a factor of 3-5 in the healthy elderly [30]. Loss of diversity (oligoclonality) is observed mostly in the T effector memory CD45RA subset (TEMRA cells) which increase in numbers following viral infections and reduce TCR diversity. These cells have shortened telomeres, exhibit cell cycle arrest, express DNA damage and an inflammatory phenotype [30].

TEMRA cells show terminal differentiation with secretory features (like effector cells) and express regulatory cell surface receptors such as killer cell-like immunoglobulin receptors (KIRs) [31]. They have reduced expression of NAD-dependent protein deacetylase sirtuin-1, which leads to increased lysosomal degradation of FOXO1, and metabolic reprogramming, which favours glycolytic activity and granzyme B production; all of which are well established changes seen with ageing [32]. In these cells, there is the activation of mitogen-activated protein kinase (p38MAPK) downstream of AMP-activated protein kinase (AMPK) and TAB-1 pathways, independent of TCR signaling [33]. JUN-N terminal kinase signaling is also activated, independent of MAPK activation [34]. In effect, TEMRA cells act autonomously, fostering inflammation, while also losing telomerase activity and telomere length.

It is necessary to maintain naïve and memory T cells in quiescence until antigen stimulation occurs. In quiescence, cell growth is slowed, cell cycles are arrested and have low mTORC (mammalian target of rapamycin complex) metabolic activity. But this is disrupted in the elderly because of certain factors like fibroblast growth factor 2 (FGF2), present in aged lymphoid niches [35]. This leads to a partially differentiated or ‘senescent’ T cell population which has irreversible cell cycle block (TEMRA cells have irreversible cell cycle block), high transcriptional activity, high lysosomal activity and a senescence associated secretory phenotype (SASP). The pro-inflammatory phenotype has been seen at an epigenetic level as well, with increased expression of miR21 and miR146a and reduced expression of miR181 with ageing [36, 37].

With ageing, immune-supporting stromal cells like fibroblasts and epithelial cells can acquire a senescence associated secretory phenotype. In general, senescence is associated with the slowing of cellular functions, which has a central role in controlling tumour progression. But with SASP
phenotype, it was found that these cells lose tumour suppressor genes like p53, gain oncogenes like RAS and can secrete proinflammatory cytokines like IL-6, chemokines like IL-8, MCP-2, growth factors like insulin-like growth factor (IGF), matrix metalloproteinases and serine proteases. This was initially seen in the context of cancer and was found to aid in tumour development and progression [38]. Similar changes are seen with senescent T cells as well. SASP is one of the key mechanisms that contribute to an osteoarthritis (OA) phenotype in elderly joints [39].

In conditions such as chronic viral infections, persistent antigenic stimulation can cause a form of T-cell dysfunction called exhaustion, which intends to prevent damage due to excessive immune activation. This occurs through the activation of immune checkpoints like programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin containing domain-3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) [40]. Exhausted T cells could be the immune system’s way of checking inflammation and autoimmunity that are propagated by TemRA cells and cells with a SASP phenotype. In summary, an increase in TemRA cells, SASP and exhausted T cells are the main changes that occur in ageing T cells, contributing to immunosenescence.

Changes in B lymphocytes

Compared to T cells, age associated B cell changes are not well characterised. Most B cells in the elderly are antigen-experienced memory B cells, that develop during past microbial infections and are necessary for effective immunity [41]. In aged female mice, a unique subset of B cells expressing the integrin chain, CD11c has been identified, and are called age-associated B cells(ABCs), which have also been seen in lupus prone mice. These cells secrete autoreactive autoantibodies and depletion of these cells could decrease the autoantibodies. TLR7 signaling was found to be essential for the development of ABCs and these cells have been detected in elderly women with autoimmune diseases [42].

ABCs have been further characterized by the phenotype: B220+, CD19+, CD11c+ and lack CD21, CD23, CD43, CD95. They do not proliferate as effectively as follicular B cells after B cell receptor (BCR) cross-linking but still remain viable, as opposed to marginal zone B cells. In contrast, ABCs proliferate robustly in response to TLR7 and TLR9 ligands [43]. Even though BCR cross-linking does not promote mitosis of B cells, BCR cross- linking and TLR 7/9 activation have a synergistic effect on the same. Most studies point to the fact that ABCs do not develop de novo from the bone marrow but are derived from pre-existing B cell types [43]. Help for their development comes from B cell activating factor belonging to the TNF family (BAFF), secreted by innate resident cells and T cell cytokines, IFN-γ, IL-4 and IL-21 [44]. ABCs express the Th1 CD4+ T cell-specific transcription factor, T-bet.

B cell genesis gradually wanes with age and ABCs have been found to be a negative regulator for B cell lymphopoiesis. Using in-vitro and adoptive transfer approaches, ABCs reduce B cell generation through TNF-α [45]. This is in accordance with the dampened B cell production in the elderly. With ageing, as ABC numbers increase and follicular B cells decrease, effective B cell response depends on ABC activation with TLR 7/9 activation. ABCs show a propensity for IL-6 and IFN-γ production through TLR 7/9 activation. They are effective antigen presenters to T cells in germinal centers and drive them towards a Th17 fate [42, 46]. Thus, ABCs are the key drivers of autoimmunity in the elderly.

Effect of immunosenescence on vaccination response in the elderly

Those above 60 years form a special population that needs vaccine protection for diseases like bacterial and viral pneumonia, and shingles among others [47]. The reduced efficacy of vaccines in the elderly has been linked to immunosenescence. Influenza and herpes zoster are important vaccines for the elderly but their effectiveness reduces with age [48, 49]. Cytomegalovirus (CMV) infections seem to have a synergistic effect with immune-aging to reduce vaccine efficacy, especially as evident by trials of influenza vaccination [50].

A major clinical application of understanding immunosenescence will be to boost vaccine efficacy in the elderly. Different strategies have been tried including the use of different adjuvants, increased antigen dose, increased number of doses and modifying the route of antigen exposure [51]. Systems level biological approaches are being used to make better vaccines [52].

Effects on autoimmunity

The changes related to immunosenescence have been postulated to increase susceptibility to autoimmune disease. It is a well-known
phenomenon that the prevalence of autoantibodies like rheumatoid factor, anticitrullinated peptide antibodies (ACPA), different anti-nuclear antibodies (ANA) and others increases with age [53, 54]. However, most of these are non-pathogenic and do not translate into clinical disease. One hypothesis is that they lack specificity to cause disease. Another hypothesis is that some other hit is required to lead to disease, but the corresponding immune-paralysis or exhausted phenotypes do not allow this to happen.

The association of different autoimmune diseases with different aspects of immunosenescence is well documented. In genetic diseases with accelerated aging like Down syndrome, there is a special predisposition to autoimmune diseases [55]. Though SLE is a disease of predominantly young women, still the immune cells show an immunosenescent phenotype [56]. Even the autoimmune phenomenon seen in COVID-19 [57] can be linked to immune-ageing [58].

Senescence-associated T (SA-T) cells have been proposed with markers PD-1 and CD153 positivity [59]. These SA-T cells have been shown to be associated with immune complex deposition, metabolic stresses, and vascular damage, all hallmarks of autoimmune disease. Such cells have been shown to be active in lupus-prone mice [60]. Periods of stress or infection that lead to lymphopenia are followed by vigorous compensatory proliferation. It has been shown that such T cell exaggerated proliferation leads to autoimmunity [61]. During immunosenescence, the repertoire of T cells is reduced with a compensatory expansion of the surviving cells. This too may lead to higher autoimmunity.

Age-associated B cells are key drivers of autoimmunity in the elderly [41]. ABCs are elevated in well-characterised murine models of autoimmunity like NZB/WF1, reaching up to 15% of the splenic B cell pool by 6 months of age [44]. Their levels are increased in SLE [62], RA and systemic sclerosis [42]. Increased ABC numbers correlated with the SLE disease activity index (SLEDAI) [63] and depletion of these cells has corresponded with therapeutic response [64]. Cells with phenotypic characteristics of ABCs have been detected even in patients with common variable immunodeficiency (CVID) with autoimmune features [65].

Concept of frailty- do autoimmune diseases cause accelerated ageing?

Thus far in this review, we explained how ageing affects the immune system. Another question remains: whether patients with autoimmune disease age differently, compared to apparently normal individuals? We know that autoimmune diseases reduce life expectancy. A study by Crowson et al suggested that patients with RA were effectively 2 years older than actual age at RA incidence, and thereafter the patients underwent 11.4 effective years of aging for each 10 years of calendar time [66]. The elevated mortality rates in patients with diseases like RA is consistent with the hypothesis of accelerated ageing. Frailty is a state of increased susceptibility to stressors in the elderly (>65 years) and it has been seen that, patients of RA have changes seen with frailty at a much younger age [67]. Thus, the changes seen with RA in the immune system could lead to early senescence; possibly accelerated immunosenescence as well and this area warrants further study.

Conclusion

Immunosenescence is gradually being understood. Nevertheless, there is a long way to go to elucidate its role in various diseases in the elderly. This includes vaccine responsiveness as well the susceptibility to autoimmune diseases. Various multi-omics approaches, including single-cell based approaches have opened up newer avenues to explore. As the world population ages, neither the scientist nor the clinician can afford to close their eyes to immune-aging.

DISCLOSURE

SA has received an honorarium as speaker from Pfizer, Dr Reddy’s, Cipla, Novartis and Jansen (unrelated to the current work). TGS has no potential conflicts of interest to disclose.

FUNDING

None

AUTHOR CONTRIBUTIONS

Both authors substantially contributed to the drafting of the initial and revised versions of this review. They take full responsibility for the integrity of all aspects of the work.
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