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REVIEW

The role of immune aging in giant cell arteritis

Patricia Harkins[a, b, *], Sharon Cowley[a], Robert Harrington[a, b], David Kane[a], Richard Conway[a, b]

[a] *Rheumatology Department, Trinity College Dublin, Ireland.*
[b] *St. James Hospital, Dublin, Ireland.*

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Abstract

Giant cell arteritis (GCA) is a granulomatous vasculitis with a predilection for medium and large calibre arteries. The most significant risk factor for its development is advancing age, with a peak incidence in the seventh and eighth decades of life. Despite this, until recently, the role of aging in disease pathogenesis has been largely overlooked. Advancing age is associated with numerous alterations in both the innate and adaptive immune systems. Indeed, there is significant overlap in the cellular and molecular pathways involved in immune aging and those observed in the pathogenesis of GCA. In this review, we explore these similarities and further expand the discussion on the postulated role of accelerated immune aging in the pathogenesis of GCA. With the dramatic increase in lifespan in recent decades, elucidating the potential role of early immune aging in disease pathogenesis is extremely pertinent, with the potential to offer a new therapeutic avenue not only for those with GCA, but for all immune-mediated rheumatic diseases.

Keywords: Aging, giant cell arteritis, vasculitis, inflammaging, immunosenescence

Introduction

Giant cell arteritis (GCA) is the most common form of vasculitis affecting adults, with an incidence rate of approximately 10 per 100,000 in those over 50 years of age [1]. With the dramatic increase in lifespan in recent decades, it is postulated that by 2050, 3 million people worldwide will be living with the condition [2].

GCA is a heterogenous condition with a varied clinical presentation owing to its overlapping spectrum of clinical phenotypes, namely cranial GCA (c-GCA) and large vessel GCA (LV-GCA), with or without concomitant polymyalgia rheumatica (PMR) [3]. The vasculitis in those with c-GCA predominantly affects the cranial arteries, and causes the classical symptoms associated with GCA, specifically headache, scalp tenderness, jaw claudication, and sudden painless visual loss secondary to arteritic anterior ischemic optic neuropathy. LV-GCA, on the other hand, tends to present with more constitutional or systemic symptoms such as weight loss, fatigue, fever, and drenching night sweats. It has been reported that 40-60% of patients with GCA report symptoms of PMR, and 15-20% of those with PMR have a concomitant GCA, either at disease onset, or throughout the course of their disease [4, 5]. Moreover, c-GCA and LV-GCA frequently present together, and with advances in vascular imaging and subsequent increased detection of large vessel involvement, a concomitant rate as high as 83% has been reported [6-9].

GCA is characterized by a granulomatous inflammation, that typically affects all three layers of the vessel wall, which can culminate not only in the classic ischemic symptoms, but also in dissection and aneurysm formation with subsequent rupture [10]. Tissue-resident dendritic cells, residing in the adventitia of the arterial wall, are of utmost importance in the initiation of GCA pathogenesis [11]. When activated, these dendritic cells trigger an inflammatory cascade involving macrophages and T cells [10]. What exactly causes activation of the dendritic cell and the subsequent development of GCA remains unknown. Whilst multiple different risk factors have been implicated, the strongest risk factor is most certainly increasing chronological age. GCA occurs almost exclusively in those over the age of 50, and has a peak incidence in the seventh and eighth decades of life [12]. The explanation behind this later-in-life development remains to elucidated.

Aging is a ubiquitous complex process, typically characterized by the accumulation of cellular damage with associated alterations in tissue homeostasis and resultant increased vulnerability to adverse health outcomes [13]. Across almost all organ systems, the diseasome of aging

* Corresponding author: Patricia Harkins
Mailing address: Trinity College and St. James Hospital, Dublin, Ireland.
Email: harkinp@tcd.ie
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is the principal driver of morbidity and mortality [13]. However, chronological age is not always reflective of biological age, with numerous determinants such as genetics, lifestyle, environment, and socioeconomic factors significantly impact healthspan. Despite significant recent advances in our understanding of the aging process, such as the identification of the key hallmarks of aging [14], our understanding of the role of aging in disease pathogenesis remains in its infancy. Biological aging is associated with both structural and functional alterations in local tissues, in addition to multiple changes in both the innate and adaptive immune systems.

There is considerable overlap in the molecular and cellular pathways between the immune dysregulation, and indeed local vascular tissue abnormalities observed in those with GCA, and those seen in immune aging. Whether these changes are accelerated in those with GCA and contribute to disease pathogenesis has yet to be conclusively addressed. In this review, we highlight the current evidence on aging in GCA, and more specifically explore the potential influence of age-related immune system alterations in disease pathogenesis.

Aging and the immune system

The immune system is a complex interactive network, whose essential role is defence of the host against infectious, neoplastic and other deleterious agents, whilst also maintaining tissue repair and regeneration [15]. Although extensively interlinked, the immune system is typically categorised into innate and adaptive immunity, with specialized immune cell types connected with each. The innate immune system is the initial line of defence, and is characterized by its rapidity of action, whereas adaptive immunity tends to take several days to weeks to develop. Adaptive immunity is much more targeted and precise through antigen-specific interactions, and is also capable of long-term specific memory.

Age impacts both the innate and adaptive immune systems, as evidenced by marked changes in the distribution and competence of immune cells. Two pervasive features of immune aging are inflammaging and immunosenescence. Both inflammaging and immunosenescence have a symbiotic relationship, with the lifetime immune exposure history, or so-called "immunobiography" of the host, being central to both [16]. The term "inflammaging", was first coined in 2000, and refers to the chronic low-level pro-inflammatory response observed in the absence of overt stimuli ("sterile" inflammation) that is associated with advancing age [17]. It is strongly implicated in the pathogenesis of several diseases of the elderly, and has been correlated with aging phenotypes, including alterations in body composition and energy production [18]. Therefore, it is now established as a significant risk factor for much of the morbidity and mortality observed with advancing age. Characteristically, it is associated with an increase in the circulating levels of acute phase proteins, such as C-reactive protein (CRP), in addition to a number of pro-inflammatory cytokines, notably interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [18].

Cellular senescence is characterized by cell cycle arrest, where the cell loses its proliferative capacity, however evades apoptosis and remains metabolically active [19]. It can be triggered by a number of factors including mitochrondrial dysfunction, epigenetic alteration, cellular stress and DNA damage [19]. Although it is an essential process to halt the proliferation of damaged cells, it is imperative that senescent cells are cleared in an efficient and timely manner to maintain tissue homeostasis and ensure the resolution of inflammation. Pertinent to the concept of inflammaging, senescent cells acquire a secretory profile known as the senescence-associated secretory phenotype (SASP) [13]. This involves the secretion of a wide range of soluble molecules including chemokines (*e.g.* CXCL8/MCP-1), interleukins (*e.g.* IL-6), growth factors (*e.g.* VEGF), metalloproteinases, insoluble proteins and extracellular matrix proteins [13]. In addition to their release into the systemic circulation where they contribute to inflammaging, these secreted molecules have also been shown to function in a paracrine fashion, enabling the development of cellular senescence in neighboring cells [20]. Therefore, the defective clearance of these senescent cells, results in their accumulation, which sustains inflammaging and also propagates a cascade of other cells entering into cellular senescence. In recent years, there has been much research into targeting this pathway pharmacologically through the use of senotherapeutics [13].

Immunosenescence, which refers to the senescence of immune cells of the innate and adaptive immune systems with advancing age, is recognized as a powerful contributor to inflammaging [21]. It is a state of cellular exhaustion which results in a functional decline of the immune system, with an associated reduced ability to respond to new antigenic stimuli, and subsequent increased susceptibility to morbidity [22]. One of the defining features of immunosenescence is a reduction in naïve T cells ($CD4^+$ and $CD8^+$), which is partially caused by thymic involution, with the resultant replacement of T cell priming tissue with fibrotic and adipose tissue [23, 24]. This results in a decreased ability to respond to new antigenic stimuli when encountered. Moreover, repeated exposure to antigenic load throughout the lifespan results in the expansion of memory and effector memory T cells with age [22]. Accordingly, with advancing age, there is an increase in the number of these cells entering cellular senescence with an associated amplified proinflammatory phenotype further propagating inflammaging [16]. A similar but less well characterized profile of immunosenescence in B cells has been described [25, 26].

Innate immune system aging and GCA

The innate immune system overview

The innate immune system is composed predominantly of myeloid cells, namely monocytes and their derivatives—tissue macrophages and dendritic cells—and blood

granulocytes (eosinophils, basophils and neutrophils) [27]. Both natural killer (NK) and natural killer T (NKT) cells derived from lymphoid cells also constitute the innate immune system, as they do not have the clonotypic receptors characteristic of the adaptive immune system [27].

Innate immune cells express pattern recognition receptors (PRRs) on their surface, which sense highly conserved molecular structures of an invading pathogen, so called "pathogen-associated molecular patterns" (PAMPs) [28]. These PAMPs are essential for the life cycle of the pathogen, and their recognition through the PRRs induces the activation of complex signaling pathways, which result in different innate defense mechanisms, including phagocytosis, release of inflammatory proteins, activation of the complement system, production of acute phase proteins, secretion of chemokines and cytokines and activation of the adaptive immune system as appropriate [28]. All of this ultimately facilitates the eradication of the invading pathogen. Moreover, these PRRs also sense damage-associated molecular patterns (DAMPs), which are typically released from damaged or dying cells [29]. These DAMPs include nuclear and mitochondrial DNA, DNA-binding molecules, nucleotides, nucleosides, and RNA. PRRs include toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-1 receptors (RLRs), and DNA receptors (cytosolic sensors for DNA) [28].

Myeloid cells and aging in GCA

Monocytes are mononuclear myeloid cells, that can enter the circulation and migrate to specific tissues and organs, where they further differentiate into macrophages or dendritic cells. Macrophages demonstrate exceptional plasticity with resultant marked functional diversity [30]. They primarily function as professional phagocytic cells by identifying, phagocytosing and destroying pathogens, tissue debris, and apoptotic cells. However, they also function as professional antigen-presenting cells, a role that is crucial for initiating and maintaining adaptive immunity [30]. Therefore, macrophages are uniquely at the interface of both the innate and adaptive immune systems.

The term "macrophaging" has been coined to reflect the integral role that macrophages play in immune dysfunction associated with aging, notably the processes of inflammaging and immunosenescence [31]. With progressive age macrophage function decreases resulting in reduced phagocytosis and also an increase in the production of inflammatory cytokines contributing to inflammaging [32]. In GCA, macrophages, specifically multinucleated giant cells are the principal constituent of the granulomatous lesion reflecting their integral role in GCA pathobiology [33]. There are a number of shared similarities between the myeloid cell dysfunction observed in GCA patients and that seen with immune aging.

Age-related changes in hematopoiesis influences the production and indeed functionality of myeloid cells. With advancing age, one can sustain somatic mutations in bone marrow hematopoietic stem cells, which can lead to clones of mutated leukocytes that populate the peripheral blood, a phenomenon called "clonal haematopoiesis of indeterminate potential" (CHIP) [34, 35]. The potential of such age-related somatic mutations in myeloid cells to give rise to mutant innate immune effector cells and induce intense inflammatory activity and thus disease has been shown by the UBA1 somatic mutations observed in VEXAS syndrome [36].

In both VEXAS syndrome and GCA, advancing age is the primary risk factor, and age is also strongly correlated with CHIP. Recently, CHIP has been implicated in those with GCA in a small retrospective case-control study [37]. Although interesting, more studies are required to further explore a potential correlation.

With advancing age, changes also occur in the extracellular matrix (ECM) that alters its functions. Under normal physiological conditions, the vessel wall is inaccessible to inflammatory cells, a concept often referred to as "immune privilege" [38]. However, in those with GCA, a critical determinant of vasculitis is the ability of immune cells to enter the vascular tissue microenvironment. Matrix metalloproteinases (MMPs) have been shown to be integral in facilitating this, and interestingly, their upregulation has also been implicated in accelerated vascular aging [39]. Transcriptome analysis has demonstrated abundant transcripts for both MMP-2 and MMP-9 in GCA patient derived monocytes [40]. Moreover, macrophages from those with GCA are programmed to produce large amounts of pro-MMP-9, a pro-peptide that, when enzymatically cleaved by MMP-2 and other MMPs, yields an enzymatically active MMP-9 [40]. MMP-9, also known as type IV collagenase, plays an integral role in ECM remodeling, neoangiogenesis, and serves as a critical checkpoint in the pathogenesis of GCA by controlling the migration of both monocytes and T cells into the protected tissue niche of the vessel wall [41].

Another feature of immune privilege breakdown in GCA is the defective expression of programmed cell death ligand (PD-L1) [42]. PD-L1 is an immune-inhibitory ligand, expressed on the surface of antigen-presenting cells, including dendritic cells, that binds to the programmed cell death protein 1 (PD-1) receptor, providing a negative or inhibitory signal to T cells [42]. Therefore, hypoactivity of this PD-1/PD-L1 checkpoint, results in unopposed T cell activation, with naïve $CD4^+$ T cell differentiation into Th1, Th17 and IL-21 producing T cells [43]. The PD-1/PD-L1 axis also plays an integral role in various malignancies [44]. One may therefore postulate that the deficiency in this important immuno-inhibitory pathway is in fact an age-related pathology, given its identification in the setting of advanced age in both GCA and malignancy. However, more research is required before a clear association can be drawn.

Adaptive immune system aging and GCA

Adaptive immune system overview

The adaptive immune system is composed of T- and B- lymphocytes. It has three broadly defined functions, including clonal expansion, differentiation into effector

cells, and the generation of antigen-specific memory cells that provide lifelong immunological memory [45].

The induction of adaptive immunity depends on essential signals delivered from the innate immune system in addition to the interaction of the appropriate major histocompatibility complex (MHC) on an antigen presenting cell surface with the T or B cell receptor [46]. Therefore, adaptive immunity is a highly regulated multidirectional interaction between cells of the innate immune system, and T- and B- lymphocytes.

The aging process results in a number of changes in T cell structure and function that culminate in a reduced specificity of the immune response, with an associated dysregulation in the balance between host protection and the tolerance of self-antigens [47]. Such age-related changes in the T cell compartment have been summarized as the "T cell aging associated phenotype" (TASP) [48]. They include changes in the T cell repertoire, with a marked reduction in naïve T cells, and an expansion in the number of T cell subsets [48]. Moreover, regulatory T cells reduce, with resultant unopposed effector responses [48]. T cells also undergo functional changes, including an increased propensity for tissue invasion with heightened mobility, and a tendency for differentiation into effector cells that are cytokine hyperproducers, with significant cytotoxic ability [48].

There is a paucity of data pertaining to the molecular age-related changes observed in B-lymphocytes, however, undoubtedly, the humoral immune response alters with advancing age [46]. Thus, we will summarise age-related changes in T-Lymphocytes as they correlate to GCA pathogenesis .

Genetic and epigenetic alterations in aging T cells and GCA

T cell aging is influenced by a complex interplay of genetic and epigenetic alterations. Lifespan is inversely correlated with mutation rates, implicating genomic instability as crucial in the aging process. Examples of such genomic instability in the aging T cell arise from errors in both replication and DNA double-strand break repair, spontaneous cytosine deamination, in addition to large structural changes [49]. The accumulation of such genomic instability in aging T cells is also accompanied by diverse epigenetic alterations. Such epigenetic modifications control gene expression at the transcriptional level, typically through DNA methylation, histone modifications, and transposable elements [50]. Additional post-transcriptional regulation is achieved by non-coding RNAs such as microRNAs (miRNAs) [50]. Epigenetic alterations are heavily influenced by exposure to environmental stimuli [50, 51]. Both genetic and epigenetic alterations in aging T cells result in functional deficiencies. Epigenetic alterations in GCA that overlap with those observed in aging T cells have been observed [52, 53].

Age-related DNA methylation changes in T cells may alter regulatory mechanisms and signaling networks that predispose to autoimmunity [54]. A genome-wide DNA methylation array was performed on temporal artery tissue of those with GCA and those without GCA [52]. This epigenetic phenotyping revealed hypomethylation changes associated with increased activity of the calcineurin/nuclear factor of activated T cells (NFAT) pathway in the temporal arteries of those with GCA versus healthy controls [52].

Moreover, the miRNA, miR-21 is typically upregulated with age [55]. In activated $CD4^+$ T cells, miR-21 results in the differentiation from memory T cells into inflammatory effector T cells [55]. Interestingly, miR-21 has been demonstrated to be upregulated in actively inflamed temporal artery biopsies of those with GCA [53].

Whether these epigenetic alterations observed in aging T cells pertain to disease development in GCA remains to be elucidated, however, the above data most definitely implicates such modifications in GCA immunopathogenesis.

T regulatory (Treg) cell aging and GCA

Treg cells are immune-inhibitory, and function in both lymphoid and peripheral tissue sites to mediate effector T cell functions and maintain immunological self-tolerance [56, 57]. With advancing age, the number of Treg cells reduces, promoting a pro-inflammatory immune environment [58]. Altered Treg cell homeostasis has also been implicated in GCA immunopathogenesis [10].

$CD4^+$ T reg cells are characterized by the X chromosome-encoded transcription factor forkhead box P3 (FOXP3) [59]. FOXP3 confers the suppressive ability to $CD4^+$ Treg cells, with each of its distinct isoforms influencing Treg cell differentiation and function. Treg cells in those with active GCA, demonstrate an abundance of FoxP3 lacking exon 2 (FOXP3ΔE2) isoform [60]. This isoform is associated with Treg cell instability and an increase in the expression of inflammatory cytokines [59]. Similar to that seen in the aging immune system, in those with active GCA, these Tregs have a reduction in their suppressive capacity [60].

IL-6 is a prototypical cytokine associated with inflammaging, and is also elevated in those with GCA [61]. IL-6 inhibits FOXP3, and serves as an inhibitor of Treg cell differentiation [62]. Interestingly, treatment with the IL-6 receptor antagonist tocilizumab resulted in a complete correction of the aforementioned abnormalities observed in the Treg cells of those with active GCA [60]. Furthermore, the treatment of tocilizumab actually results in increased numbers of activated Treg cells [60].

Recently, the role of the $CD8^+$ regulatory T cell subset has garnered increased attention over its role in immune aging, and subsequent disease pathogenesis [48]. One of the cardinal features of immune aging is the progressive reduction in the naïve $CD8^+$ T cell population, which is associated with a concomitant progressive decline in the quantity of $CD8^+$ Treg cells with subsequent unopposed proinflammatory activity [63]. Under normal conditions, $CD8^+$ Treg cells exert their suppressive influence on surrounding $CD4^+$ effector T cells via the release of the enzyme NADPH oxidase 2 (NOX2) from their exosomes [63]. With advancing age, the number of these $NOX2^+CD8^+$ Treg cells decreases, a process that is in-

terestingly amplified in GCA [64]. In GCA, a reduction in NOX2$^+$CD8$^+$ Treg cells has been demonstrated, and moreover, their functional ability to inhibit effector T cell action is lost culminating in uncontrolled tissue inflammation [64]. Alterations in the NOTCH signaling pathway have been implicated in this aberrant Treg cell activity. More specifically, NOTCH4 signalling via RAB GTPases, suppresses the release of exosomes containing NOX2. Without NOX2, the functional influence of CD8$^+$ Treg cells is lost [54]. This age-associated CD8$^+$ Treg cell dysfunction has also been demonstrated in GCA, where there is an upregulation in NOTCH4, with associated altered RAB gene expression in CD8$^+$ Treg cells [64]. Additionally, *in vivo*, the inhibition of NOTCH4 signaling resulted in restoration of CD8$^+$ Treg cell function in addition to suppression of vessel wall inflammation [64]. This, coupled with the identification of NOX2 as a critical component in Treg cell homeostasis, identifies two promising targets of Treg cell aging for therapeutic exploitation.

T cell senescence and GCA

Secondary to persistent antigenic stimulation over the course of a lifespan, T cells enter into repetitive cycles of differentiation, eventually becoming exhausted and acquiring a senescent-like phenotype. Such exhausted or senescent T cells demonstrate inferior efficiency in protecting the host, whilst exhibiting an exaggerated proinflammatory response pattern. Such T cell senescence is now widely accepted as an integral driver of the inflammaging implicated in many chronic inflammatory conditions [65]. Uniquely, given that T cells do not undergo irreversible cell cycle arrest, they don't fulfil criteria for the classical definition of a senescent cell phenotype. Instead, there is a reduction in their cell cycle activity, whilst maintaining their proliferative capacity. Similar to other senescent cell types, they do secrete a range of mediators, including proinflammatory cytokines or SASP [54].

With advancing age, naive CD8$^+$ T cells experience a greater decline in absolute and relative cell numbers, with a subsequent higher expression of senescence markers than CD4$^+$ T cells [47, 66]. Additionally, with progressive age, the T cell compartment become enriched with CD28 negative, end differentiated T effector memory cells, so-called "TEMRA" cells [49]. These cells have an exaggerated proinflammatory response, and secrete SASP, however similar to other typical senescent T cells, they maintain their cell cycle activity [67].

Their function is dependent on multiple pathways, including the mechanistic target of rapamycin (mTOR) signaling [68]. mTOR measures and responds to intracellular energy reserves, in addition to autophagy and mitochondrial function signals, to regulate cell growth, proliferation and death [69]. mTOR complex 1 (mTORC1) is now established as one of the central metabolic sensors responsible for the regulation of cellular longevity via senescence mechanisms [70]. Loss of mTORC1 activity supports longevity, whilst increased activity promotes cellular senescence [71]. Notably, increased mTORC1 activity has been demonstrated in the CD4$^+$ T cells of those with GCA [70].

One of the key regulators of mTORC1 are the sirtuins (SIRTs). SIRTs are a protein family of nicotinamide adenine dinucleotide (NAD$^+$)-dependent histone deacetylases, comprising seven members [72]. SIRT1 inhibits mTORC1 via the activation of AMP-activated protein kinase (AMPK). Reduction in NAD$^+$ levels with increasing age, result in a decrease in SIRT1 activity, and subsequent increased mTORC1 activity [70]. Interestingly, a decline in SIRT1 expression was demonstrated in peripheral blood mononuclear cells of those with GCA, versus age matched healthy controls [73].

Additional pathways implicated in the regulation of mTORC1 activity, are the Jagged1-NOTCH1 and the CD28-PI3K-AKT pathways. Again, both of these signalling pathways have been found to be upregulated in GCA T cells, in addition to other diseases of accelerated aging such as Alzheimer's disease and Parkinson's disease [74-76].

In both temporal artery biopsies and peripheral blood of those with GCA, levels of CD4$^+$CD28$^-$ T cells are increased [66]. Moreover, these cells, similar to the senescent T cells previously described in rheumatoid arthritis [77], show upregulation of the natural killer (NK) receptor NKG2D [78]. In GCA, this upregulation of NKG2D is associated with increased activity of Th1 and Th17 cells, with the subsequent over expression of associated proinflammatory cytokines [78].

SASP encompasses a diverse category of proinflammatory cytokines, chemokines, and growth factors, that have multiple functions, in addition to the promotion of paracrine senescence in surrounding healthy cells [13]. The SASP cytokines IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) have both been demonstrated to be successful therapeutic targets in GCA [79, 80].

Moreover, a recent study demonstrated increased expression of p21 and p16 in the inflamed temporal arteries of those with GCA [81]. Both p21 and p16 are associated with the activation of senescence pathways, and by inference their increased expression in the inflamed temporal arteries of those with GCA may be reflective of senescence. However, non-senescent cells are also capable of expressing these markers, particularly in the setting of an inflammatory disease, and so results should be interpreted with caution. Additionally, this study [81] also demonstrated previously reported findings of an increased expression of the senescence marker p53 [82] and the infiltration of NKG2D$^+$CD28$^-$ senescent like T cells in the temporal arteries of those with GCA [78].

Recently, targeting T cell senescence via pharmacological agents (senotherapeutics) both to enhance longevity and also to modulate aging associated immune diseases has garnered momentum [83]. There are two kinds of senotherapeutics: senolytics, which induce cell death of senescent cells, and senomorphics, which attenuate the pathological pro-inflammatory SASP [13]. Given the integral role of mTOR in T cell senescence, it has become a key target for senotherapeutics. For example, the mTOR inhibitor rapamycin (sirolimus) has undergone evaluation in multiple rheumatic diseases [13, 84, 85], and the widely

used oral hypoglycemic agent metformin is also a promising pharmacological target, given its role as an AMPK activator, with subsequent repression of mTOR [86, 87].

Conclusions

Our understanding of the immunopathogenesis of GCA is continually increasing, and with it the role of aging in its pathogenesis is becoming more appreciated. We have discussed how advancing age is associated with significant restructuring of both the innate and adaptive immune systems, rendering the host more susceptible to autoimmunity and disease pathogenesis (Table 1). Whilst there are a number of similarities between the aged immune system and the immunopathogenesis of GCA, it is currently unclear to what extent immune aging is contributing to the development of GCA. With the prolongation of lifespan, understanding the influence of accelerated biological aging on disease pathogenesis, including that of GCA, is of paramount importance. Long-term prospective studies assessing accelerated aging prior to the onset of GCA, and indeed other immune-mediated diseases are needed. Establishing the mechanisms underlying accelerated immune aging in GCA, and other immune-mediated pathologies, could help identify novel therapeutic targets that not only improve disease outcomes, but also extend quality of life, and improve healthspan globally.

Declarations

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Table 1. Summary of innate and adaptive immune system changes shared by both accelerated immune aging and GCA.

Innate immune system	Adaptive immune system
Somatic mutations in hematopoiesis—"Clonal hematopoiesis of indeterminate potential" (CHIP)	Epigenetic alterations -Hypomethylation, with increased activity of NFAT pathway -Increased miR-21
Increased MMP-2 and MMP-9 on circulating monocytes, and increased levels of pro-MMP-9	T-regulatory cells -Increased levels of FOXP3 lacking exon 2 isoform (reduced suppressive capacity) -Reduced $NOX2^{+}CD8^{+}$ Treg cells -Increased NOTCH4 signaling
Decreased PD-L1 expression on dendritic cells and macrophages with resultant hypoactivity of PD-1/PD-L1 checkpoint	T cell senescence -Increased mTORC1 activity -Decreased SIRT1 expression -Increased NOTCH1 signaling -Upregulation of NK receptor NKG2D -Increased P13K-AKT signaling -Increased p21, p16, and p53

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