

# Sustained immune youth risks autoimmune disease in the aging host

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Immune responses underlying autoimmune diseases follow the same principles that protect individuals from infection and malignancies. However, while protective immunity wanes with progressive age, the risk for autoimmune disease steadily increases; incidence rates for many autoimmune diseases peak in later life. Here, we discuss whether aging predisposes to autoimmunity, arguing that disease progression in the autoimmune vasculitis giant cell arteritis is driven by age-inappropriate sustenance of immune competence. Stem-like memory CD4<sup>+</sup> T cells (T<sub>SCM</sub>) that reside near the vasculitic lesions provide a continuous supply of pathogenic effector T cells. Antigen-presenting cells lacking inhibitory ligands further impede peripheral tolerance mechanisms. In the context of aging-associated accumulation of neoantigens, this incessant immune competence sets the stage for unopposed autoimmunity. We propose that sustained immune youthfulness can be detrimental to the aging host, while immune aging may be a beneficial adaptation to balance reactivity to self-antigens and non-self-antigens and thus protect from autoimmunity in aging.

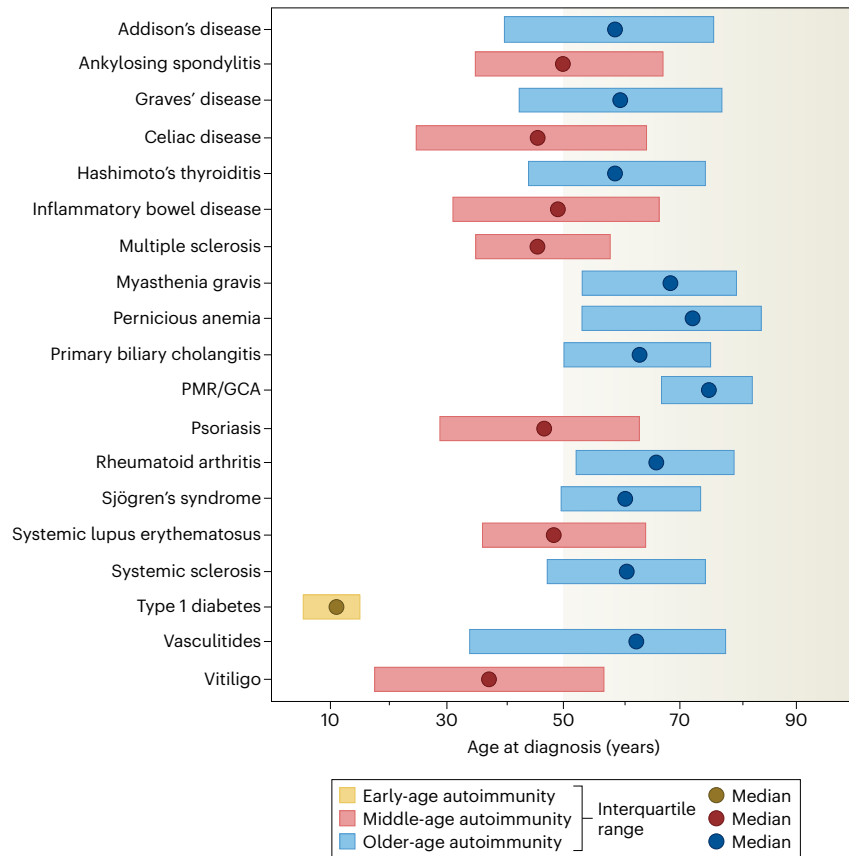
Older adults are less competent in defending themselves against cancer and infections and often fail to develop protective immunity in response to vaccines<sup>1–3</sup>. The underlying process, the progressive decline in the innate and the adaptive arms of the immune system, is considered a major culprit in age-related communicable and noncommunicable diseases, including cardiovascular and neurodegenerative disorders<sup>4,5</sup>. Recent global estimates of disease burden and mortality have reiterated the need to reach a better understanding of how immune aging affects life quality and longevity, given that increasing life expectancy has created a world population that lives longer but in poorer health<sup>6</sup>. Immune aging is nonlinear, and multiomic studies have indicated inflection points in the mid 40s and at the age of 60 years<sup>7</sup>. Clinical evidence of immune aging arises after 50 years of age<sup>8</sup>; case fatality ratios follow a U-type shape for most infections, with a change in slope at that age<sup>9</sup>.

The human immune system consists of 1.8 trillion cells, equally distributed among lymphocytes (40%) and neutrophils (40%), and weighs 1.2 kg<sup>10</sup>. Thus, innate and adaptive immune cells make an equal contribution to the overall immune cell number but are sequestered in distinct tissue sites (neutrophils in the bone marrow and lymphocytes

in lymphoid organs)<sup>10</sup>. T cells are long-lived cells that age owing to the proliferative stress imposed by progressive differentiation and the need to serve as precursors for new T cells in the process of post-thymic homeostatic proliferation<sup>11,12</sup>. Neutrophils and monocytes are short-lived (hours to days)<sup>13</sup>; their aging process is mostly determined by the aging of hematopoietic stem cells (HSCs). HSC aging is best captured by clonal hematopoiesis, an aging-related phenomenon in which a mutated HSC gains a survival advantage and forms a genetically distinct subpopulation of blood cells<sup>14,15</sup>.

Successful host immune protection not only requires swift and comprehensive recognition of danger (malignant cells, microorganisms and so on), it also requires effective immunity with minimal ‘collateral damage’, achieved by the avoidance of anti-self-reactivity. Self-tolerance is imprinted into the immune system, and loss of self-tolerance leads to autoimmune disease, typically manifesting with persistent and destructive tissue inflammation. Recognition of autoantigen involves identical cells, molecules and pathways as defensive immunity against infected and malignant cells. One would therefore expect that the decline of immune competence in the aging

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**Fig. 1 | Age as a risk factor of autoimmunity.** The burden of autoimmune disease increases over the lifetime, with incidence rates across individual diseases variably peaking at older age. Although the most striking example is PMR/GCA, similar trends are observed for many autoimmune diseases, suggesting that aging-associated processes contribute to autoimmunity. Age- and sex-

standardized incidence rates of 19 diseases were previously described based on the records of about 22 million individuals between 2000 and 2019 in the UK Clinical Practice Research Datalink<sup>16</sup>. The illustration shows median age and interquartile range at the time of diagnosis as given in figure 2 of ref. 16.

host goes in lockstep with reduced incidence of autoimmune disease, consistent with the current perception that the typical patient with autoimmunity is a young individual.

### Autoimmune disease clusters in older adults

A recent population-wide study of 22 million people enrolled into the UK Biobank confirmed that 10% of the population is diagnosed with an autoimmune disorder over lifetime, highlighting that autoimmunity with pathogenic consequences is a frequent event<sup>16</sup>. Notably, the likelihood of receiving a diagnosis of malfunctioning self-tolerance is age dependent. In an analysis of the 19 most frequent autoimmune diseases, most patients became sick during the second half of their life (Fig. 1).

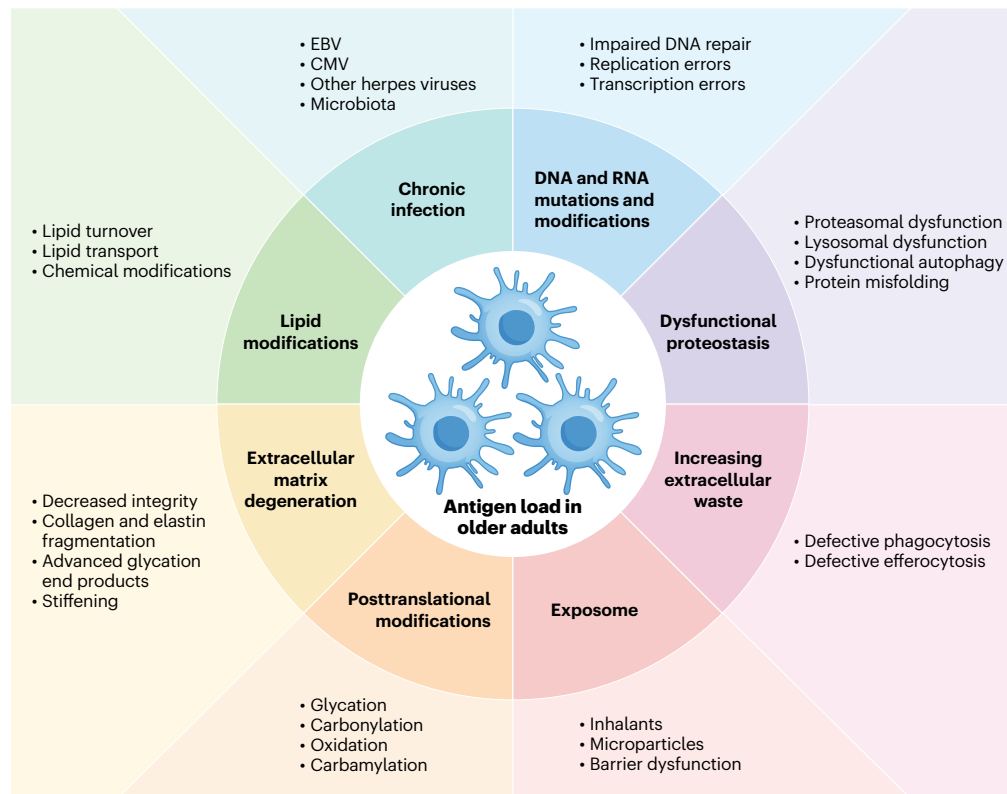
This study came as a surprise, challenging the wide-held opinion that autoimmune disease is a problem of young women. Instead, older adults are at the highest risk of developing clinically relevant autoimmunity. At the extreme, the diagnosis of polymyalgia rheumatica (PMR) or giant cell arteritis (GCA) (PMR/GCA) is exclusively made in individuals >50 years of age. These data support the concept that the aging immune system renders individuals susceptible to infection and cancer but also to autoimmune disease, suggesting that age-dependent mechanisms cause tumor immunity to fail and autoimmunity to accelerate. Autoimmune diseases such as GCA serve as an ideal model system to understand how immune aging predisposes not only to immunodeficiency but also to inappropriate autoantigen recognition. Understanding the effect of progressive age on the risk of succumbing to infection, the risk of failing in eliminating cancerous cells and the risk of generating autoreactive inflammation holds

promise in gaining deeper insight into the mechanisms of all three types of immunodeficiency. Data from the population-wide cohort of 22 million people strongly suggest a spectrum of mechanisms; indeed, each autoimmune syndrome displays a unique distribution of incidence rates over lifetime<sup>16</sup>, indicative of disease-specific abnormalities (Fig. 1).

### Neoantigen flooding in older adults

The current paradigm holds that self-tolerance is imprinted into the adaptive immune system through an educational program. During their development, T cells and B cells are trained to recognize and not respond to host antigens, with self-reactive lymphocytes being depleted or inactivated through 'negative selection'. Young T cells encounter autoantigen in the thymus, young B cells in the bone marrow. Central tolerance is fortified by a second layer of tolerance mechanisms occurring in peripheral tissues (peripheral tolerance), again relying on elimination or functional inactivation of self-reactive lymphocytes. However, self-antigen recognition does not always result in negative selection; it also provides survival and toning signals for mature lymphocytes and, as such, is a critical component in keeping the immune system functional<sup>17,18</sup>.

A major modulator of autoantigen recognition in the aging host is antigenic load and access to autoantigens. Figure 2 summarizes a series of processes that all challenge the aging host by expanding self-antigen exposure. Chronic infections confront the aging immune system not only through chronic antigen release, but also through damage to host tissues, thus enhancing the supply of self-antigen. Chronic herpes virus infections (Epstein-Barr virus (EBV), cytomegalovirus (CMV) and so on) are considered inducers of immune exhaustion due to relentless



**Fig. 2 | Increase of the immunogenic antigen load with age.** The scheme shows age-associated processes that increase the burden of potentially immunogenic antigens and neoantigens. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/2sk4i5e>.

stimulation of antigen-reactive T cells and have been cited as inducers of immune aging<sup>19,20</sup>.

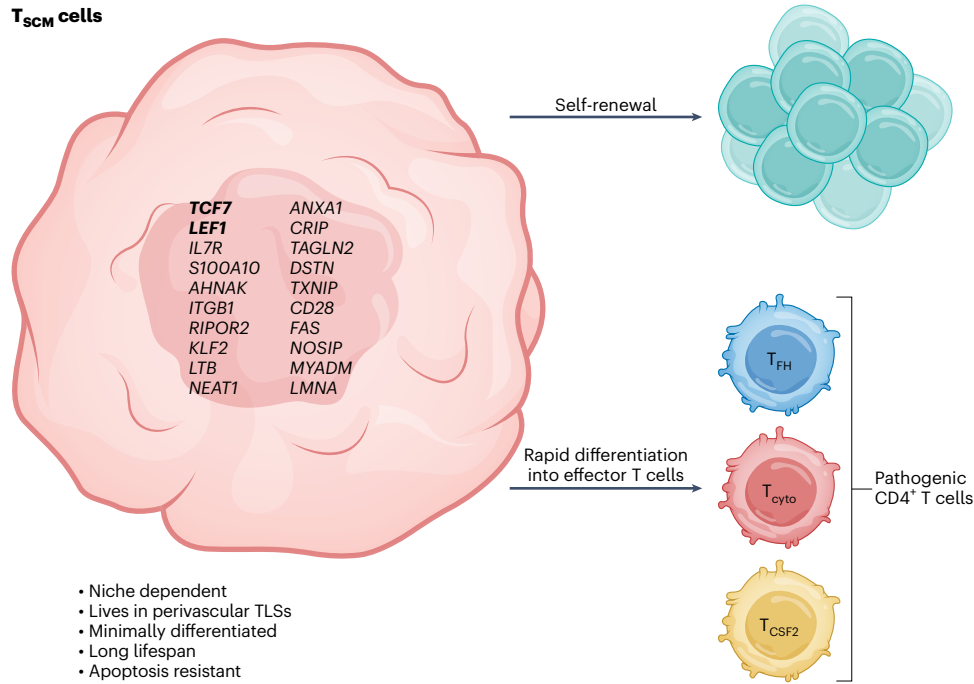
Age-related increases in DNA and RNA mutations sustain the formation of neoantigens to which the aging host has not been tolerized. This is an important defense mechanism against tumors<sup>21</sup> but may support autoimmunity in non-tumorous tissues. Immune-mediated side effects of checkpoint inhibitor therapy in patients with cancer have been attributed to the unleashing of T cell responses against self-antigens<sup>22,23</sup>.

Increasing evidence for environmental exposure has emphasized the accumulation of microparticles, nanoparticles, inhalants, and so on with progressive age<sup>24</sup>. The term ‘gero-exposome’ has been coined to describe the age-related increase in inhaled and ingested particles that are stored in the tissue and elicit strong inflammatory responses<sup>25,26</sup>. Release of autoantigens by ‘littering’ T cells has been identified as a signature defect of older T cells<sup>27,28</sup>. Here, aging-induced decay of intracellular pathways engaged in the generation, storage, processing and destruction of proteins is the major culprit in disrupting proper waste management. In the case of older T cells, the release of waste-filled exosomes creates pro-inflammatory effector T cells<sup>27</sup>. Age-induced failure of proteostasis is recognized as a hallmark of the aging process and holds relevance in phagocytic cells engaged in the clearing of debris from aging tissue<sup>29–31</sup>. A relevant example is the insufficiency of efferocytosis, needed to eliminate dead and dying cells to remove inflammation-triggering materials from the tissue microenvironment. Lacking efferocytosis has been implicated in driving atherosclerosis, a hybrid process of tissue degeneration and inflammation<sup>32</sup>.

Posttranslational protein modifications drive a large expansion of the proteome, providing antigenic determinants not seen earlier in life. A typical example of age-dependent chemical modification of proteins and amino acids is carbamylation, induced when isocyanic

acid, a decomposition product of urea, reacts with lysine residues. Alternatively, myeloperoxidase catalyzes the oxidation of thiocyanate, a frequent event in leukocyte-rich inflamed tissue sites. In patients with the autoimmune disease rheumatoid arthritis, carbamylation, citrullination and acetylation yield neoantigens, which induce disease-specific autoantibodies implicated in rheumatoid arthritis pathogenesis<sup>33</sup>. Tissue accumulation of carbamylated proteins is considered a distinguishing feature of aging<sup>34</sup>, where it may have a particular role through the continuous carbamylation of long-lived matrix proteins, including type I collagen and elastin<sup>34–36</sup>. Oxidation, glycation, carbonylation and hydroxylation all contribute to modification of extracellular matrix, leading to reduced integrity, stiffening, collagen fragmentation and the accumulation of advanced glycation end products. Collagens and elastic fibers are prone to these age-related changes<sup>36,37</sup>, given their low turnover. In older adults, tissues with high content of elastin, collagen and other matrix proteins should be particularly susceptible to targeting by inflammatory processes. This is certainly true for the vascular system, which is exposed to high mechanical stress over the lifetime (Fig. 2).

In summary, there is a flood of neoantigens in older adults to which they have not been tolerized earlier in life. Inevitably, this should lead to increasing rates of autoimmune diseases with age, as reported by Conrad et al.<sup>16</sup>. The question is on which adaptations can the aging immune system rely to deal with the abundance of neoantigens. Amplifying numbers and efficiencies of immunosuppressive regulatory T cells ( $T_{reg}$ ) would be a host-protective strategy. Little is known about the aging of  $T_{reg}$  populations, but most data suggest that there is a substantial increase in the frequency of  $T_{reg}$  cells in aged animals and that they are detrimental by suppressing anti-pathogen immune responses<sup>38–40</sup>. It is questionable whether the aging host does have the capability to generate new antigen-specific  $T_{reg}$  populations as neoantigens accumulate in aging tissues. Indeed, in patients with GCA,



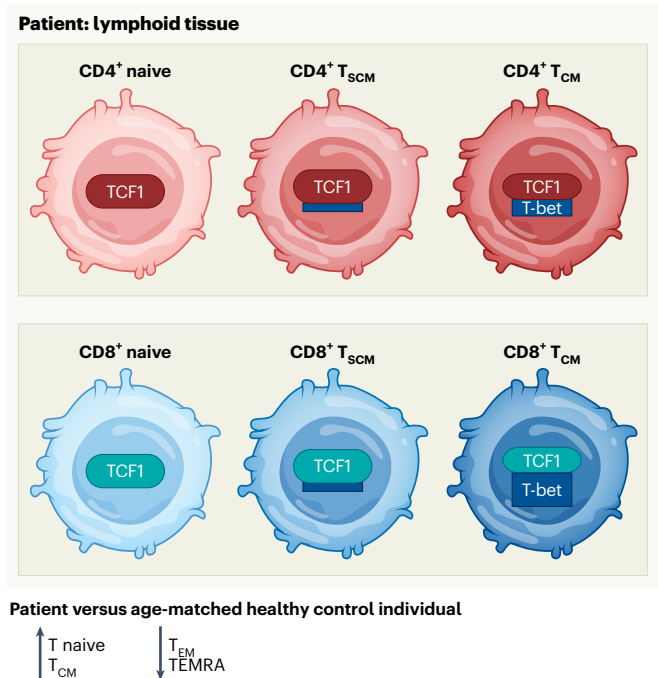
**Fig. 3 | T<sub>SCM</sub> cells in autoimmune vasculitis.** T<sub>SCM</sub> cells regulated by TCF1 maintain immune memory. They are long-lived and have self-renewal capacity. Generally, TCF1 expression declines with age, contributing to the decline in adaptive immunity. In patients with GCA, CD4<sup>+</sup> T<sub>SCM</sub> cells are sustained despite the host's older age and account for the chronicity of disease by feeding

effector T cells to the inflamed tissue. T<sub>cyto</sub>, cytotoxic T cell; T<sub>CSF2</sub>, T cell producing colony stimulating factor 2. Classical marker genes are in bold. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/fuv0pyg>.

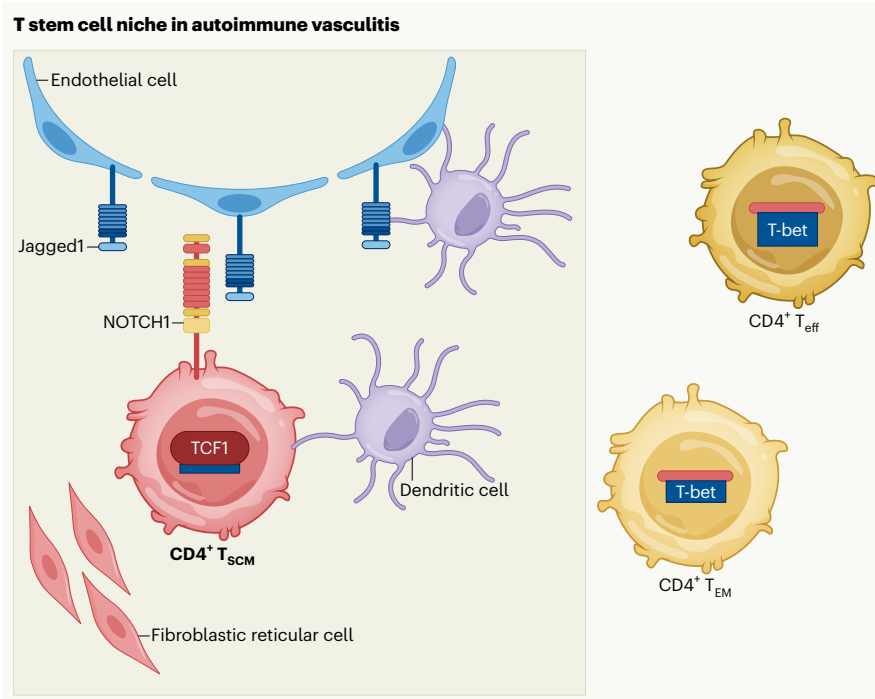
T<sub>reg</sub> cells fail due to rerouting of endosomal trafficking<sup>41</sup>. Here, the adaptive immune system would serve older adults best by attenuating the system's efficiency, for example, reducing diversity, memory formation, longevity and functional activity of individual effector T cells. All these are hallmarks of the aging immune system, supporting the hypothesis that immune aging is a host-beneficial process, shielding individuals from tissue-destructive autoreactivity during the second half of life.

### PMR/GCA as a model system for autoimmune disease in the older adult

The cardiovascular system stands out as enduring lifelong mechanical stress, leading to cellular and molecular aging<sup>42</sup>. Vascular aging is associated with remodeling of the arterial wall, increased stiffness, loss of elasticity and overall wall thickening<sup>43,44</sup>. Age-dependent deterioration of matrix composition leads to reduction in proteoglycans, production of thickened and more linear collagen fibers and loss of elastogenic potential. Remodeling of vascular extracellular matrix with age causes elastic fiber fragmentation and release of elastin degradation products, known as elastin-derived peptides, which have strong pro-inflammatory functions<sup>45</sup>. Low turnover and high susceptibility to posttranslational modifications convert matrix proteins into immunogenic reservoirs. Nevertheless, frank autoimmune disease in the arterial tree is infrequent, pointing toward effective barrier mechanisms between the vessel wall and the immune system. Clinically relevant autoimmunity in the wall of the medium and large elastic arteries manifests as GCA, a granulomatous vasculitis affecting the aorta and its major branch vessels<sup>46-48</sup>. PMR is a predisease of GCA. PMR and GCA persist over years and decades, exclusively occurring in individuals over 50 years of age and causing autoimmune aortitis<sup>49,50</sup>. Aortic dissection and aneurysm formation require resection of the damaged tissue. As most patients are untreated at the time of surgery, tissue samples collected during aortic repair surgery provide the opportunity to study



**Fig. 4 | Youthfulness of peripheral T cell subset distribution in autoimmune vasculitis.** Immune aging is associated with the loss of naive CD4<sup>+</sup> and CD8<sup>+</sup> T cells, in part due to a shift in the balance of the lineage-determining transcription factors. As TCF1-expressing T cells decline, effector T cells expressing T-bet accumulate. In patients with the autoimmune vasculitis GCA, this process is delayed, and age-associated changes in global T cell subset distributions are attenuated. T<sub>CM</sub>, central memory T cells; T<sub>EM</sub>, effector memory T cells; TEMRA, terminally differentiated effector memory T cells. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/6ij3356>.



**Fig. 5 | The survival niche for stem-like CD4<sup>+</sup> T cells in vasculitis.** In the inflamed vascular tissue of patients with GCA, TLSs are formed that serve as a tissue niche for T<sub>SCM</sub> cells. These T<sub>SCM</sub> cells receive signals from dendritic and endothelial cells

through NOTCH–Jagged interaction, maintain themselves by self-replication and seed the tissue with effector T cells. T<sub>eff</sub>, effector T cells. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/62xx81c>.

undisturbed autoimmune inflammation. GCA is distinguished from other autoimmune diseases by the following criteria: strict tissue tropism, strict age restriction and a long predisease period during which at-risk individuals display a metabolic phenotype of low body mass index, low glucose and low lipids<sup>51–54</sup>.

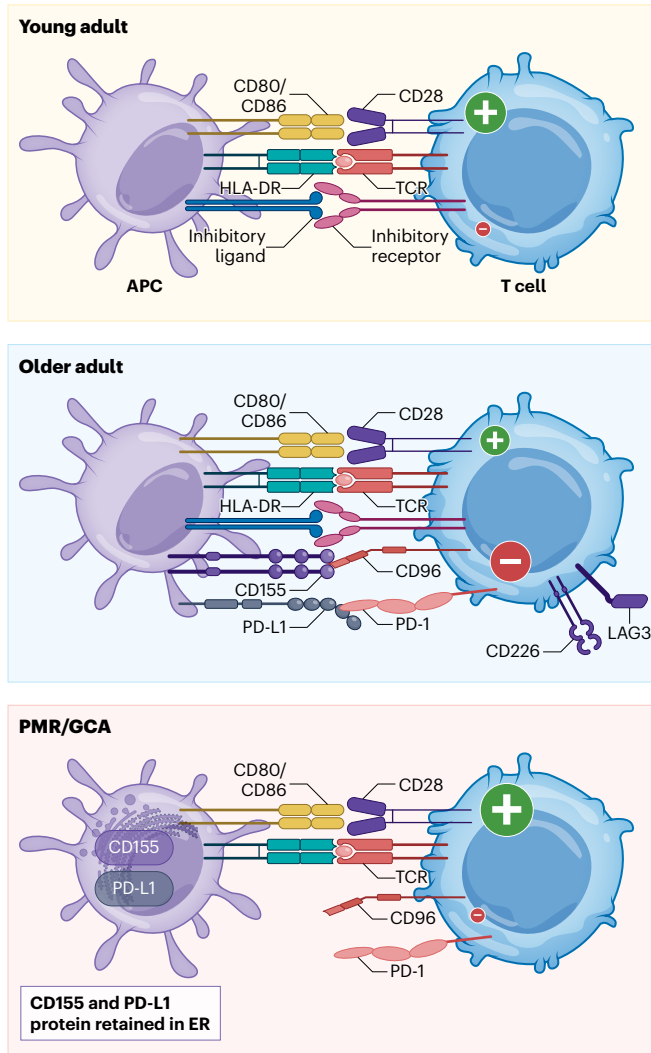
Recent studies in PMR/GCA-induced aortitis have shed light on the interplay between the aging vessel wall and the aging immune system. Topographic analysis of the inflamed arterial wall has identified two major ‘regions of interest’: T cell- and macrophage-rich granulomas, almost always localized in the vascular smooth muscle cell-rich medial layer; and T cell-rich perivascular structures mapping to the adventitial layer<sup>52,55</sup>. The granulomatous structures in the media are typically localized in nucleus-free patches, in close vicinity of the fragmented elastic laminae. Here, immune cells can encounter the highest density of modified matrix proteins. These areas of the vessel wall are nonvascularized and thus cannot provide access for circulating wall-infiltrating T cells and macrophages. This access must come through distantly located adventitial microvessels, allowing nutrients, oxygen and cells to reach the vessel wall. Aggregates of T cells and sometimes B cells grouped around adventitial microvessels<sup>55</sup> identify this tissue site as the entrance for infiltrating immune cells. Basement membranes around the adventitial microvessels build a natural shield against cellular infiltration. In patients with GCA, circulating monocytes are equipped to break this protective shield by degrading the basement membrane, opening access for myeloid cells and lymphocytes<sup>56</sup>.

Tissue-infiltrating CD4<sup>+</sup> T cells consist of five subpopulations, which have been distinguished by single-cell RNA sequencing<sup>55</sup>. Unexpectedly, almost a quarter of tissue CD4<sup>+</sup> T cells are cycling, consistent with in situ T cell replenishment. Three subpopulations of differentiated effector T cells participate in lesions: T-bet-expressing type 1 helper T (T<sub>H1</sub>) cells, B cell lymphoma 6 (BCL6)-expressing follicular helper T (T<sub>FH</sub>) cells and eomesodermin (EOMES)-expressing cytotoxic T cells. The largest CD4<sup>+</sup> T cell subset has the following features: a discernible gene expression signature (*TCF7*, *LEF1*, *IL7R*, *KLF2*, *CD28* and *FAS*), localization distant from effector cell populations, homing

to the adventitia and high proliferative activity. Together, these properties identify these tissue-residing CD4<sup>+</sup> T cells as T<sub>SCM</sub> cells<sup>55</sup> (Fig. 3). T cell receptor sequencing studies have confirmed that TCF1<sup>hi</sup>CD4<sup>+</sup> T cells serve as precursors for differentiated effector cells, including T-bet-expressing T<sub>H1</sub>-like populations, EOMES<sup>+</sup> cytotoxic T cells and BCL6-expressing T<sub>FH</sub>-like cells. While TCF1<sup>hi</sup>CD4<sup>+</sup> T cells are restricted to the adventitia, differentiated effector T cells infiltrate into the vessel wall and move towards medial granulomas. In serial transplantation experiments, interleukin (IL)-7 receptor-expressing TCF1<sup>hi</sup>CD4<sup>+</sup> T cells can transfer the autoimmune disease, classifying these CD4<sup>+</sup> T cells as autoimmune T stem cells<sup>55</sup>.

### Sustained T cell stemness in autoimmune vasculitis

T cells with stem-like properties were originally described in the CD8<sup>+</sup> compartment<sup>57,58</sup>. T<sub>SCM</sub> cells possess the ability to self-renew and to rapidly generate differentiated effector T cells. As such, they have an important function in repopulating the adaptive immune system and maintaining long-term immune memory of previous antigen encounters. Expression of the transcription factor TCF1 is also characteristic of the precursor of exhausted cells in chronically infected mice and protects them from exhaustion<sup>59</sup>. Such stem-like exhausted precursor cells are part of the tumor-infiltrating T cell population where they contribute to the proliferative burst induced by programmed cell death protein 1 (PD-1)-targeted immunotherapy<sup>60</sup>. T<sub>SCM</sub> cells are susceptible to age-related decline, with loss of TCF1 considered crucial in immune aging and exhaustion<sup>61–63</sup>. Decreased population size, functional impairment and age-related shifts in epigenetic modifications have been identified as mechanisms of T<sub>SCM</sub> aging, directly affecting the immune competence of the aging host. Most patients with PMR/GCA are >65 years and should be subject to a decline in number and fitness of their T<sub>SCM</sub> pool. Recent data indicate that patients with GCA lose CD4<sup>+</sup> T<sub>SCM</sub> and CD8<sup>+</sup> T<sub>SCM</sub> cells at a slower rate, shifting the balance between ‘young’ and ‘mature’ T cells in favor of the less-differentiated naive and central memory populations (Fig. 4). Relevance of sustained



**Fig. 6 | Non-inhibitory APCs and non-exhaustible CD4<sup>+</sup> T cells in vasculitis.** In young adults, stimulatory ligands are dominant on APCs, leading to ‘go’ signals in T cells. In older adults, APCs accumulate multiple inhibitory ligands, mediating ‘stop’ signals and inducing T cell exhaustion. In patients with GCA, APCs lack pluri-inhibitory function due to the entrapment of PD-L1 and CD155 in the ER, avoiding negative signaling to T cells. HLA, human leukocyte antigen; LAG3, lymphocyte-activating protein 3; TCR, T cell receptor. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/4g2mh85>.

T cell youthfulness for autoimmune disease has come from data localizing CD4<sup>+</sup> T<sub>SCM</sub> cells in specialized lymphoid structures surrounding the disease lesions<sup>35</sup> (Fig. 5). CD4<sup>+</sup> T<sub>SCM</sub> cells are an absolute requirement for autoimmune vasculitis and transfer the disease in a humanized mouse model<sup>55</sup>. Whether the increased resilience of T<sub>SCM</sub> cells in GCA is selective for T cells recognizing vasculitic antigens or whether it reflects a globally higher immunocompetence is currently unclear. Patients with GCA are at increased risk of systemic infections, particularly early after diagnosis<sup>64,65</sup>, when on the highest doses of immunosuppressive treatment with glucocorticoids. In contrast to many other autoimmune diseases<sup>66,67</sup>, the risk for developing cancer is not increased in GCA<sup>68</sup>.

### Survival mechanisms for T<sub>SCM</sub> cells in GCA

Which mechanisms can counteract the aging-related deterioration of stem cell numbers and fitness and supply the host with excess T<sub>SCM</sub> cells? In aortic tissues collected from patients with GCA, CD4<sup>+</sup> T<sub>SCM</sub> cells occupy a distinct tissue niche, supporting the hypothesis that maintenance of stemness involves a specialized cellular, metabolic and matrix

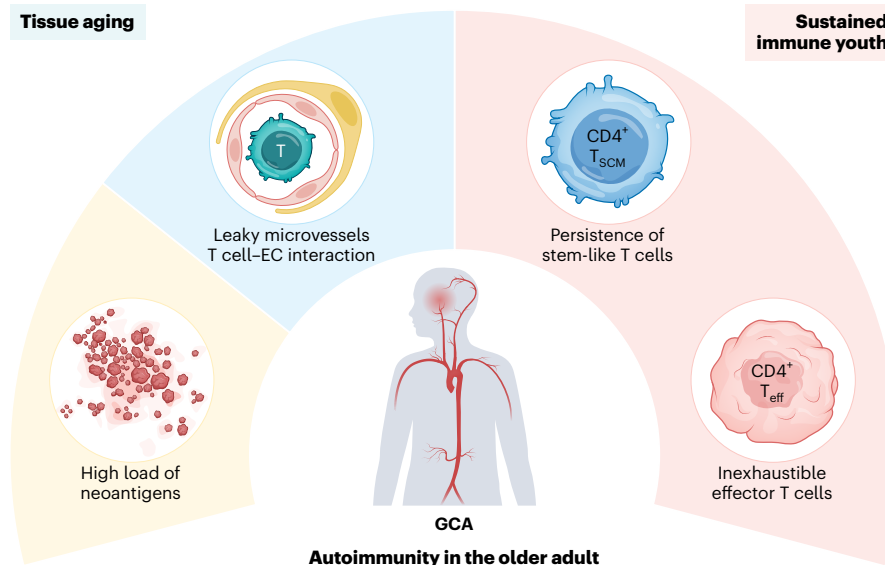
environment (Fig. 5). Development of this tissue niche appears to be an age-dependent phenomenon even in older adults who did not have GCA or PMR as shown in a recent autopsy study<sup>69</sup>. In GCA, autoimmune CD4<sup>+</sup> T<sub>SCM</sub> cells are embedded into intra-wall pockets of adventitial microvessels and make direct contact with endothelial cells and fibroblastic reticular cells. Most of the TCF1<sup>hi</sup> T<sub>SCM</sub> cells undergo proliferation in cellular aggregates composed of CD4<sup>+</sup> T cells and CD11c<sup>+</sup> dendritic cells. Only in some instances are B cells part of these aggregates, and such cellular clusters qualify as tertiary lymphoid structures (TLSs). Thus, CD4<sup>+</sup> T<sub>SCM</sub> cells appear not to require support from B cells but always colocalize with CD11c<sup>+</sup> dendritic cells, fibroblastic reticular cells and endothelial cells. The cellular composition and positioning of the T<sub>SCM</sub> niche in GCA is unique. In most settings, T<sub>SCM</sub> cells localize to regional lymph nodes<sup>70,71</sup>; in GCA, they reside at the periphery of the disease lesions, where direct access to neoantigens could contribute to their formation, preservation and, ultimately, the loss of self-tolerance. The importance of the immediate tissue environment for stem cell survival and fitness has been studied in hair follicle stem cells (HFSCs), which facilitate skin wound healing and hair growth<sup>72</sup>. Using single-cell RNA sequencing to define aging-related changes in HFSCs, the authors describe that aged HFSCs retain their fate and remain undifferentiated. However, they undergo age-related functional loss correlating with the induction of extracellular matrix genes. In transplantation assays, neonatal dermis rejuvenates aged HFSCs, whereas aged dermis fails to nurture young stem cells, emphasizing that sustained stem cell fitness imposes high requirements on the immediate tissue environment.

Signaling pathways relevant for T<sub>SCM</sub> survival have been identified in GCA. In aortic tissues resected from patients with GCA, endothelial cells lining the adventitial microvessels aberrantly express Jagged1, a ligand activating signaling of NOTCH family receptors<sup>73</sup>. Jagged1 induction on adventitial microvessels has been attributed to vascular endothelial growth factor (VEGF) signaling produced by endothelial cells, which is an abundant growth factor in patients with GCA<sup>74</sup>. Notably, circulating and tissue-infiltrating CD4<sup>+</sup> T cells in patients with GCA aberrantly express the NOTCH1 receptor<sup>75</sup>. T cell–endothelial cell interactions dependent on Jagged1–NOTCH1 binding regulate T cell fate decisions. NOTCH signaling determines T cell fate and lineage decisions early in T cell development, occurring in the thymic microenvironment and facilitating the preservation of T cell stemness<sup>76,77</sup>. In support of this, NOTCH1 agonism is an effective inducer of a stem cell memory phenotype in chimeric antigen receptor T cells, enhances antigen responsiveness and proliferative capacity in vivo<sup>78</sup> and functions as a T cell rejuvenator.

### Sustained T cell stemness with age in nonvasculitic conditions

The survival of T<sub>SCM</sub> cells in GCA despite older age is linked to the perivascular development of secondary lymphoid tissues that provide a protective tissue niche. Similar findings hold true for tumor-infiltrating T cells. TCF1 expression is important in maintaining the responsiveness of pre-exhausted T cells to checkpoint inhibitor treatment. These stem-like PD-1<sup>+</sup> T cells are typically found in TLSs surrounding tumors, while terminally differentiated exhausted cells are mostly in the tumor parenchyma<sup>59</sup>. TLS-free tumors are also very low in these stem-like T cells. Interestingly, the presence of TLSs is predictive for improved responses of solid tumors treated with immune checkpoint blockade<sup>79</sup>. Vice versa, treatment responsiveness can therefore be taken as a surrogate for the presence of T<sub>SCM</sub> cells. In clinical studies, response rates in younger and older patients are not significantly different<sup>80,81</sup>. Older adults have slightly higher immune-related adverse events, which may reflect a lowered threshold for stimulation<sup>82</sup>. Of particular interest, such adverse events include manifestations resembling GCA<sup>83</sup>.

TLSs are also found in other autoimmune diseases that are more frequent with age, including the synovial tissues of patients



**Fig. 7 | A disease model for autoimmunity in the older adult.** Immune competence declines progressively with age, but individuals >50 years become susceptible to developing the autoimmune vasculopathy GCA. Four processes contribute to the risk of age-related autoimmunity: (1) tissue aging produces a high load of neoantigens in the matrix-rich and mechanically challenged arterial wall, (2) tissue aging leads to leakiness of the blood–tissue barrier, with endothelial cells (ECs) expressing T cell-stimulatory ligands, (3) age-inappropriate conservation of immune youth provides the host with long-lived,

self-renewing stem-like CD4<sup>+</sup> T cells, enabling the continued replenishment of disease-inducing effector T cells and (4) age-inappropriate extension of immune youth prevents T cell exhaustion by removing inhibitory immune checkpoint signaling. The delay in T cell aging endows the patient with resource cells generating lasting memory responses against tissue-derived neoantigens. Original figure created in BioRender. Weyand, C. (2025) <https://BioRender.com/h97oj2t>.

with rheumatoid arthritis<sup>84</sup>. However, there are currently no data on similar stem-like T cell populations in other autoimmune conditions. By contrast, in rheumatoid arthritis, CD4<sup>+</sup> T cells have a signature of accelerated T cell aging, characterized by a high load of nuclear and mitochondrial DNA and metabolic abnormalities predisposing even naive CD4<sup>+</sup> T cells to premature death<sup>85–89</sup>.

In sum, sustained T cell stemness protects older adults against cancer yet renders them susceptible to autoimmunity, adding T<sub>SCM</sub> persistence to the list of disease risk factors. Emerging data suggest that age-inappropriate stemness of CD4<sup>+</sup> T cells may be the result of a survival advantage provided by a specialized tissue neighborhood, which secures T<sub>SCM</sub> longevity and functional fitness to the detriment of the host (Fig. 5). Targeting these survival pathways, such as interfering with the formation of tertiary lymphoid follicles, could be an approach to eliminate T<sub>SCM</sub> cells that sustain vasculitic inflammation in GCA and may therefore represent a curative intervention. In tumor immunology, numerous checkpoints exist, and it remains to be seen how selective their expression is and whether checkpoint inhibition to unleash tumor immunity can be accomplished without causing autoimmunity.

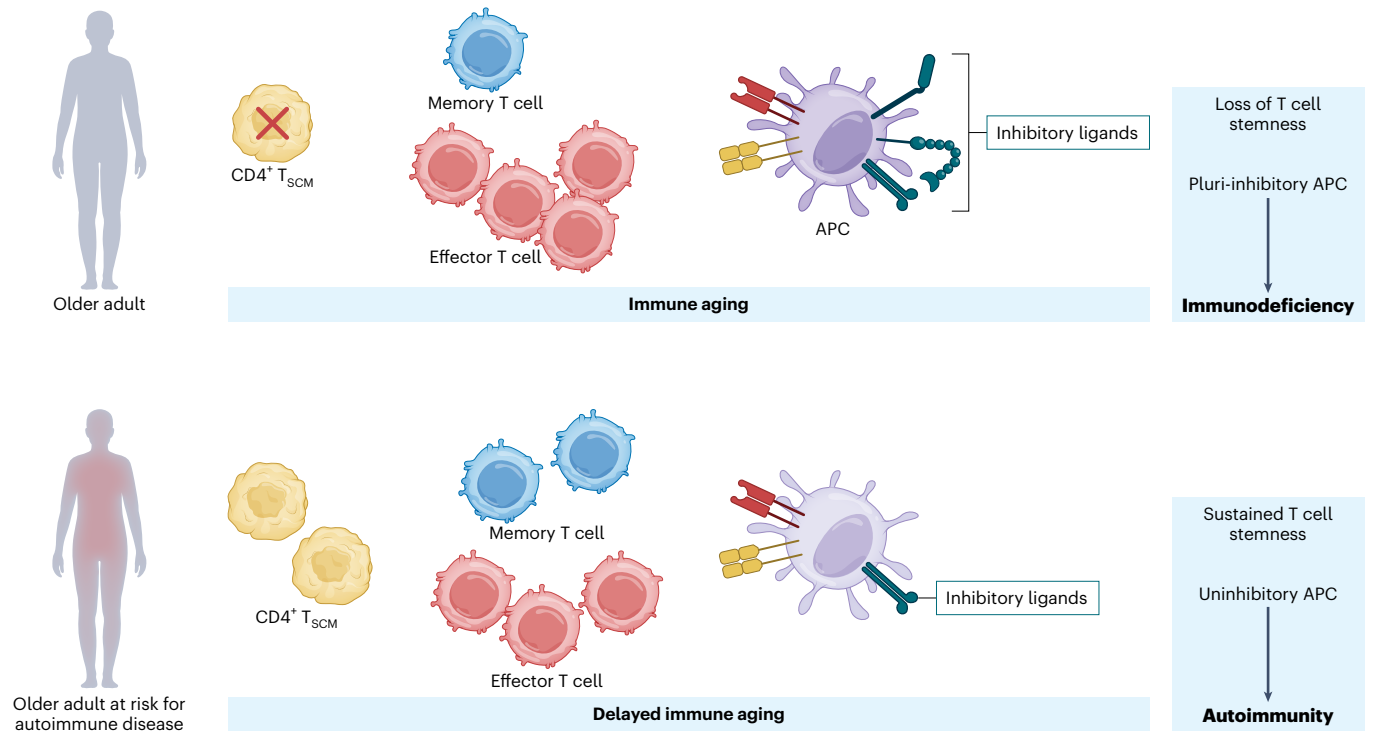
### Non-exhaustible CD4<sup>+</sup> effector T cells in autoimmune vasculitis

Tissue aging will inevitably lead to the accumulation of neoantigens against which the host has not been tolerized. Neoantigen formation is particularly high in the vessel wall, due to its richness in low-turnover matrix and high mechanical demand (Fig. 2). The current paradigm predicts that tolerance against neoantigens is maintained through peripheral tolerance mechanisms, one of which is the upregulation of inhibitory ligands on antigen-presenting cells (APCs), driving responding T cells into exhaustion<sup>90–92</sup>. T cell exhaustion is a state of decreased T cell function, characterized by low proliferative capacity and diminished effector capabilities<sup>93,94</sup>. T cell exhaustion-associated immunodeficiency is dependent on age, mostly due to chronic antigen exposure and rapid upregulation of inhibitory checkpoint receptors on aging T cells<sup>95–98</sup> (Fig. 6). T cell exhaustion due to chronic exposure

of cancer-derived neoantigens can be therapeutically targeted by blocking inhibitory immune checkpoints, most famously, the PD-1–programmed cell death ligand 1 (PD-L1) checkpoint<sup>99</sup>. Immune checkpoint therapy in patients with cancer is complicated by the induction of immune-mediated side effects, essentially iatrogenic autoimmune disease due to unleashing of autoreactive T cells, resulting in tissue damage<sup>100,101</sup>. This clinical observation confirms that T cell exhaustion serves the host in situations of persistent viral infection or cancer by preventing uncontrolled immune activation.

In GCA, the host-protective mechanism of T cell exhaustion is no longer intact (Fig. 6). Once differentiated into effector T cells, CD4<sup>+</sup> T cells from patients with GCA are uninhibited and unexhausted<sup>102–106</sup>. Three lineages of differentiated CD4<sup>+</sup> T cells have been identified in vasculitic lesions: interferon  $\gamma$ -producing T<sub>H</sub>1 cells, IL-21-producing T<sub>FH</sub> cells and EOMES<sup>+</sup> cytotoxic T cells<sup>55,107</sup>. All these differentiated CD4<sup>+</sup> T cells express high levels of inhibitory checkpoint receptors, including PD-1 and CD96 (refs. 102,106). However, they have not entered a state of exhaustion due to a lack of inhibitory ligands expressed on APCs.

The molecular defects in GCA macrophages enabling inexhaustible CD4<sup>+</sup> T cells to persist have been identified. In essence, fully differentiated and chronically stimulated CD4<sup>+</sup> T cells are partnered with APCs that fail to bring the inhibitory ligands PD-L1 and CD155 to the cell surface<sup>102</sup> (Fig. 6). Patient-derived macrophages have entered a state of chronic stress of the endoplasmic reticulum (ER), a molecular state previously identified in aged macrophages<sup>108,109</sup>. ER stress leads to trapping of CD155 in the cytosol and produces macrophages ‘naked’ of PD-L1 and CD155. This mechanism disrupts the functionality of at least two inhibitory checkpoints in GCA, the PD-1–PD-L1 and the CD96–CD155 pathways, and leaves the patient with highly functional effector T cells. Defective expression of checkpoint ligands on myeloid cells may be a sign of delayed or accelerated immune aging. Inflammatory pathways in myeloid cells of older adults are constitutively activated, and the associated induction of negative regulatory pathways has been implicated in dampening the responsiveness of older myeloid cells to stimuli<sup>110</sup>. In GCA, myeloid cells are hyperactivated, suggesting



**Fig. 8 | Delayed immune aging predisposes to autoimmune disease.** Immune aging is associated with the loss of T cell stemness and the emergence of pluri-inhibitory presenting cells (APCs). This leads to a state of immunodeficiency and protects the host from autoimmunity. Delayed immune aging promotes

persistence of CD4<sup>+</sup> T<sub>SCM</sub> cells, supplying memory and effector T cells, prolonging T cell immunity. APCs lacking inhibitory ligands jeopardize peripheral tolerance mechanisms. Together, sustained T cell stemness and stimulatory APCs create high risk for autoimmune disease.

that these pathways may be defective and that this hyperactivation results in disproportional ER stress. By contrast, CD155 expression in APCs is increased in patients with coronary artery disease, also an age-associated disease, suggesting that CD155 deficiency is not a hallmark of macrophage aging<sup>11</sup>.

In essence, continuous supply of effector T cells from locally residing T stem cells combines with the aging-related deficiency of APCs to sustain negative signaling, which essentially undermines T cell exhaustion as a host-protective process.

### A new disease paradigm for aging-related autoimmunity

Aging is, by far, the strongest risk factor for cancer and infectious disease, consistent with aging-induced immunodeficiency. Progressive age also is the strongest predictor for cardiovascular and neurodegenerative disease, consistent with failure of immune system-dependent tissue repair and maintenance. Counterintuitively, immune responses against autoantigens resulting in autoimmune disease occur most frequently in individuals older than 50 years of age. While specific mechanisms by which immune aging predisposes to autoimmunity may vary from disease to disease, mechanistic insights in one autoimmune condition, PMR/GCA, support a new paradigm that informs the broader field of immune aging-dependent disease.

The tolerance breakdown in PMR/GCA emanates from four age-dependent abnormalities (Fig. 7): (1) tissue-damaging monocytes grant access to neoantigens formed in the matrix-rich arterial wall, (2) microvascular endothelial cells transform into high endothelial venules and communicate with CD4<sup>+</sup> T cells via NOTCH1–Jagged1 interaction, (3) long-lived CD4<sup>+</sup> T<sub>SCM</sub> cells seek residence in perivascular lymphoid structures, from where they continuously replenish autoreactive effector T cells and (4) aged APCs fail to bring inhibitory checkpoint ligands to their surface, leaving autoimmune effector T cells unopposed.

The overall emerging theme is that the aging of T cells and APCs is a necessary element to protect the aging host from autoimmunity (Fig. 8). Primary tolerance mechanisms imposed by thymic selection are obviously insufficient to provide a lifelong safeguard against autoimmunity. The flood of neoantigens produced by tissue aging overwhelms secondary tolerance mechanisms. Thus, the age-related decline in innate and adaptive immunity emerges as a host-protective process.

This model predicts that rejuvenation of the human immune system during the second half of life has the potential complication of giving rise to pathogenic autoimmunity. Calls for maintaining and improving immune competence in older adults, believed to lead to a more functional and healthier world population that is better equipped to fight pathogens and cancers, may need to consider that there is a price to pay for immune youthfulness. The question arises of whether restoring a functional immune system in older adults would have the inevitable side effect of increasing the number of autoimmune diseases, subtracting from the benefits of immune system rejuvenation.

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## Author contributions

C.M.W. and J.J.G. conceptualized the manuscript. C.M.W. wrote the manuscript, and C.M.W. and J.J.G. edited the manuscript.

## Competing interests

C.M.W. has received consulting fees from AbbVie, Bristol Myers Squibb, Novartis, Ono Pharmaceutical, Boehringer Ingelheim and Sparrow Pharmaceuticals. J.J.G. has received consulting fees and stock options from Retro Biosciences.

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