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Review

Immunosenescence and human healthspan. Lessons from centenarians

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Immunosenescence is a multidimensional remodeling of immunity, characterized by inflammaging, cellular senescence, T-cell exhaustion, and thymic involution, that raises infection and disease risk with age. Emerging evidence, notably from centenarians, shows immune aging follows divergent trajectories: rather than a uniform decline, extreme longevity often reflects adaptive remodeling and a maintained immune equilibrium. Centenarian immune profiles are characterized by selective retention of naïve T cells, expansion of cytotoxic CD4+ and CD8+ subsets, tightly regulated inflammatory signaling, and systemic protective mechanisms such as enhanced oxidative-stress resistance, preserved epigenetic regulation, and extracellular vesicle-mediated T-cell modulation. Progress is constrained by cohort heterogeneity and limited longitudinal, harmonized multi-omic data; addressing these gaps could produce biological-age biomarkers and inform immunometabolic or senotherapeutic strategies to extend healthspan. In this narrative review, we describe that immunosenescence should be viewed as a trajectory-dependent process in which balanced immune function, not mere preservation of youthful markers, determines resilience and healthy aging.

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Introduction

Immunosenescence refers to the gradual decline in immune efficacy linked to aging, resulting in heightened susceptibility to infections and an elevated risk of age-related diseases, such as cancer, neurodegenerative and autoimmune disorders, and cardiovascular diseases [1,2]. This phenomenon plays a critical role in the aging process, significantly influencing the overall healthspan and lifespan. The implications of immunosenescence extend beyond mere susceptibility to disease; they encompass the complexities of inflammation, immune response, and the maintenance of health during the aging process, prompting extensive research into therapeutic interventions aimed at enhancing immune function in the elderly [3,4]. Immunosenescence features two main types: Replicative Senescence (RS), driven by telomere shortening, and Stress-Induced Premature Senescence, triggered by oxidative damage, DNA damage, and other stressors [5]. Given the multidimensional nature of immunosenescence, its evaluation requires integrated molecular, cellular, and functional approaches (Table 1).

Centenarians, individuals aged 100 years and older, offer valuable insights into the interplay between immunosenescence and longevity. As a rapidly growing demographic, centenarians exemplify resilience against age-related diseases and often maintain cognitive and physical independence [6,7]. The fact that centenarians demonstrate reduced disease rates throughout their lives contests the assumption that an extended lifespan necessarily results in increased disease prevalence [8]. Research highlights that many centenarians possess a unique immune profile that allows for effective responses to health challenges, including resilience against infectious diseases such as COVID-19 [5].

The study of immunosenescence in relation to centenarians has uncovered critical mechanisms underlying successful aging, including the management of chronic inflammation, known as inflammaging [9], and the maintenance of immune homeostasis [10]. Centenarians often exhibit lower levels of chronic inflammation, which may contribute to their longevity and quality of life [11]. The connection between immunosenescence, age-related disorders, and the extraordinary health of centenarians has generated interest in elucidating the underlying mechanisms and formulating treatment

Nomenclature

ABCs Age-associated B cells
AID Activation-induced cytidine deaminase
AMPK AMP-activated protein kinase
BCR B-cell receptor
CD Cluster of differentiation
CCR7 C-C chemokine receptor type 7
CFSE Carboxyfluorescein succinimidyl ester
CM Central memory (T cells)
CMV Cytomegalovirus
CRP C-reactive protein
CT Computed tomography
DAMPs Damage-associated molecular patterns
DNA Deoxyribonucleic acid
EM Effector memory (T cells)
EVs Extracellular vesicles
Flow-FISH Flow cytometry fluorescence in situ hybridization
G-CSF Granulocyte colony-stimulating factor
HIV Human immunodeficiency virus
IFN-γ Interferon gamma
IGF-1 Insulin-like growth factor 1
IGFBPs Insulin-like growth factor-binding proteins
IL Interleukin
IPD Individual participant data
JAK-STAT Janus kinase-signal transducer and activator of transcription
KLRG1 Killer cell lectin-like receptor subfamily G member 1
LAG-3 Lymphocyte-activation gene 3
miRNA microRNA
MRI Magnetic resonance imaging
mTOR Mechanistic target of rapamycin
NAD+/NADH Nicotinamide adenine dinucleotide (oxidized/reduced forms)
NFAT Nuclear factor of activated T cells
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NK Natural killer cells
NLR NOD-like receptor
NLRP3 NOD-like receptor family pyrin domain-containing 3
PBMC Peripheral blood mononuclear cells
PD-1 Programmed cell death protein 1
p16INK4a Cyclin-dependent kinase inhibitor 2A
p21CIP1 Cyclin-dependent kinase inhibitor 1A
p53 Tumor protein p53
qPCR Quantitative polymerase chain reaction
RANTES Regulated on Activation, Normal T Cell Expressed and Secreted
RNA-seq RNA sequencing
ROS Reactive oxygen species
RS Replicative senescence
SA-β-Gal Senescence-associated beta-galactosidase
SAHF Senescence-associated heterochromatin foci
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
SASP Senescence-associated secretory phenotype
SAT cells Senescence-associated T cells
SenePy Senescence profiling algorithm
SIPS Stress-induced premature senescence
T-bet T-box transcription factor TBX21
TCR T-cell receptor
TEMRA Terminally differentiated effector memory T cells re-expressing CD45RA
Tfh T follicular helper (cells)
TIGIT T-cell immunoreceptor with Ig and ITIM domains
TIM-3 T-cell immunoglobulin and mucin-domain containing-3
TLR Toll-like receptor
TLR4 Toll-like receptor 4
TLSs Tertiary lymphoid structures
TNF-α Tumor necrosis factor alpha
TOX Thymocyte selection-associated high mobility group box
γδ T cells gamma delta T cells

approaches to enhance immunological function in the elderly. This narrative review examines the mechanisms and implications of immunosenescence as derived from studies of centenarians, contrasting the pathways of progressive immune decline versus the adaptive longevity observed in extreme aging (Figure 1).

Mechanisms of immunosenescence

The aging immune system, via intrinsic molecular changes and altered intercellular interactions, actively drives systemic aging and organ decline [12]. Immunosenescence is best understood as the interaction of three interrelated but mechanistically distinct processes: 1) inflammaging, a chronic low-grade inflammation state driven partly by the senescence-associated secretory phenotype (SASP, see below) of senescent cells and mitochondrial dysfunction, 2) immune exhaustion, marked by inhibitory receptor upregulation and impaired effector responses, and 3) cellular senescence, defined by p16/p21-mediated cell-cycle arrest and sustained SASP activity (Table 2) [9,12,13].

These interconnected mechanisms arise from thymic involution, persistent antigenic exposure, and cell-intrinsic factors such as telomere shortening, collectively contributing to diminished immune plasticity and increased

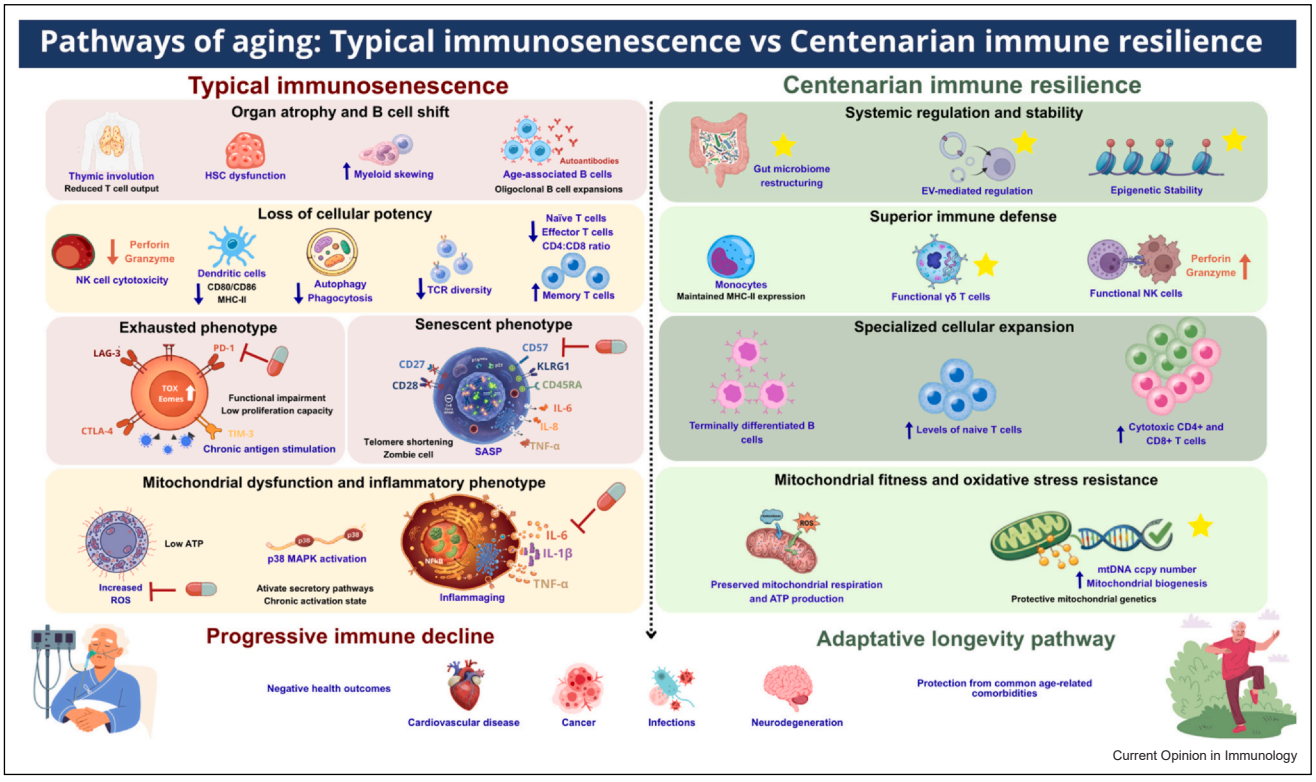
Table 1

Methodological approaches to evaluate cellular senescence and immunosenescence, and their relevance in centenarians.

Approach	Biological level	Key markers	Strengths/limitations	Findings in centenarians
Flow cytometry/ Immunophenotyping	Cellular	Inverted CD4/CD8 ratio; CD8+CD28–; CD57+; KLRG1+; PD-1+; naïve T cells (CD45RA+CCR7+); ABCs (CD19+CD11c+T-bet+)	High-resolution single-cell profiling/ mostly peripheral blood	Retention of naïve CD8+ T cells; expansion of cytotoxic CD8+ and γδ T cells; heterogeneous but distinct immune cluster profiles
Functional proliferation assays	Cellular	Reduced proliferation (CFSE dilution); IL-2 production; cytotoxicity assays	Functional readout/ influenced by ex vivo conditions	Preserved cytotoxic responses in selected subsets; maintained antiviral signatures in some cohorts
Senescence-associated β-galactosidase (SA-β-Gal)	Cellular	Lysosomal β-galactosidase activity (at pH 6.0)	Classical marker/not fully specific	Limited direct data in centenarians
Cell-cycle regulators	Molecular	p16INK4a, p21CIP1, p53 expression	Core senescence markers/ context-dependent	Increased expression expected with age; unclear whether centenarians show delayed accumulation or functional buffering
Telomere length analysis	Genomic	Telomere shortening (qPCR, Flow-FISH)	Direct link to RS/high variability	Telomere shortening present but not necessarily extreme; survival may reflect resilience despite attrition
Epigenetic profiling	Epigenomic	DNA methylation clocks; histone modifications	Reflects biological age/ tissue-specific variation	Some centenarians display younger epigenetic age signatures or adaptive methylation remodeling
Transcriptomics (bulk/single-cell)	Systems	SASP signatures; exhaustion markers; metabolic gene programs	High-dimensional/ requires bioinformatics	Distinct transcriptomic remodeling; enhanced antiviral and cytotoxic programs; adaptive immune signatures
Proteomics/cytokine profiling	Systemic	IL-6, TNF-α, IL-1β, CRP; SASP-related factors	Clinically translatable/ reflects systemic state	Elevated pro- and anti-inflammatory cytokines; evidence of regulated inflammaging rather than suppression
Metabolic assays	Cellular	ROS levels; mitochondrial respiration; NAD+/NADH; AMPK/mTOR activity	Links immunometabolism to aging	Greater resistance to oxidative stress; enhanced glutathione responses; improved redox control
Imaging (MRI/CT)	Organ level	Thymic atrophy; fatty replacement	Non-invasive/indirect immune marker	Thymic involution is present, but peripheral compensation is observed
Microscopy	Cellular	Enlarged morphology; heterochromatin foci (SAHF); lipofuscin accumulation	Morphological validation/ low throughput	Limited data; cellular enlargement likely, but systemic resilience predominates
Extracellular vesicle profiling	Systemic	EV cargo (miRNAs, cytokines, proteins)	Emerging biomarker/mechanistic relevance evolving	EVs modulate T-cell activation differently compared to younger adults; potential role in immune regulation
Computational immune age algorithms	Systems	SenePy; immune age scores; machine-learning clustering	Integrative/dataset dependent	Distinct immune-age trajectories; centenarians cluster separately from typical elderly
Animal models (aging models)	Experimental	Immune subset shifts; lifespan models	Mechanistic insight; species limitations	Used to model immune remodeling, but the human centenarian phenotype remains unique

ABCs: age-associated B cells; AMPK: AMP-activated protein kinase; CCR7: C-C chemokine receptor type 7; CD: cluster of differentiation; CFSE: carboxyfluorescein succinimidyl ester; CIP1: cyclin-dependent kinase inhibitor 1; CRP: c-reactive protein; CT: computed tomography; DNA: deoxyribonucleic acid; EV: extracellular vesicle; Flow-FISH: flow cytometry fluorescence in situ hybridization; IL: interleukin; KLRG1: killer cell lectin-like receptor subfamily G member 1; miRNA: microRNA; MRI: magnetic resonance imaging; mTOR: mechanistic target of rapamycin; NAD+/NADH: nicotinamide adenine dinucleotide (oxidized/reduced forms); PD-1: programmed cell death protein 1; p16INK4a: cyclin-dependent kinase inhibitor 2A; p21CIP1: cyclin-dependent kinase inhibitor 1A; p53: tumor protein p53; qPCR: quantitative polymerase chain reaction; RNA-seq: RNA sequencing; ROS: reactive oxygen species; SA-β-Gal: senescence-associated beta-galactosidase; SAHF: senescence-associated heterochromatin foci; SASP: senescence-associated secretory phenotype; SenePy: senescence profiling algorithm; T-bet: T-box transcription factor TBX21; TNF-α: tumor necrosis factor alpha.

Figure 1



Divergent trajectories of immune aging. This schematic illustrates two contrasting trajectories of immune aging. The conventional pathway (left) is characterized by progressive immune decline driven by thymic involution, reduced naïve T-cell output, oligoclonal expansions of age-associated B cells, impaired NK-cell cytotoxicity, mitochondrial dysfunction with increased reactive oxygen species (ROS), and chronic antigenic stimulation. These processes promote T-cell exhaustion (PD-1+, CTLA-4+, LAG-3+, TIM-3+), cellular senescence (CD57+, KLRG1+, CD45RA re-expression), telomere shortening, and acquisition of a senescence-associated secretory phenotype (SASP), contributing to inflammaging and elevated levels of IL-6, IL-1β, and TNF-α. Pharmacological symbols (capsules) and inhibitory arrows represent therapeutic strategies aimed at attenuating immune dysfunction, chronic inflammation, or cellular senescence associated with immunosenescence. This inflammatory and dysfunctional state underlies increased susceptibility to cardiovascular disease, cancer, infections, and neurodegeneration. In contrast, centenarians follow an adaptive longevity pathway (right) characterized by preserved naïve T-cell pools, expansion of cytotoxic $CD4^+$ and $CD8^+$ T cells, and maintenance of functionally competent NK cells and γδ T lymphocytes. Additional features include oxidative stress resistance, gut microbiome restructuring, epigenetic stability, and extracellular-vesicle–mediated regulation. Stars indicate emerging biological mechanisms and potential therapeutic targets associated with exceptional longevity. Together, these coordinated mechanisms promote balanced inflammatory signaling, metabolic resilience, and preserved immune surveillance, enabling functional independence despite extreme chronological age. Abbreviations: ATP, adenosine triphosphate; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; EV, extracellular vesicle; IFN-γ, interferon gamma; IL, interleukin; KLRG1, killer cell lectin-like receptor subfamily G member 1; LAG-3, lymphocyte activation gene 3; NK, natural killer; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TNF-α, tumor necrosis factor alpha; γδ T cells, gamma delta T lymphocytes.

susceptibility to chronic disease [9,12,13]. At the cellular level, aging is associated with reduced numbers and functional capacity of T cells, B cells, and natural killer (NK) cells, accompanied by cytokine shifts that favor pro-inflammatory signaling overprotective immune responses [13]. This remodeling compromises pathogen control, tissue repair, and vaccination efficacy, thereby increasing susceptibility to chronic disease during aging.

Cell-specific remodeling

At the cellular level, immunosenescence is expressed through subset-specific remodeling rather than uniform decline. Both T and B lymphocytes undergo quantitative and qualitative shifts that reflect the combined influence of thymic involution, chronic antigenic exposure, and cell-intrinsic aging mechanisms.

T cells and immunosenescence

T cells are particularly affected by immunosenescence. As individuals age, T cells undergo senescence characterized by the loss of costimulatory molecules such as CD27 and CD28, diminished production of growth factors like IL-2, and increased secretion of pro-inflammatory cytokines [12,14]. In parallel, chronic antigenic stimulation drives the accumulation of late-differentiated and exhausted T-cell subsets characterized by

Table 2

Main characteristics of immunosenescence phenotypes [9,12,13].

Characteristic	Inflammatory	Exhausted	Senescent
Core mechanism	Chronic low-grade inflammation driven by SASP, innate immune activation, and mitochondrial dysfunction	Sustained antigenic stimulation leading to inhibitory receptor upregulation and impaired effector responses	Irreversible proliferative arrest mediated by p16/p21-driven cell-cycle blockade and sustained SASP activity.
Primary drivers	DAMPs, cellular debris, and chronic NLRP3 activation	Chronic infections (e.g. CMV, HIV), persistent immune activation, and lifelong antigenic load	Telomere shortening, DNA damage, oxidative stress, and replicative history
Cellular and molecular markers	TLR4, NLRP3, cytokine receptors (e.g. IL-6R), NF-κB activation and C-reactive protein	PD-1+, TIM-3+, LAG-3+ and TIGIT+, TOX and NFAT dysregulation	CD28–, CD57+, KLRG1+, CD45RA+ (TEMRA), p16INK4a, p21CIP1 and SA-β-Gal activity
Secretory profile	Acute-phase reactants and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β)	Impaired/Low (Reduced IL-2, IFN-γ, and TNF-α)	SASP: Proteases, IGFBPs, and pro-inflammatory cytokines
Functional consequences	Tissue damage, metabolic dysregulation, and increased risk of age-related diseases.	Diminished cytotoxicity, reduced pathogen clearance, impaired vaccine responses, and increased susceptibility to infection.	Halted proliferation, altered chromatin; SASP secretion, loss of immune plasticity, reduced regenerative capacity, and accumulation of dysfunctional cells.

CMV: cytomegalovirus; DAMPs: damage-associated molecular patterns; HIV: human immunodeficiency virus; IFN-γ: interferon-gamma; IGFBPs: insulin-like growth factor-binding proteins; IL: interleukin; LAG-3: lymphocyte-activation gene 3; NFAT: nuclear factor of activated T cells; NF-κB: nuclear factor kappa-light-chain enhancer of activated B cells; NLRP3: NOD-like receptor family pyrin domain–containing 3; PD-1: programmed cell death protein-1; p16INK4a: cyclin-dependent kinase inhibitor 2A; p21CIP1: cyclin-dependent kinase inhibitor 1A; SA-β-Gal: senescence-associated β-galactosidase; SASP: senescence-associated secretory phenotype; TLR4: toll-like receptor 4; TIM-3: T-cell immunoglobulin and mucin-domain containing-3; TIGIT: T-cell immunoreceptor with Ig and ITIM domains; TNF-α: tumor necrosis factor-alpha; TOX: thymocyte selection-associated high mobility group box; TEMRA: terminally differentiated effector memory T cells re-expressing CD45RA.

inhibitory receptor expression (e.g. PD-1, TIM-3) and reduced effector function. Thymic involution further restricts the output of naïve T cells, leading to a pronounced narrowing of the T-cell receptor (TCR) repertoire and expansion of oligoclonal memory and TEMRA populations [15]. Aging also reshapes γδ T cells, promoting oligoclonal expansions and TEMRA-like phenotypes that diminish epithelial surveillance and tissue repair [16]. Such changes significantly compromise the body's ability to mount effective immune responses to pathogens and can exacerbate the severity of infections, including viral infections such as SARS-CoV-2 [13].

Importantly, impaired immune competence in aging does not appear to result solely from catastrophic loss of TCR diversity. Modeling and sequencing studies suggest that profound holes in the repertoire are uncommon unless population sizes are drastically reduced. Rather, defects in lymphoid microenvironments (such as age-associated fibrosis of lymph nodes) and diminished IL-7 receptor (IL-7R) signaling compromise homeostatic maintenance and clonal balance, particularly in CD8+ T cells. Epigenetic alterations at the *IL7R* locus and altered transcriptional regulation further impair survival and self-renewal capacity in aged T cells [17]. These alterations reflect not only cellular exhaustion but also integration of the broader triad of immune aging: persistent antigenic stimulation drives exhaustion, telomere attrition contributes to replicative limitation, and SASP-related inflammatory signaling reinforces inflammaging within the T-cell compartment.

B cells and immunosenescence

B cell-specific immunosenescence is characterized not only by quantitative decline but by profound phenotypic and functional remodeling. Aging is associated with reduced overall B-cell numbers, a contraction of switched memory B cells, and the expansion of pro-inflammatory age-associated double-negative (IgD– CD27–) B cells capable of producing inflammatory cytokines and autoreactive antibodies [14]. Additional age-related alterations include impaired B-cell receptor signaling, reduced somatic hypermutation, and diminished class-switch recombination, reflecting defective germinal center reactions and reduced T follicular helper cell support [18]. These subsets exhibit metabolic reprogramming, increased T-bet expression, and features of intrinsic activation, linking inflammaging to intrinsic B cell dysfunction. Alterations in B-cell signaling, reduced expression of activation-induced cytidine deaminase (AID), impaired class-switch recombination, and increasing oligoclonality collectively contribute to diminished humoral responses and reduced vaccine efficacy [14].

The decline in B-cell counts (CD3– CD19+) is not primarily driven by age itself but largely associated with chronic cytomegalovirus (CMV) infection and inflammaging (IL-6). Thus, CMV and inflammaging should be considered when interpreting immune aging trajectories in extreme longevity [19].

Emerging evidence suggests that B cells may play an active role in shaping T-cell immunosenescence. In

murine models, aged mice lacking B cells or with B cell-specific insulin receptor deletion preserve larger naïve CD4+ T-cell pools, display fewer PD-1+ and effector-memory T cells, and exhibit reduced TCR clonal restriction and inflammatory scores [20]. These findings indicate that B cells may contribute to the propagation of adaptive immune aging and represent potential modulators of age-related immune decline [20].

Antibody responses decline with age, leading to increased frequency and severity of infectious diseases and reduced protective effects of vaccination [14]. In addition, a significant prevalence of autoantibodies in centenarians has been reported, maybe linked to immunosenescence [21]; nonetheless, centenarians typically do not exhibit autoimmune diseases, or if they do, such occurrences are markedly few [7].

Inflammation and the senescence-associated secretory phenotype

A critical aspect of immunosenescence is the phenomenon known as the SASP [22], in which senescent immune cells, including T and B cells, acquire a pro-inflammatory secretory profile characterized by the release of cytokines, chemokines, growth factors, and matrix-remodeling enzymes that contribute to systemic inflammation [22]. This chronic, low-grade inflammation is a hallmark of aging and is associated with the activation of innate immune receptors, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which can further exacerbate inflammatory responses and lead to tissue damage over time [23]. However, measuring SASP presents technical and biological challenges due to its complexity and heterogeneity [23].

Age-dependent formation of tertiary lymphoid structures (TLSs), enriched for senescence-associated T (SAT) cells and age-associated B cells (ABCs), creates local hubs of antigen presentation, cytokine production, and maintenance of stem-like pathogenic T cells that promote tissue damage and the development of chronic diseases [24]. The persistence of these ectopic immune niches sustains localized inflammatory circuits and may accelerate age-related tissue pathology. Modulating immune-aging processes and TLS development is therefore a promising strategy to recalibrate maladaptive tissue inflammation and improve outcomes in multiple age-related diseases.

Impact on age-related diseases

The clinical implications of immunosenescence extend across multiple organ systems and are increasingly recognized as central drivers of age-related pathology [25,26]. A defining feature is the coexistence of impaired immune surveillance and persistent low-grade inflammation, a combination that accelerates tissue degeneration and promotes chronic disease progression. In this context, inflammaging and the SASP contribute to endothelial dysfunction, metabolic imbalance, and structural tissue remodeling, processes that are strongly linked to cardiovascular disease, metabolic disorders, and frailty syndromes [25,26].

The nervous system provides another clear illustration of how immune aging translates into clinical disease [27]. Age-related alterations in peripheral and central immune cells, including microglial activation and chronic neuroinflammation, have been implicated in the pathogenesis and progression of neurodegenerative disorders such as Alzheimer's and Parkinson's disease [27]. These processes appear to involve impaired clearance of pathological proteins, sustained inflammatory signaling, and progressive neuronal injury, suggesting that immunosenescence is not merely a consequence of aging but an active contributor to neurodegeneration [27].

Importantly, the biological impact of immunosenescence is not uniform across individuals. The absence of a universally accepted panel of biomarkers and the frequent reliance on peripheral blood measurements limit our ability to fully characterize tissue-specific immune aging [25–27]. This heterogeneity is particularly evident in populations that reach extreme longevity, where immune remodeling does not necessarily translate into the expected burden of chronic disease, highlighting the need to interpret immunosenescence within a broader phenotypic and life-course framework [25–27]. As a result, current assessments likely underestimate the complexity and compartmentalization of immune aging across different organs and disease states.

Characteristics and health of centenarians

Centenarians represent a rapidly expanding demographic group and an increasingly important population for understanding the biology of human aging and longevity. Rigorous age validation is essential in studies of extreme longevity to avoid biases related to age misreporting, and well-designed cohorts typically confirm chronological age through official registries and historical records [28]. Importantly, biological age appears to be a more meaningful predictor of functional health than chronological age in this population. From a demographic perspective, the number of centenarians has increased markedly over recent decades, reflecting broader improvements in survival and reductions in mortality at advanced ages [29].

Despite their exceptional longevity, centenarians are far from homogeneous. Many present complex health profiles, including functional limitations, cognitive impairment, and vulnerability to acute stressors, underscoring the biological heterogeneity of extreme aging [30]. At the same time, a substantial proportion retain the capacity to perform basic activities of daily living and report

satisfactory well-being, illustrating the coexistence of vulnerability and resilience that characterizes this population [31,32]. This balance highlights the importance of interpreting centenarian health within a life-course and phenotypic framework rather than assuming a uniform model of healthy aging [30].

The longevity of centenarians, as with almost all human traits, is attributed to a combination of hereditary and environmental factors, in which genetic influence accounts for 55% [33]. The interplay of these factors significantly contributes to both lifespan and healthspan [33].

Beyond inherited variation, epigenetic regulation, lifestyle, and environmental context play crucial roles in shaping longevity trajectories. Gene expression and epigenetic studies suggest partial preservation of cellular regulatory networks in some centenarians, while environmental and behavioral factors (including diet, physical activity, social engagement, and healthcare access) consistently influence survival and functional outcomes [34–36]. These findings indicate that extreme longevity emerges from dynamic interactions between biological, behavioral, and social determinants.

Cognitive resilience and neuro-immune links in centenarians

Centenarians show wide variability in cognitive aging: while dementia increases with age, many maintain preserved cognition or stable performance over the years [37]. Determinants of cognitive health at extreme ages differ from midlife risk factors (frailty, nutrition, depression, sensory or physical decline matter more), and neuropathology (amyloid deposition and neurofibrillary tangles) often dissociates from clinical decline. Genetic and molecular evidence implicates immune, endolysosomal, and cellular-clearance pathways in protection. Overall, cognitive resilience in extreme longevity appears to be a systems-level brain-body phenomenon driven by systemic health, genetic protection, and regulatory (including neuro-immune) mechanisms rather than absence of neurodegenerative pathology [38–41]. Thus, neurocognitive preservation in centenarians provides indirect but compelling evidence that immune aging trajectories influence organ-specific outcomes. Rather than being confined to infection susceptibility, immune remodeling appears to shape long-term tissue resilience, including within the central nervous system.

The immune system in centenarians: distinctive features and functional adaptations

The immune system of centenarians does not simply reflect an advanced stage of decline but rather a complex remodeling process characterized by selective preservation, functional adaptation, and substantial inter-individual variability [7]. Studies across different populations indicate that immunosenescence in extreme longevity cannot be interpreted as a uniform deterioration; instead, it appears to involve compensatory mechanisms that maintain immune competence despite profound age-related changes Recent single-cell and multi-omics analyses further confirm that extreme longevity is associated with a unique immune resilience state, marked by preserved naïve T cells, expanded cytotoxic lymphocytes, and dampened pro-inflammatory transcriptional programs (Table 3) [42–52].

Centenarians show distinctive immune remodeling rather than simple preservation of youth: they retain substantial naïve (especially CD8+) T cells alongside expanded memory/terminally differentiated subsets, with heterogeneity influenced by factors like CMV and antigen exposure. Innate-like lymphocytes (e.g. γδ T cells) and cytotoxic CD8+ cells may compensate for adaptive declines. Single-cell immune atlases reveal that centenarians maintain robust γδ and NK-cell functionality, preserved innate sensing pathways, and selective reinforcement of antiviral and cytotoxic networks despite chronological aging [51]. Successful aging is linked to adapted innate signaling (preserved/increased certain TLRs, controlled inflammasome activity) and a balanced cytokine milieu (elevated pro- and anti-inflammatory mediators but regulated inflammaging) [42–49]. Centenarians also display greater resistance to oxidative stress (better glutathione responses, lower intracellular ROS levels), widespread molecular and epigenetic remodeling in T cells (DNA methylation, gene expression, microRNAs), and distinct transcriptomic/biological-age signatures. Extracellular vesicle-mediated intercellular signaling further contributes to age-dependent immune regulation [42–49].

Together, these findings suggest that the immune phenotype of centenarians is best described as a dynamic equilibrium characterized by chronic low-grade inflammation, preserved functional responses in selected cell subsets, adaptive remodeling of lymphocyte populations, and molecular mechanisms that maintain immune homeostasis despite advanced age (Table 3).

Despite the growing body of evidence, several important gaps remain. Most studies have been conducted in European and East Asian cohorts, often with small sample sizes, limiting generalizability and the ability to disentangle genetic from environmental influences. Heterogeneity in definitions of successful aging, variability in immunophenotyping protocols, and cross-sectional designs limit comparability across studies and preclude causal inference. Also, the functional implications of many observed immune alterations remain unclear. It is still uncertain which immunological features are protective, which are merely adaptive, and which are

Table 3

Summary of key studies describing immune characteristics in centenarians.

Study	Population	Immune component studied	Main findings	Interpretation
Cossarizza et al. [42]	Centenarians compared with younger elderly controls	CD45 isoforms, T-cell subsets	Persistence of naïve T cells and altered memory balance	Slower or remodeled immunosenescence trajectory
Ligotti et al. [43]	Semi- and supercentenarians compared with other age groups	T-cell subsets, CMV-related differentiation	High variability in naïve and terminally differentiated subsets	Immune remodeling influenced by antigenic history
Ligotti et al. [44]	Semi- and supercentenarians	γδ T-cell immunophenotype	γδ T-cell remodeling (Vδ1 TEMRA expansion) reflects adaptive immune aging associated with extreme longevity.	Innate-like immunity may contribute to longevity
Grechenko et al. [46]	Centenarians compared with elderly adults	Cytokine profiles	Elevation of both pro- and anti-inflammatory cytokines	Regulated inflammaging rather than uncontrolled inflammation
Khasanova et al. [45]	Centenarians compared with other age groups	Pattern-recognition receptors (TLR/NLRP3 pathways)	Preserved or modulated expression of an innate immune receptor	Balanced innate immune activation associated with successful aging
Sizzano et al. [47]	Semisupercentenarians and elderly controls	Oxidative stress responses in lymphocytes	Improved resistance to oxidative stress and enhanced antioxidant responses	Redox resilience may support immune function
Zhao et al. [48]	Centenarians compared with newborns and middle-aged individuals	Epigenome of CD4+ T cells	Large-scale DNA methylation and transcriptional remodeling	Active immune remodeling across the lifespan
Alberro et al. [50]	Centenarians compared with younger age groups	Extracellular vesicles and T-cell responses	EVs modulate T-cell activation and cytokine production	Intercellular immune regulation via EVs changes with age
Zhang et al. [49]	Lifespan cohorts, including supercentenarians	Immune cell transcriptomic atlas	Distinct immune cell compositions and gene expression signatures at extreme ages	Immune aging follows distinct biological trajectories
Añé-Kourí et al. [52]	Centenarians compared with elderly adults and disease cohorts	Multivariate immune profiling	Distinct immune cluster profiles associated with successful aging	Centenarians show unique immune signatures
Wang et al. [51]	Centenarians and supercentenarians (longevity group) compared with elderly controls	Single-cell transcriptomics of PBMC; T cells, NK cells, monocytes, B cells	Enrichment of CD8+ effector memory T cells and differentiated B cells; activation signatures in NK cells and enhanced antigen presentation in monocytes	Adaptive immune remodeling and enhanced antiviral functional signatures in longevity
Anaya et al. [11]	Colombian centenarians	Serum 20-cytokine panel and flow-cytometry immunophenotyping of T/B-cell subsets	Higher biological age was associated with higher RANTES and G-CSF, and a distinct CD8+ differentiation pattern (↑ CD8+ CD27−CD28+ CM/EM; ↑ KLRG1−CD57+ TEMRA; ↓ KLRG1+CD57+ TEMRA); average CD4/CD8 ratio 4.8	Uniform immunosenescence pattern in centenarians, supporting selective immune remodeling and controlled inflammaging linked to biological aging heterogeneity
Tedone et al. [53]	High-performing centenarians, low-performing centenarians, and elderly controls	T-cell proliferation, telomere length, and telomerase activity upon *in vitro* stimulation	High-performers exhibit significantly higher T-cell proliferation, longer telomeres, and superior telomerase induction post-stimulation compared to low-performers and younger elderly controls	Immune fitness in extreme longevity is not uniform; successful aging is linked to the maintenance of T-cell replicative capacity and telomere homeostasis under antigenic challenge

CD4: Cluster of Differentiation 4 (CD4+ T cells); CD8: Cluster of Differentiation 8 (CD8+ T cells); CM: Central Memory (T cells); CMV: Cytomegalovirus; EM: Effector Memory (T cells); EVs: Extracellular Vesicles; G-CSF: Granulocyte Colony-Stimulating Factor; KLRG1: Killer Cell Lectin-Like Receptor subfamily G member 1; NLRP3: NLR Family Pyrin Domain Containing 3 (inflammasome component); NK: Natural Killer cells; PBMCs: Peripheral Blood Mononuclear Cells; RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted; TEMRA: Terminally Differentiated Effector Memory T cells re-expressing CD45RA; TLR: Toll-Like Receptor(s); γδ (T cells): Gamma Delta T cells.

epiphenomena of survival bias. Furthermore, longitudinal studies linking immune trajectories to clinical outcomes in centenarians are still scarce.

These limitations highlight the need for integrative, multi-omics, and longitudinal research to better understand how immune remodeling contributes to exceptional longevity and to translate these insights into strategies to promote healthy aging in the broader population.

Translational opportunities: immune-targeted interventions

Research on centenarians suggests that the impact of immune aging on healthspan can be modulated by preserving immune balance, controlled inflammation, and functional reserve rather than completely avoiding immunosenescence. Translational priorities include developing immune-based biomarkers of biological age and targeting immunometabolic pathways (mitochondrial function, oxidative stress, chronic inflammation) to preserve immune competence. Centenarian studies prioritize interventions that maintain immune homeostasis, resilience to infection and metabolic stress, and recovery capacity. Future work should combine longitudinal immune profiling, multi-omics, and systems biology to identify actionable, personalized targets for extending healthspan [54,55].

Centenarians offer a natural model of delayed biological aging characterized by resilience, adaptation, and preserved physiological balance across systems. They often maintain physical performance, nutrition, and cognition (interconnected domains tied to functional independence). Biologically, centenarians show adaptive immune remodeling (balanced inflammation, oxidative stress resistance, distinct T-cell signatures) that supports physiological reserve. Cognitive resilience can mask structural brain pathology, implicating systemic and immune factors. Adequate long-term nutrition and metabolic balance also support reduced frailty. Studying centenarians can reveal biomarkers of resilience and mechanisms to target for extending healthspan.

Multiple interventions (diet, microbiome, immunotherapies, senotherapeutics, partial reprogramming) could ameliorate aspects of immune aging in models, making the immune system a central, actionable target to extend healthspan [12]. Current human senotherapeutic interventions are predominantly in Phase I/II clinical trials. A search of ClinicalTrials.gov using 'senolytic' as an intervention retrieves a limited number of registered studies (n = 21; March 10, 2026), none of which are explicitly designed to evaluate effects on biological aging. This landscape delineates several research gaps: empirically, there is a paucity of interventional evidence in humans; from a knowledge view, robust, peer-reviewed data remain largely unavailable; methodologically, existing protocols are not structured to interrogate validated biomarkers of biological age; and at the data level, the absence of harmonized, longitudinal datasets precludes meaningful inference. Under these conditions, any assertion of comparative or even standalone efficacy in humans remains premature. Future research should prioritize rigorously designed trials integrating multidomain aging metrics (such as epigenetic clocks, functional phenotypes, and resilience markers) to determine whether senotherapeutic interventions can meaningfully modify immunosenscence and the trajectory of human biological aging.

Conclusions

Studies of centenarians show immunosenescence is often remodeling, not just a decline, selective preservation of immune functions, balanced inflammation, and maintained systemic resilience. This indicates immune aging trajectories vary across individuals rather than being uniformly harmful. Centenarians therefore provide a valuable model for understanding the mechanisms that link immune function to healthy lifespan. Insights derived from this population may help refine biomarkers of biological aging, clarify the pathways that drive resilience or vulnerability, and guide the development of interventions aimed at preserving immune competence throughout life. As the global population continues to age, translating these lessons into strategies to extend healthspan will remain a central objective of aging research.

CRediT authorship contribution statement

Juan-Manuel Anaya: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Ivan David Lozada-Martinez:** Writing – original draft, Writing – review & editing. **Yeny Acosta-Ampudia:** Writing – original draft, Writing – review & editing. **Gabriel Tobón:** Writing – original draft, Writing – review & editing.

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Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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