

# The long-lived immune system of centenarians

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## Abstract

Centenarians – individuals aged 100 years or older – constitute a biologically distinct human population that achieves exceptional longevity while frequently retaining functional independence and avoiding major age-related diseases or postponing their onset. Despite their advanced age, many centenarians show relatively preserved immune function and resistance to conditions linked to immunosenescence and chronic low-grade inflammation (inflammageing). These features are especially pronounced in semi-supercentenarians (105–109 years) and supercentenarians ( $\geq 110$  years), whose immune profiles often resemble those of much younger individuals. In this Review, we explore how centenarians modulate key hallmarks of immune ageing across innate and adaptive immune compartments. We discuss evidence that they limit the pathological effects of inflammageing, potentially through reduced NLRP3 inflammasome activation, enhanced autophagy and a tempered senescence-associated secretory phenotype. Omics studies further reveal transcriptomic, epigenetic and microbial signatures consistent with preserved immune function, including youth-like gene expression patterns in circulating immune cells and beneficial shifts in gut microbiome composition. Together, these findings suggest that centenarians achieve longevity through coordinated adaptations that maintain immune homeostasis and disease resistance and may inform strategies to enhance healthspan in ageing societies.

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## Introduction

Centenarians (individuals more than 100 years old) represent one of the fastest-growing demographic groups worldwide. As of 2024, approximately 722,000 centenarians were living globally, a number projected to increase to nearly 4 million by 2054 (ref. 1). Asia currently has the largest absolute number of centenarians, the highest being Japan (~146,000 centenarians; 12 per 10,000 individuals) followed by the USA (>100,000), China (60,000), India (48,000) and Thailand (38,000)<sup>1</sup>. Projections indicate sharp increases in centenarian prevalence over the coming decades, especially in Thailand (49 per 10,000 individuals), Japan (40 per 10,000), USA (14 per 10,000) and China (6 per 10,000)<sup>1</sup>. In Europe, the total centenarian population is expected to increase from ~96,000 in 2019 to nearly half a million by the year 2050 (ref. 2). Despite this rapid growth, centenarians remain rare, comprising only ~0.009% of the global population<sup>1</sup>, and gains in lifespan may be slowing<sup>3</sup>. Notably, a pronounced sex disparity is a striking and consistent feature in exceptionally long-lived people. For instance, in the USA in 2020, 79% of centenarians were women<sup>4</sup> and the average probability of current birth cohorts in the eight countries with the longest-lived populations, Hong Kong and the USA surviving to age 100 is 5.1% for females and 1.8% for males<sup>3</sup>.

What distinguishes centenarians is not only exceptional lifespan but also an apparent ability to delay – or even escape – major age-related

diseases, such as cancer<sup>5</sup> (Box 1) and, to a lesser degree, cardiovascular disease (CVD)<sup>6</sup>. Both conditions are tightly linked to immune dysfunction and chronic inflammation<sup>7–9</sup>, a persistent activation state that can disrupt immune homeostasis and contribute to pathology<sup>10</sup>, as discussed below. In addition, centenarians may display resistance to autoimmune conditions<sup>11</sup> (Box 2) and infectious diseases, including coronavirus disease 2019 (COVID-19)<sup>12–14</sup> (Box 3), reflecting preserved, balanced immune responses over time. This distinctive disease resistance, particularly evident among semi-supercentenarians and supercentenarians, provides a model for testing whether (and how) immune homeostasis contributes not only to an extended lifespan but also to a prolonged healthspan.

In this Review, we first consider the limited studies addressing haematopoiesis and thymic function in centenarians. We then discuss immunosenescence and how its trajectories may diverge across innate and adaptive immune compartments in long-lived individuals. Next, we discuss the concept of inflammageing and how centenarians might mitigate its harmful consequences. We also highlight transcriptomic and epigenomic studies that shed light on the molecular underpinnings of their immune profiles. In addition, we review emerging evidence on the gut microbiome and intestinal barrier integrity as contributors to immune function preservation. Finally, we identify key knowledge gaps and discuss the potential clinical implications of understanding the immune system of centenarians.

## Box 1 | Centenarians are resilient to cancer

A review of studies conducted in the USA, Europe, Japan, New Zealand and Brazil indicated that both cancer incidence and mortality decline markedly at extreme old age, with a threefold reduction after age 90 and rates falling to 0–4% in individuals aged 100 and older<sup>5</sup>. Moreover, when malignancies do occur in centenarians, they tend to exhibit a more indolent course and are less likely to spread aggressively<sup>7</sup>. Analysis of global age-specific cancer mortality trends from 2000 to 2014 further supported this pattern, showing that for most cancer types — excluding prostate and breast cancers — and in both sexes, mortality rates increase with age but decelerate or plateau after approximately 85 years<sup>190</sup>.

Population-based studies reinforce these observations. In northern Spain, centenarians had fewer cancer diagnoses (17.1% than non-centenarians (40.5%)), largely avoided highly aggressive malignancies (pancreatic, liver and lung cancers) and rarely developed metastases<sup>191</sup>. Notably, these individuals had minimal exposure to cancer treatments (radiotherapy or chemotherapy) and showed extended survival following both first and last cancer diagnoses<sup>191</sup>. Similarly, Swedish centenarians exhibited lower age-specific incidence rates of various cancers (including colorectal, breast and prostate) from as early as age 60 compared with shorter-lived individuals<sup>6</sup>. In a large UK cohort of 35,867 individuals, centenarians were less likely to die from cancer (4.4% of deaths on average, 95% confidence interval 4.2–4.6%) than those aged 80–84 years (24.5%, 95% confidence interval 24.6–25.4%)<sup>192</sup>.

Analyses of patient records from the Surveillance, Epidemiology and End Results (SEER) cancer registries, combined with the 2000 US census, revealed that cancer incidence generally peaks between ages 75 and 90, followed by a sharp decline at more advanced ages<sup>193</sup>. Among centenarians, incidence often approaches zero, suggesting either decreased susceptibility or a much attenuated

disease phenotype<sup>193</sup>. These findings are consistent with an independent SEER-based analysis (1979–2003), which showed that nearly all cancers reach their highest incidence around age 80, with centenarians remaining largely asymptomatic or rarely diagnosed<sup>194</sup>. According to National Cancer Institute SEER data, when cancer does occur in centenarians, diagnosis is usually delayed, with a mean onset of 80.7 years, compared with 63.2 years in the general population<sup>195</sup>. Autopsy studies from Japan further corroborate these trends, revealing lower rates of metastatic disease and cancer-related death in centenarians (37.5% and 16.7%, respectively) compared with individuals aged 90–94 years (50.5% and 24.7%)<sup>196</sup>. At the extreme end of the lifespan, supercentenarians might represent the pinnacle of cancer resistance: a study of supercentenarians from Okinawa, Japan, found no clinical history of cancer<sup>197</sup>.

Notably, the phenomenon of reduced cancer mortality at extreme ages is not unique to humans. Studies of exceptionally long-lived pet dogs found that cancer mortality closely mirrors that seen in human centenarians<sup>198</sup>. For example, only 19% of extreme-aged Rottweilers living beyond 13 years (the 95th percentile for the breed) died of cancer, compared with 82% of dogs with a typical lifespan of 9–10 years<sup>198</sup>. Comparable cancer resistance has been documented in long-lived rodents, including the naked mole rat (*Heterocephalus glaber*) and the blind mole rat (*Spalax ehrenbergi*), in which no spontaneous malignancies have been reported across large colonies monitored over many years<sup>199</sup>. Similarly, cetaceans, particularly large whales such as the bowhead whale (*Balaena mysticetus*), exhibit strikingly low cancer incidence despite their long lifespan<sup>200</sup>. Genomic studies of these species have revealed unique adaptations in DNA repair, tumour suppressor pathways and immune function, which probably contribute to their low cancer incidence<sup>200</sup>.

## Box 2 | Centenarians show resistance against autoimmune diseases

Autoimmunity results from a breakdown in immune tolerance to self-antigens, leading to inappropriate immune responses against host tissues<sup>201</sup>. This loss of tolerance generally increases with age, as immunosenescence disrupts regulatory mechanisms and exacerbates age-associated systemic inflammation (inflammageing)<sup>84,202,203</sup>. Consequently, advancing age is associated with an increased risk of several autoimmune diseases, such as rheumatoid arthritis<sup>204</sup>, giant cell arteritis<sup>205</sup>, autoimmune thyroid disease<sup>206</sup> and autoimmune gastritis<sup>207</sup>, as well as with greater disease severity, as seen in multiple sclerosis<sup>208</sup>.

Centenarians, however, display a striking paradox. Although circulating autoantibodies are frequently detected (including anti- $\beta_2$ -glycoprotein I<sup>209</sup>, anticardiolipin<sup>210,211</sup>, antinuclear<sup>210–212</sup> and antineutrophil cytoplasmic antibodies<sup>211</sup>, as well as rheumatoid factor<sup>211,212</sup>), clinical autoimmune disease is rare in this population<sup>11</sup>. Rather than reflecting latent autoimmunity, which is characterized by the presence of pathogenic autoantibodies without overt disease<sup>213</sup>, centenarians primarily exhibit natural autoimmunity. This form of autoimmunity is characterized by a protective network of largely IgM autoantibodies that promote apoptotic cell clearance, microbiota homeostasis and neutralization of pathogenic autoantibodies<sup>11,214</sup>. Consistent with this concept, non-organ-specific autoantibodies, such as anticardiolipin and antinuclear antibodies and rheumatoid factor, are common in centenarians<sup>210–212</sup>, whereas organ-specific autoantibodies, such as antithyroglobulin and anti-TPO antibodies, are less prevalent than in younger controls<sup>215,216</sup>. Notably, a study in Italian centenarians reported a lower prevalence of antithyroglobulin and anti-TPO antibodies compared with older adults (70–85 years), with levels comparable to those of young controls (<50 years)<sup>215</sup>. In line with this, centenarians showed the lowest levels of CD5<sup>+</sup> B cells —

a subset that is responsible for producing low-affinity, polyreactive antibodies and that is predominant during fetal life — compared with both younger adults and older adults<sup>215</sup>. A similarly reduced prevalence of thyroid autoantibodies in centenarians was reported in another cohort<sup>216</sup>. Moreover, autoantibodies typically associated with systemic autoimmune disease, such as anti-extractable nuclear antigen and anti-double-stranded DNA antibodies, were not detected in healthy Italian centenarians, despite the frequent presence of non-organ-specific autoantibodies, supporting the concept of preserved immune tolerance rather than latent autoimmunity<sup>210</sup>.

B cells in centenarians also exhibit functional features that favour immune tolerance. Although autoreactive B cells and autoantibodies are present, they appear to serve predominantly non-pathogenic roles, such as facilitating debris clearance and tissue repair, rather than mediating immune damage<sup>11</sup>. This suggests that subclinical autoimmunity in centenarians represents an adaptive and protective mechanism rather than a precursor to disease<sup>11</sup>. Enhanced regulation of autoreactive immune responses, particularly through regulatory T cells, further contributes to this autoimmune resistance<sup>217</sup>. Supporting this, a study in community-dwelling Chinese centenarians found a significantly lower T helper 17 (T<sub>H</sub>17) cell:regulatory T cell ratio than that of both older adults and younger adults<sup>90</sup>.

Genetic and epigenetic factors may also underpin preserved self-tolerance in centenarians. Specific variants within the HLA system and other immune-regulatory genes have been linked to reduced autoimmune risk<sup>11</sup>. In addition, epigenetic modifications, particularly histone marks such as H3K4me3 (activation) and H3K27me3 (repression), fine-tune immune responses<sup>11</sup> and potentially limit autoreactivity while preserving host defence in centenarians<sup>11</sup>.

## The immune context of centenarians

### Haematopoietic and thymic function

Immune cells are generated in the bone marrow and thymus, both of which undergo profound changes with age, including in centenarians. Haematopoiesis and haematopoietic cytokine production have been evaluated in the peripheral blood from centenarians, as well as from healthy young and older adults<sup>15</sup>. A trend towards lower absolute numbers of CD34<sup>+</sup> progenitor cells was found in older adults and centenarians, a difference that reached significance when these groups were pooled and compared with young adults, with no additional decline from old age to centenarian status<sup>15</sup>. Nevertheless, progenitor cells from both older adults and centenarians retained the capacity to respond to haematopoietic cytokines and to form erythroid colonies, granulocytes, macrophages and, when stem cell factor was added, mixed colonies that were indistinguishable in number, size and morphology from those of young subjects<sup>15</sup>. Moreover, serum levels of stem cell factor increased linearly with age<sup>15</sup>.

Clonal haematopoiesis of indeterminate potential (CHIP) is a common, age-associated phenomenon in which haematopoietic stem cells acquire somatic mutations that confer a competitive advantage, leading to genetically distinct blood cell subpopulations. CHIP is associated with a more than tenfold increased risk of haematological malignancies and with elevated CVD risk<sup>16</sup>. This phenomenon has been specifically investigated in centenarians<sup>17</sup>. In that study, high depth whole-genome sequencing of 81 individuals aged 105+ or 110+ years (mean age 107) and

36 healthy, geographically matched controls (mean age 68) revealed that the exceptionally long-lived individuals had a distinctive genetic background associated with efficient DNA repair, evident in both germline variants and somatic mutation patterns<sup>17</sup>. Analysis of the seven genes most frequently affected by CHIP (*ASXL1*, *DNMT3A*, *JAK2*, *PPM1D*, *SF3B1*, *TET2* and *TP53*) showed that centenarians carried a significantly lower mutation burden (median of one mutation versus two in controls), with the largest differences observed in *ASXL1* and *DNMT3A*<sup>17</sup>. These findings suggest that a reduced CHIP-related mutation burden may contribute to healthy longevity, although confirmation in larger cohorts is needed.

The thymus undergoes marked involution with age, profoundly shaping the T cell compartment. Thymic function was assessed in 44 centenarians by quantifying T cell receptor rearrangement excision circles<sup>18</sup>. Most centenarians (84%) had undetectable levels of T cell receptor rearrangement excision circle-positive cells, accompanied by extremely low numbers of naive T cells. By contrast, central memory and effector memory T cells were markedly increased, while terminally differentiated cells were present at levels comparable to those in young and middle-aged donors<sup>18</sup>. Nonetheless, haematopoietic and thymic function at extreme ages remains insufficiently explored.

### Immunosenescence

Ageing is accompanied by profound and complex changes in the immune system<sup>19</sup>, collectively referred to as immunosenescence (Fig. 1).

## Box 3 | Centenarians and COVID-19

The survival of centenarians following SARS-CoV-2 infection — famously exemplified by the French nun Sister André, who recovered from coronavirus disease 2019 (COVID-19) and celebrated her 117th birthday on 11 February 2021 (ref. 218) — sparked interest in how extreme age influences resistance to infection. Epidemiological studies, however, have yielded mixed results. A study from Italy found that COVID-19-related mortality was higher in nonagenarians and centenarians, particularly among women, compared with individuals aged 50–80 years<sup>219</sup>. Similarly, a study of French nursing home residents reported substantially higher mortality (50%) among centenarians than among younger residents (21.3%), despite a lower hospitalization rate<sup>220</sup>.

By contrast, other population-based analyses suggest a more nuanced picture. Data from German long-term care facilities showed markedly lower COVID-19-related hospital admission rates among centenarians but higher in-hospital mortality once admitted, particularly among women<sup>221</sup>. A Spanish study spanning 2020–2022 found that although centenarians had a higher proportion of documented COVID-19 cases (29%) than non-centenarians (23%)<sup>12</sup>, they exhibited extended survival following SARS-CoV-2 infection, with no recorded intensive care unit admissions and survival curves resembling those of 50-year-old individuals rather than octogenarians or nonagenarians<sup>12</sup>. Similarly, a study in Colombia reported higher survival rates among centenarians than among individuals aged 80–99 years<sup>13</sup>. In Japan, the absolute number of

centenarians increased by 12.8% between 2020 and 2022, despite a temporary decline in overall life expectancy during the COVID-19 pandemic<sup>14</sup>.

Intriguingly, early-life exposure to the 1918 H1N1 influenza pandemic may have conferred long-term survival advantages. Among Belgian centenarians who turned 100 during the COVID-19 pandemic, those born before 1 August 1918 — the date of the first reported influenza-related deaths in Belgium — had a lower risk of excess mortality in 2020 than those born later<sup>222</sup>. In line with this observation, Sicilian centenarians born before 1919 showed no increase in mortality during the COVID-19 pandemic compared with prepandemic years<sup>223</sup>. Together, these findings are consistent with the hypothesis that early-life exposure may act as a selective pressure, favouring the survival of individuals with a more robust immune system<sup>224</sup>. Immunological studies lend further support to this idea. Sicilian centenarians, including semi- and supercentenarians, exhibited exceptionally high neutralizing antibody titres against the 1918 H1N1 pseudotype virus (approximately 50-fold higher than in 70-year-old controls), suggesting persistence of immunological memory for over a century<sup>224</sup>. Brazilian supercentenarians who survived COVID-19 before vaccination had high levels of IgG and neutralizing antibodies, alongside an enrichment of plasma proteins and metabolites related to innate immunity and host defence<sup>225</sup>. Finally, a case report demonstrated that centenarians can mount long-term memory B cell responses following SARS-CoV-2 infection<sup>226</sup>.

This process is characterized by changes in immune function that are associated with increased susceptibility to infection, reduced vaccine responses, higher incidence of autoimmunity and impaired cancer immunosurveillance<sup>20,21</sup>. On the cellular level, ageing is associated with a gradual expansion of circulating myeloid cell populations relative to lymphoid cell populations<sup>22</sup>. In part, this shift reflects both the declining thymic output of new T cells and age-related alterations in myelopoiesis and lymphopoiesis in the bone marrow<sup>23</sup>. For instance, in aged mice, haematopoietic stem cells exhibit clonal skewing towards the myeloid lineage<sup>24,25</sup>. Correspondingly, flow cytometric studies in humans have shown increased circulating monocytes with age<sup>19</sup>.

Although all immune cells can be affected by ageing, immune changes vary across populations<sup>26</sup> and between individuals<sup>27</sup>, underscoring the heterogeneity of immune ageing and suggesting that ageing per se is not directly causal. Sex is also an important modifier of age-related immune changes (Box 4). Single-cell RNA sequencing (scRNA-seq), mass cytometry and flow cytometry studies have identified several age-associated changes in circulating T cell populations. For CD4<sup>+</sup> helper T cells, ageing is associated with decreased frequencies of naive cells<sup>28–31</sup>, recent thymic emigrants<sup>32</sup> and interferon (IFN)-activated subsets<sup>33</sup>, alongside an expansion of effector T cells<sup>31</sup>. Among CD8<sup>+</sup> cytotoxic T cells, ageing is marked by declines in naive populations<sup>28–31</sup> and increases in effector memory cells<sup>29,31,33</sup>, granzyme K-expressing (predominantly CD28<sup>+</sup>CD57<sup>-</sup>) cells<sup>33</sup> and CD57<sup>+</sup> cells<sup>27</sup>.

In some older individuals, especially those with chronic cytomegalovirus infection, ageing is associated with a preferential expansion of highly differentiated, senescent-like regulatory CD8<sup>+</sup>CD28<sup>-</sup> T cells, whereas CD4<sup>+</sup> T cells undergo a relative decline<sup>34</sup>. This imbalance

contributes to an ‘immune risk profile’, characterized by a CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratio of less than 1, which predicts impaired immune function and increased mortality<sup>34,35</sup>. Another feature of ageing T cells is the expression of natural killer (NK) cell markers, such as CD56 (ref. 36) and CD57 (ref. 37). Although these markers are typically associated with NK cell cytotoxicity, their expression on CD8<sup>+</sup> T cells (such as in human immunodeficiency virus infection) reflects reduced proliferative capacity<sup>36,38</sup>. With ageing, CD8<sup>+</sup> T cells may retain some cytotoxic potential (for example, expression of perforin and granzymes)<sup>36–38</sup> but exhibit impaired proliferation and functional exhaustion<sup>37–40</sup>, thereby limiting their ability to respond to novel immune challenges<sup>35–37</sup>.

$\gamma\delta$  T cells, which comprise 1–10% of circulating mature T cells (the majority of which are  $\alpha\beta$  T cells)<sup>39</sup>, play important roles in antimicrobial defence, cancer immunosurveillance and regulation of inflammation<sup>40</sup>. Unlike  $\alpha\beta$  T cells,  $\gamma\delta$  T cells recognize antigens in an MHC-independent manner and can exert cytotoxic effects directly or via cytokine-mediated activation of other immune cells<sup>41</sup>. Human  $\gamma\delta$  T cells are broadly divided into V $\delta$ 1<sup>+</sup> cells, predominant in cord blood and mucosal tissues, and ‘mature’ V $\delta$ 2<sup>+</sup> cells, which represent the majority of circulating  $\gamma\delta$  T cells in adults<sup>41</sup>. With ageing, circulating  $\gamma\delta$  T cells decline<sup>42,43</sup>, largely due to reduced numbers of V $\delta$ 2<sup>+</sup> cells<sup>43</sup>. Nevertheless, despite this numerical decrease, V $\delta$ 2<sup>+</sup> T cell functionality appears relatively preserved in older individuals<sup>44–46</sup>.

On the B cell side, ageing is associated with reduced frequencies of B-1 cells (CD19<sup>+</sup>CD20<sup>+</sup>CD27<sup>-</sup>CD38<sup>low/mid</sup>CD43<sup>+</sup>)<sup>47</sup> and ZBTB32<sup>+</sup> subsets (CD27<sup>+</sup>CD38<sup>low/mid</sup>)<sup>33</sup> in blood, as shown by scRNA-seq and cytometric analysis. In addition, somatic mutations accumulate across lifespan, from fewer than 500 per cell in newborns to more than 3,000 per cell in

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centenarians<sup>48</sup>, which might contribute to reduced antibody diversity<sup>49</sup> and increased risk of B cell leukaemia<sup>50</sup>.

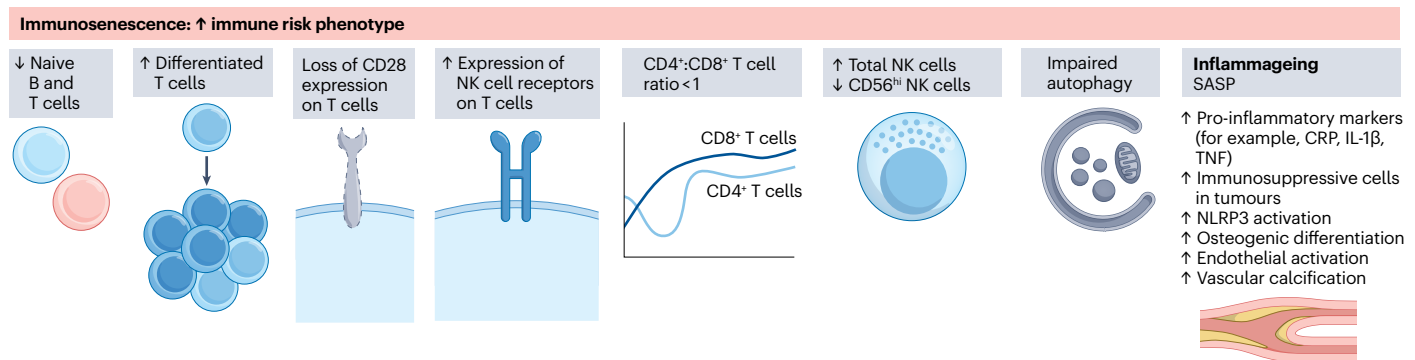
Innate immunity is also affected by ageing. Studies report either increased absolute numbers<sup>51</sup> or higher proportions of NK cells<sup>26,52</sup>, accompanied by a reduction in the CD56<sup>hi</sup> subset and an expansion of CD56<sup>lo</sup> CD16<sup>+</sup> NK cells<sup>52</sup>. Nevertheless, a large cross-sectional study reported relative maintenance of NK cell counts and proportions with ageing<sup>29</sup>. Functional impairments may still occur; for example, in individuals up to age 60, NK cells were shown to exhibit reduced perforin secretion and diminished cytotoxic capacity compared with younger individuals<sup>53</sup>.

Notably, centenarians, particularly semi-supercentenarians and supercentenarians, do not uniformly exhibit these age-associated changes. As discussed below, they may preserve or adapt specific immune components in ways that help to maintain immune competence across the lifespan (see also Table 1 and Supplementary Information Table 1 for a summary of the literature in the field).

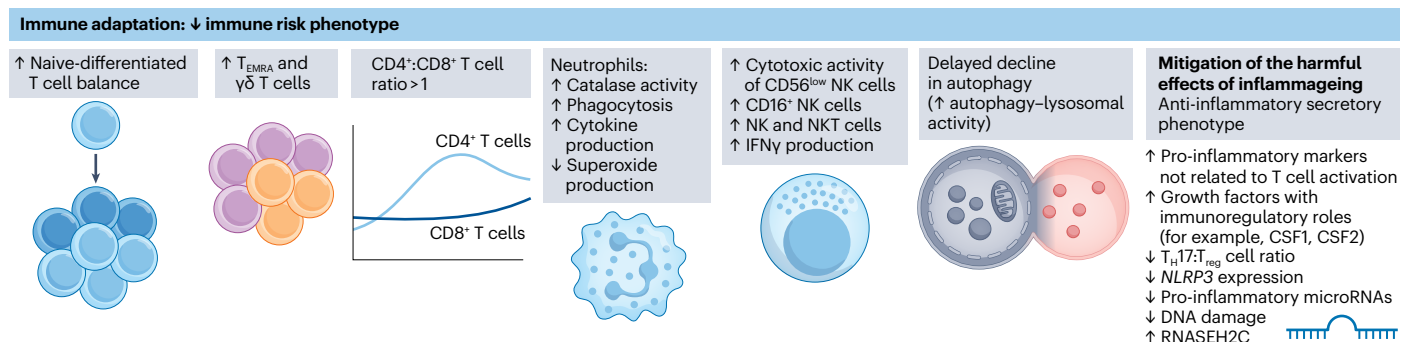
## Innate immunity in centenarians

**The complement system.** The complement system is a core component of innate immunity that acts as a double-edged sword in ageing. On the one hand, complement activation fuels inflammation through opsonization, chemotaxis and crosstalk with cytokine networks; on the other hand, it facilitates the clearance of apoptotic debris and molecular waste, thereby limiting sterile inflammation and preserving homeostasis<sup>54,55</sup>. Early studies suggested that complement function is relatively well preserved in centenarians and older adults<sup>56</sup>. More recently, the substantial presence of complement proteins in the blood of centenarians, particularly those participating in protein–protein interaction networks, compared with younger old people, has illustrated their dual capability to promote inflammatory responses while also establishing regulatory conditions<sup>57</sup>. These observations are consistent with the hypothesis that precise modulation of complement pathways contributes to immune robustness, potentially minimizing autoimmune disease risk despite the presence of autoantibodies<sup>57</sup>.

### a Typical age-related immune phenotype



### b Centenarian's immune phenotype



**Fig. 1 | Immune phenotype in typical ageing versus centenarians.** **a**, Typical ageing is associated with immunosenescence characterized by smaller naive B and T cell pools, accumulation of differentiated memory and effector T cells, loss of CD28 expression on T cells and increased expression of natural killer (NK) cell receptors on T cells. The CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratio reduces to less than 1, total NK cell numbers may increase whereas CD56<sup>hi</sup> NK cells decline, autophagy is impaired and a chronic low-grade inflammatory state (‘inflammaging’) develops. A senescence-associated secretory phenotype (SASP) further amplifies systemic inflammation and is linked to pro-inflammatory markers (such as C-reactive protein (CRP), IL-1 $\beta$  and TNF), immunosuppressive cells in tumours, NLRP3 activation, osteogenic switching, endothelial activation and vascular calcification, collectively contributing to an ‘immune risk phenotype’. **b**, Despite some heterogeneity, many centenarians – especially semi-supercentenarians and supercentenarians – show immune adaptation with a more favourable naive

to differentiated T cell balance, increased numbers of terminally differentiated effector memory cells re-expressing CD45RA (T<sub>EMRA</sub> cells) and  $\gamma\delta$  T cells and a CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratio greater than 1. Innate features include neutrophils with higher catalase activity, preserved phagocytosis and cytokine production, and lower superoxide output and NK cell compartments with more CD16<sup>+</sup> and CD56<sup>low</sup> cytotoxic NK cells, more NK cells and NKT cells, and greater interferon- $\gamma$  (IFN $\gamma$ ) production. Autophagy decline appears delayed (increased autophagy–lysosomal activity). Despite measurable inflammatory mediators, centenarians often exhibit resistance to the harmful effects of inflammaging. This includes an anti-inflammatory secretory phenotype with immunoregulatory growth factors (CSF1 and CSF2), a lower T helper 17 (T<sub>H</sub>17) cell:regulatory T (T<sub>reg</sub>) cell ratio, reduced NLRP3 expression, fewer pro-inflammatory microRNAs and less DNA damage with upregulation of RNASEH2C, collectively buffering pathology.

## Box 4 | Sex dimorphism in immune ageing

Immune responses — both innate and adaptive — are generally stronger in women than in men, contributing to lower susceptibility to infections and malignancies and enhanced vaccine responses, but also a higher risk of autoimmune disease<sup>227</sup>. Sex-specific trajectories in immune ageing have been described, particularly within the adaptive immune system, and inflammageing also exhibits sex bias<sup>228</sup>. Whether and how these differences persist into extreme old age in centenarians remains to be explored in depth.

Single-cell RNA sequencing studies have shown that ageing ( $\geq 65$  years) is associated with a higher proportion of circulating NK cells and a stronger inflammatory transcriptional signature in men<sup>229</sup> — a finding paralleled by flow cytometry data from a Sicilian cohort, including semi-supercentenarians and supercentenarians<sup>52</sup>. However, another study reported that older women ( $>70$  years) exhibited more robust NK cell function than age-matched men<sup>230</sup>. Women also exhibit sex-specific monocyte phenotypes with ageing, including differences in subset distribution and activation markers, despite an overall age-related decline in phagocytic function<sup>231</sup>. Several studies indicate a more pronounced age-related decline in B and T cell numbers in men than in women<sup>189,232</sup>, whereas very old females (86–94 years) retain higher proportions of naive CD8<sup>+</sup> T cells<sup>233</sup>. Women also show higher circulating plasma cell frequencies and stronger activation of the BAFF–APRIL system, consistent with enhanced humoral responses<sup>229</sup>. A meta-analysis further demonstrated greater immunogenicity and efficacy of influenza vaccination in women compared with men after — but not before — age 65 (ref. 234).

Multi-omics approaches corroborate these findings. Integrated ATAC-seq, RNA sequencing and flow cytometry analyses revealed that age-associated epigenomic changes — declining naive T cells and increased monocyte and cytotoxic cell activity — were more pronounced in men, along with a male-specific decline in

B cell-related loci<sup>235</sup>. Sex differences in immune-related genomic signatures became stronger after age 65, with men showing greater innate and inflammatory activity but reduced adaptive immune function<sup>235</sup>.

Sex chromosomes also play an important role in immune dimorphism. The X chromosome contains the highest density of immune-related genes in the human genome<sup>236</sup>, whereas the Y chromosome is primarily enriched in genes involved in spermatogenesis and male-sex determination<sup>237</sup>. The X chromosome also contains approximately 10% of all human microRNAs (miRNAs), whereas only two are encoded by the Y chromosome<sup>227</sup>. In females, one X chromosome undergoes random epigenetic inactivation during development to balance gene dosage compensation. With ageing, this random pattern may become skewed towards preferential inactivation of one X chromosome — a phenomenon termed X chromosome inactivation skewing<sup>238,239</sup>, which has been implicated in late-onset X-linked disorders and may contribute to increased susceptibility to autoimmunity<sup>238,239</sup>. Consistent with this, daughters of centenarians exhibit less X chromosome inactivation skewing than daughters of non-centenarians, reflecting delayed age-related loss of X-linked cellular mosaicism and supporting its broader contribution to healthy ageing and longevity<sup>240</sup>.

Finally, genome-wide association studies have revealed sex-specific genetic determinants of longevity. In Chinese cohorts, pathways enriched for immune and inflammatory responses were more strongly associated with longevity in men<sup>241</sup>, whereas polygenic genetic associations with longevity were, on average, stronger in women than in men<sup>242</sup>. Emerging evidence also suggests sex-specific differences in gut microbiota ageing, with male and female centenarians showing enrichment of bacterial species associated with unhealthy and healthy ageing, respectively<sup>165</sup>.

The complexity of age-related changes in the complement system was further underscored by a proteomic study in centenarians, in which complement was the only pathway to show bidirectional changes in protein expression when comparing centenarians with younger controls<sup>58</sup>. Proteins upregulated in centenarians included alternative pathway components, complement factor D, complement factor H-related proteins (CFHR1, CFHR2 and CFHR5) and membrane attack complex proteins (C7 and C9)<sup>58</sup>. As the membrane attack complex is the terminal step of the cascade regardless of the initiating pathway, these findings suggest an overall increase in complement activation in centenarians, accompanied by the concurrent upregulation of regulatory components (such as CFHR proteins). Comprehensive proteomic and standardized functional studies are now needed to define whether fine-tuning of complement is a determinant of disease resistance at extreme ages.

**Neutrophils.** Neutrophils are the most abundant type of granulocyte and account for 40–70% of white blood cells in humans. These cells play a central role in host defence and may also exert cytotoxic effects against tumours<sup>59</sup>. A seminal study found a higher proportion and absolute number of granulocytes in Japanese centenarians compared with middle-aged individuals<sup>60</sup>. In addition, granulocyte function was altered: phagocytic activity and cytokine production were enhanced in centenarians, whereas superoxide production was reduced. Notably,

these functional shifts were observed regardless of health status, suggesting a unique immune adaptation in centenarians<sup>60</sup>. In a subsequent report, middle-aged adults from Spain showed a more dysfunctional neutrophil profile, characterized by reduced chemotaxis and phagocytosis and increased adherence and oxidative burst, compared with both young adults and healthy centenarians<sup>61</sup>. In the latter, neutrophil functions more closely resembled those of young adults<sup>61</sup>. In addition, healthy centenarians exhibited the highest catalase activity across all groups and preserved total glutathione levels comparable to those of young adults, supporting the hypothesis that preservation of neutrophil antioxidant systems could contribute to healthy exceptional longevity<sup>61</sup>.

**NK cells.** Several studies report an overall expansion of NK cells in centenarians, similar to other aged populations, as outlined below. For instance, flow cytometry analyses show that Italian centenarians display increased numbers of NK cells<sup>62</sup>. In addition, a study from China combining scRNA-seq with fluorescence-activated cell sorting revealed increased expression of genes associated with the Fc receptor signalling pathway in CD16<sup>hi</sup>CD56<sup>low</sup> NK cells from centenarians and supercentenarians compared with elderly controls, despite broadly similar global transcription profiles<sup>63</sup>.

Evidence from other populations supports this pattern. Japanese centenarians have higher numbers of NK and NKT cells relative to

younger adults, together with enhanced IFN production<sup>60</sup>. It was originally proposed that this cytokine milieu, particularly driven by NKT cells, may be central to maintaining lymphocyte function in centenarians<sup>60</sup>. Similarly, healthy US centenarians show NK cell cytotoxic activity against the human K562 tumour cell line comparable to that of younger controls<sup>64</sup>, and Spanish centenarians preserve cytotoxic function against the same target despite functional decline in septuagenarians<sup>65</sup>. More recently, a study spanning two Chinese cohorts and one Japanese cohort, using cytometry by time-of-flight and scRNA-seq, showed that centenarians have a higher proportion of NK cells with ‘young’ transcriptional signatures, characterized by upregulation of the transcription factor RUNX3 and enhanced cytotoxicity<sup>66</sup>.

Overall, these findings suggest that NK cells in centenarians are not only numerically expanded but also maintain and, in some cases, enhance their cytotoxic and cytokine-producing functions. This dual preservation of quantity and function probably contributes to effective tumour surveillance and the maintenance of tissue homeostasis in exceptional longevity.

## Adaptive immunity in centenarians

**B and T cells.** Numerous studies indicate that adaptive immunity undergoes profound changes at extreme ages. In healthy US centenarians, CD4<sup>+</sup> T cell numbers were reduced by more than 50% compared with younger controls<sup>64</sup>. Likewise, Italian centenarians displayed decreased absolute lymphocyte counts, largely reflecting proportional reductions in CD4<sup>+</sup> and CD8<sup>+</sup> T cells and B cells<sup>67</sup>. A study from Denmark further showed that plasma TNF levels increase with age, with octogenarians exhibiting a higher proportion of TNF-producing T cells, whereas centenarians did not display this pro-inflammatory shift<sup>68</sup>, suggesting a potential selective advantage among individuals who reach extreme ages.

Further complexity was revealed by a study of semi-supercentenarians and very old adults (93–105 years) from Sicily, which showed that the oldest centenarians exhibited the lowest proportions of naive T cells – as expected – but the highest proportions of terminally differentiated effector memory cells re-expressing CD45RA (T<sub>EMRA</sub> cells)<sup>69</sup>. Although T<sub>EMRA</sub> cells are often associated with exhaustion or pro-inflammatory activity, in this context, they might reflect an adaptive change in T cell responses that support immune competence at extreme ages.

At the molecular level, scRNA-seq combined with a novel ageing clock model in seven supercentenarians revealed that their blood biological age ranged from 80 to 103 years<sup>70</sup>. Compared with model-predicted ageing trajectories, supercentenarians showed increased proportions of naive CD8<sup>+</sup> T cells and reduced proportions of cytotoxic CD8<sup>+</sup> T cells and memory CD4<sup>+</sup> T cells<sup>70</sup>. Single-cell analysis identified an enrichment of cell populations with high ribosomal activity, which Bayesian network inference linked to lower inflammatory states and slower ageing<sup>70</sup>. Experimental inhibition of ribosome-inflammation balance to this phenotype<sup>70</sup>. Together, these findings provide mechanistic insight into how immune competence may be preserved despite classical features of T cell ageing.

**γδ T cells.** Circulating γδ T cells are reduced in centenarians compared with younger individuals<sup>71,72</sup>, largely due to a decline in Vδ2<sup>+</sup> cells<sup>71</sup>. Functionally, γδ T cells from centenarians produce more TNF than those from young adults<sup>71,72</sup>, while maintaining similar cytotoxic potential<sup>71</sup>, and display elevated expression of the activation marker CD69, probably reflecting chronic low-grade inflammation<sup>72</sup>. Another study reported impaired proliferative capacity and increased susceptibility to apoptosis among γδ T cells from centenarians<sup>42</sup>. By contrast, a study in Sicilian centenarians identified a marked expansion of the T<sub>EMRA</sub> cell subset within the Vδ1<sup>+</sup> T cell population<sup>73</sup>.

Taken together, the expansion of CD8<sup>+</sup> T<sub>EMRA</sub> cells<sup>69</sup>, Vδ1<sup>+</sup> T<sub>EMRA</sub> cells, γδ T cells<sup>73</sup> and NK cells<sup>62</sup> observed in semi-supercentenarians and supercentenarians might represent adaptive compensatory immune mechanisms shaped by lifelong antigenic exposures, including persistent viral infections such as cytomegalovirus. These changes may collectively contribute to tumour resistance and preservation of immune function in exceptional longevity.

## Autophagy and immunity in centenarians

Age-related decline in proteostatic mechanisms, including autophagy, is thought to contribute to functional impairment across multiple cell types<sup>74</sup>, including immune cells<sup>75</sup>. In CD8<sup>+</sup> T cells from older healthy donors, reduced basal autophagy has been linked to classical features of T cell dysfunction<sup>76</sup>. In this context, analysis of FAS and FASL isoforms in peripheral blood T cells from centenarians revealed a balanced

**Table 1 | Convergent immune and inflammatory features in extreme age**

Centenarian trait	Core immune feature	Potential immune relevance	Key references
Attenuation of systemic inflammation	Lower levels of composite inflammatory indices compared with older adults or low levels of inflammatory biomarkers in general	Suggests partial uncoupling of extreme ageing from chronic low-grade inflammation	70,95,102
Preserved anti-inflammatory balance	Maintenance of anti-inflammatory cytokines and increased regulatory T cell-associated cytokine profiles	Supports preserved immune homeostasis despite advanced age	68,90,91,93
Shift towards cytotoxic lymphocyte programmes	Increased cytotoxic CD4 <sup>+</sup> and CD8 <sup>+</sup> T cell subsets and expansion of terminally differentiated effector memory cells re-expressing CD45RA populations	Reflects adaptive remodelling of cellular immunity rather than immune collapse	63,69,73,79,134,135,137
Reduction of naive lymphocyte compartments	Decreased frequencies of naive T cells with age	Consistent with immune maturation and long-term antigen exposure	63,69,79,134,135
Natural killer cell preservation and enhancement	Increased frequency and preserved cytotoxic function of natural killer cells and ‘young-like’ transcriptional signatures	Maintains innate immune surveillance in extreme longevity	62,66,189
Transcriptomic deceleration of immune ageing	Immune transcriptomes and inflammatory clocks indicate biological ages younger than chronological age	Suggests delayed immune ageing at the molecular level	66,70,120

# Review article

production of pro-apoptotic molecules (membrane-bound FAS and FASL) and anti-apoptotic molecules (soluble FAS)<sup>77</sup>. This equilibrium may help to preserve immune competence at extreme ages, although whether the FAS–FASL axis contributes through mechanisms beyond apoptosis remains unclear.

Transcriptomic analyses further support a role for autophagy in exceptional longevity. In Chinese centenarians, genes involved in the autophagy–lysosomal pathway were upregulated compared with younger controls (namely, the spouses of centenarians' offspring)<sup>78</sup>. Notably, overexpression of four of such genes (*ATG4D*, *ATP6VOC*, *CTSB* and *WIP1I*) in a fibroblast cell line derived from a young donor lead to suppression of senescence markers in vitro<sup>78</sup>, suggesting broader antisenesescence potential. Consistently, scRNA-seq analysis of the oldest Spanish woman (age 116) showed an autophagy-related transcriptome similar to that of young adult women<sup>79</sup>.

At the protein level, healthy Italian centenarians exhibited higher circulating levels of beclin 1, a central regulator of autophagy, than both younger healthy and unhealthy controls<sup>80</sup>. In addition, near-centenarians and centenarians (98–103 years) with stable health showed lower circulating concentrations of acyl-coenzyme A-binding protein, a tissue hormone that inhibits autophagy in multiple cell types, compared with peers (90–108 years) hospitalized for acute disease exacerbation<sup>81</sup>. However, the evidence is not entirely consistent. In Jewish Ashkenazi centenarians, activation-induced autophagy in CD4<sup>+</sup> T cells was better preserved in their offspring compared with age-matched controls, whereas autophagy levels in the centenarians themselves declined similarly to controls<sup>82</sup>. These findings suggest that while the age-associated decline in T cell autophagy may be delayed in longevity-prone families, it is not completely prevented.

## Inflammaging

With advancing age, and particularly during the post-reproductive period, the mechanisms responsible for resolving inflammation progressively deteriorate. As a consequence, many older adults develop

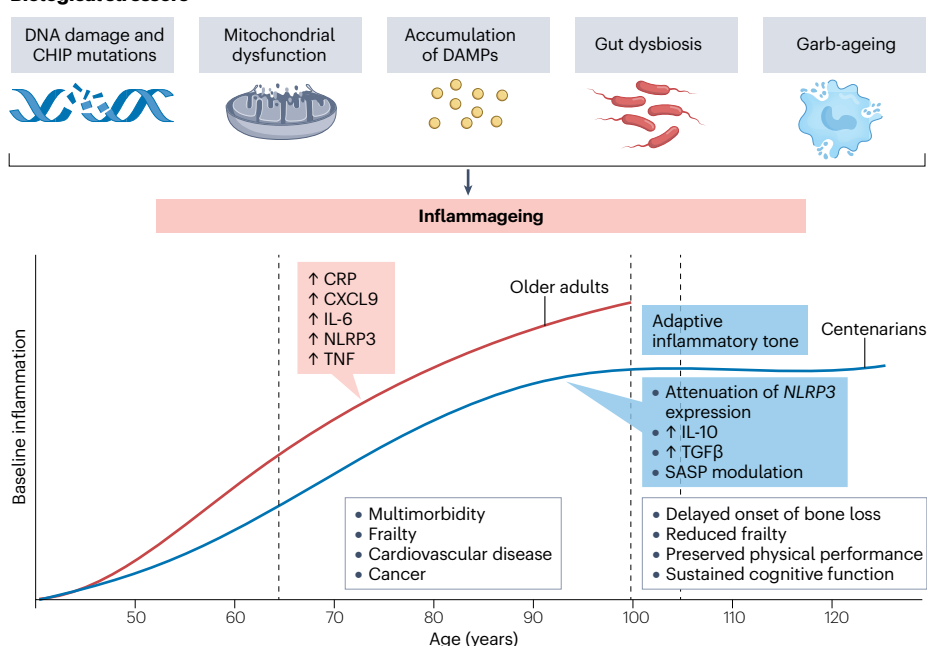
a persistent state of systemic low-grade chronic inflammation<sup>10</sup>. This condition, termed inflammaging<sup>83</sup> (Fig. 2), is usually characterized by elevated levels of cytokines (such as IL-1 $\beta$  and TNF), chemokines and acute-phase proteins such as C-reactive protein (CRP), in the absence of overt infection or autoimmune disease<sup>10</sup>, and is recognized as a hallmark of ageing<sup>74</sup>. However, no single biomarker defines this state; instead, studies rely on heterologous panels of markers and composite indices, which vary across cohorts (see 'Inflammaging clocks' below).

## Inflammaging as a source of disease

Inflammaging is thought to arise from the cumulative burden of ageing-associated stressors, including cellular senescence, mitochondrial dysfunction, DNA damage, gut dysbiosis and the accumulation of damage-associated molecular patterns<sup>10,84</sup>. Endogenous cellular debris, such as misfolded proteins, damaged organelles (notably damaged mitochondria) and immunogenic nucleic acids, acts as a persistent stimulus for innate immune activation<sup>84</sup>. This process, referred to as 'garb-ageing', establishes a feedforward loop of sterile inflammation by chronically engaging pattern-recognition receptors, such as Toll-like receptors and inflammasomes, thereby sustaining low-grade immune activation in the absence of pathogens<sup>84</sup>.

CHIP represents an additional, age-associated amplifier of inflammaging. Accumulating evidence links CHIP to heightened systemic inflammation<sup>85</sup>, probably through increased pro-inflammatory cytokine production from mutant myeloid clones and enhanced pattern-recognition receptor signalling, although causal pathways in humans remain incompletely defined<sup>85</sup>. In the context of cancer, inflammaging promotes oncogenesis not only by increasing cellular turnover<sup>74</sup> and interacting with CHIP<sup>16</sup> but also, at least partly, by shaping an immunosuppressive tumour microenvironment<sup>86</sup>. This includes the accumulation of myeloid-derived suppressor cells, M2-like macrophages and FOXP3<sup>+</sup> regulatory T (T<sub>reg</sub>) cells<sup>87</sup>. Inflammaging also plays a central role in CVD pathogenesis by promoting endothelial dysfunction, atherogenesis and thrombogenesis<sup>87,88</sup>.

### Biological stressors



**Fig. 2 | Inflammaging in centenarians.** Biological stressors experienced across lifespan fuel age-related, low-grade inflammation ('inflammaging'). These stressors include DNA damage and clonal haematopoiesis of indeterminate potential (CHIP)-associated mutations, mitochondrial dysfunction, accumulation of damage-associated molecular patterns (DAMPs), gut dysbiosis and garb-ageing (persistent cellular debris), all of which converge on chronic biological stress. Typically, inflammatory tone increases with age and tracks with increased C-reactive protein (CRP), CXCL9, IL-6, NLRP3 and TNF levels, accompanying multimorbidity, frailty, cardiovascular disease and cancer. Yet centenarians often display a different, adaptive inflammatory tone – characterized by attenuated *NLRP3* expression, higher IL-10 and transforming growth factor- $\beta$  (TGF $\beta$ ) levels and senescence-associated secretory phenotype (SASP) modulation – supporting preserved function (such as delayed bone loss, reduced frailty, maintained physical performance and cognition) despite advanced age.

## Inflammageing in centenarians

Despite often displaying higher levels of circulating pro-inflammatory markers than younger individuals<sup>89–91</sup>, many centenarians are remarkably resistant to inflammation-driven diseases such as cancer and CVD. This apparent paradox raises the possibility that immune activation in centenarians reflects not pathological inflammation but rather a distinct, adaptive state of immune function. A refined mechanistic model, as outlined below, proposes that the downstream effects of elevated cytokines are attenuated or redirected through tightly controlled compensatory signalling networks, immune training and counterbalancing anti-inflammatory pathways, involving T<sub>reg</sub> cells<sup>90</sup>, anti-inflammatory cytokines<sup>90</sup>, soluble cytokine receptors<sup>91</sup> and epigenetic and post-transcriptional regulation<sup>92,93</sup>, as discussed below. This framework underpins the concept of an ‘adaptive inflammatory tone’ – a low-toxicity immune activation state that supports effective immunosurveillance and tissue repair without precipitating chronic pathology. Such an adaptation may explain how centenarians tolerate elevated cytokine levels without adverse clinical consequences. Apparent discrepancies across centenarian cohorts probably reflect context-dependent inflammatory axes rather than biological uniformity.

**Pro-inflammatory markers.** Studies in Chinese<sup>90</sup> and Italian<sup>89,94</sup> centenarians have reported higher levels of several pro-inflammatory markers and cytokines, such as CRP<sup>90</sup>, IFN $\gamma$ <sup>90</sup>, IL-6 (refs. 90,94), IL-12 (ref. 90), IL-22 (ref. 89) and TNF<sup>90,94</sup>, relative to younger adults<sup>89,90,94</sup>. Growth factors with immunoregulatory roles, including CSF1 and CSF2, have also been found to be upregulated in centenarians<sup>94</sup>. Nevertheless, findings are heterogeneous. For example, one study noted no age-related differences in IFN $\gamma$ <sup>94</sup>, whereas others observed increased IFN $\gamma$  levels in centenarians<sup>90</sup>. This heterogeneity is further illustrated by a study in Cuban centenarians, in which most individuals exhibited low serum levels of pro-inflammatory cytokines and CRP, alongside relatively good health status: 22% had no comorbidities and nearly half were only moderately dependent<sup>95</sup>. A study of Chinese centenarians described a more mixed inflammatory profile: whereas CRP, IFN $\gamma$ , IL-6, IL-12, TNF and the anti-inflammatory cytokine IL-10 were elevated, levels of IL-1 $\beta$ , IL-17A, IL-23 and transforming growth factor- $\beta$  (TGF $\beta$ ) were comparable to those in young adults<sup>90</sup>. Notably, centenarians showed a lower ratio of pro-inflammatory T<sub>H</sub>17 cells to anti-inflammatory T<sub>reg</sub> cells. Functionally, T<sub>H</sub>17 cells secreted fewer pro-inflammatory cytokines, whereas T<sub>reg</sub> cells secreted higher levels of anti-inflammatory mediators, suggesting a shift towards a regulatory immune phenotype<sup>90</sup>.

A study of Russian centenarians further emphasized the importance of this regulatory balance by contrasting individuals with ‘unfavourable ageing phenotypes’ or ‘successful ageing’<sup>96</sup>. The former group had higher IL-6 levels and lower levels of IL-10 and TGF $\beta$ , suggesting that loss of anti-inflammatory control contributes to frailty and multimorbidity in extreme old age<sup>96</sup>. Taken together, these findings support the notion that healthy centenarians maintain a finely tuned regulatory immune environment, favouring anti-inflammatory control despite a pro-inflammatory milieu. Consistent with this interpretation, an acute bout of physical exercise was shown to downregulate some pro-inflammatory cytokines – most notably, TNF – in centenarians compared with a control resting condition<sup>97</sup>. In younger individuals, this same stimulus typically induces a transient inflammatory response (for example, temporary TNF increases<sup>98</sup>), further highlighting the distinct immune adaptability of centenarians.

More broadly, evidence from diverse cohorts challenges the view that chronic low-grade inflammation is an inevitable consequence

of ageing. Although CRP, IL-6 and TNF often increase with age, individuals who maintain good health and favourable exposome profiles throughout life can reach advanced age without such elevations. This has been shown in cohorts spanning 20–102 years (women and men from the general population)<sup>99</sup>, 62–88 years (healthy women)<sup>100</sup> and 26–90 years (women and men of different ethnic origins)<sup>101</sup>. Together these findings reinforce the concept that inflammageing is a highly heterogeneous process, shaped by genetic background, cumulative antigenic exposure, microbiota composition, metabolic health and lifestyle and environmental factors<sup>84,101</sup>.

**Semi-supercentenarians and supercentenarians.** Semi-supercentenarians and supercentenarians may demonstrate even greater resistance to inflammageing than centenarians. For instance, in Italian cohorts, the aggregated inflammation score and systemic inflammation response index of semi-supercentenarians and supercentenarians were similar to those of younger adults but lower than those of younger centenarians<sup>102</sup>. Similarly, age-related immune phenotype values did not differ significantly between semi-supercentenarians and supercentenarians and the other groups<sup>102</sup>.

A case report of a 108-year-old Italian man – the oldest individual in the country at the time – found elevated IL-6 and aggregated inflammation scores<sup>103</sup>, yet his immune phenotype (including naive CD4<sup>+</sup> T cell counts, CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratio and the balance between naive and effector/memory CD4<sup>+</sup> T cells) resembled that of young adults, suggesting a functionally youthful immune system<sup>103</sup>. Consistent with this, Italian semi-supercentenarians were shown to have lower CRP and IL-6 levels than very old adults (93–105 years), although IL-6 was higher than in younger old adults (68–87 years)<sup>69</sup>. A larger study involving Japanese centenarians, semi-supercentenarians, supercentenarians, centenarians’ offspring, unrelated family members and community-dwelling very old adults found that CRP, IL-6 and TNF levels were highest in the semi-supercentenarians and supercentenarians<sup>104</sup>. Remarkably, supercentenarians tended to have more ‘youthful’ CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratios (median 1.6), exceeding those observed in centenarians and semi-supercentenarians and even surpassing the ratios seen in centenarian offspring<sup>104</sup>. In this cohort, inflammatory biomarkers correlated with survival, physical performance and cognitive outcomes, but not with multimorbidity, which underscores a degree of preserved functionality despite systemic inflammation<sup>104</sup>. Supporting this concept, a longitudinal Swedish study showed that individuals who reached 100 years of age maintained higher CD4<sup>+</sup> T cell:CD8<sup>+</sup> T cell ratios across life, thereby avoiding the ‘immune risk profile’ associated with increased mortality in older adults<sup>105</sup>. Together, these findings emphasize that in extreme old age, qualitative organization and regulation of immune responses, rather than absolute cytokine levels, appear to be key determinants of health and longevity.

**Disease resistance and anti-inflammageing.** Centenarians display marked heterogeneity in systemic inflammation. Although some exhibit elevated inflammatory markers, others, particularly those with healthier ageing phenotypes, show minimal pro-inflammatory activity<sup>95</sup>. This variability underscores the existence of distinct ageing trajectories. Notably, a subset of centenarians remains free<sup>89</sup> (or relatively free<sup>90</sup>) of major diseases and maintains functional independence<sup>89</sup> despite increased circulating inflammatory mediators<sup>89,90</sup>, raising important questions about the mechanisms that buffer the pathological effects of inflammageing.

One explanation is that centenarians retain the ability to modulate the source, intensity and/or downstream consequences of cytokine signalling. Pro-inflammatory mediators originate from diverse tissues and cell types, including immune cells, adipose tissue and skeletal muscle, and their biological effects may depend on tissue context and microenvironment. For example, IL-6 promotes tumour progression when produced within the tumour microenvironment yet acts as a metabolic regulator and even has anti-inflammatory effects when released by contracting skeletal muscle<sup>98,106</sup>. In addition to cytokine abundance, signalling outcomes are shaped by the availability of soluble receptors. For example, levels of the soluble IL-6 receptor and its co-receptor gp130 increase with age in women until around the seventh decade and subsequently decline<sup>91</sup>, potentially reshaping IL-6 signalling dynamics in advanced age. Elevated cytokine levels in centenarians may therefore reflect compensatory or adaptive responses rather than immune pathology. Such responses may be part of an individual's 'immunobiography' – the cumulative imprint of lifelong exposures, infections and metabolic stressors on immune regulation<sup>84</sup>. From this perspective, the inflammatory profile observed in some centenarians may represent adaptive calibration rather than dysfunction, supporting an adaptive inflammatory tone that preserves rapid immune responsiveness while limiting collateral tissue damage<sup>107</sup>.

Genetic and epigenetic mechanisms probably contribute to this resilience. In a Sicilian cohort spanning young adults to supercentenarians, circulating levels of four miRNAs involved in inflammation – miR-126-3p, miR-21-5p, miR-146a-5p and miR-181a-5p – increased with age but reverted to levels comparable to those of adults under 50 years in supercentenarians<sup>92</sup>. Although efficient DNA repair mechanisms favour longevity across evolution<sup>74</sup>, activation of the DNA damage response machinery can trigger inflammation and upregulate type I IFN signalling, both of which contribute to age-related diseases and may ultimately limit lifespan<sup>93</sup>. Thus, restrained activation of DNA damage-induced inflammatory pathways may represent an additional protective layer in long-lived individuals. Supporting this hypothesis, fibroblasts from Italian semi-centenarians exhibited a distinctive anti-inflammatory molecular profile characterized by reduced DNA damage, preserved telomere length and low expression of IFN $\beta$ , IL-6 and pro-inflammatory miRNAs<sup>93</sup>. These cells also showed high expression of the RNase H2 subunit RNASEH2C and reduced accumulation of cytoplasmic RNA:DNA hybrids, which are known to promote genomic instability and inflammatory signalling<sup>93</sup>. Furthermore, extracellular vesicles derived from centenarians' cells induced RNASEH2C expression and attenuated inflammatory gene expression in recipient myeloid cells, fibroblasts and cancer cells<sup>93</sup>.

Reduced expression of NLRP3 may further contribute to disease resistance in centenarians<sup>108</sup>. In the general ageing population, *NLRP3* expression in T cells increases markedly after approximately age 65 compared with young adults<sup>109</sup>. By contrast, healthy centenarians have been found to maintain *NLRP3* expression levels comparable to those of young individuals, whereas unhealthy centenarians show significantly higher expression<sup>109</sup>. Mouse studies corroborate the importance of this pathway: deletion of *Nlrp3* results in a phenotype reminiscent of healthy centenarians, including delayed bone loss, reduced immunosenescence and frailty, lower incidence of age-related diseases and a 34% extension of mean lifespan<sup>110–112</sup>.

Attenuation of cellular senescence and its associated senescence-associated secretory phenotype (SASP) – a major driver of inflammaging – has also been proposed as a mechanism of disease resistance in ageing<sup>113</sup>. Transcriptomic and biomarker studies support

this idea, revealing upregulation of autophagy-related pathways in centenarians<sup>78,80</sup>. By promoting clearance of damaged organelles and macromolecules, and maintaining lysosomal and mitochondrial homeostasis, enhanced autophagy may suppress SASP activity and reduce intracellular stress<sup>114</sup>. Efficient cellular repair mechanisms might further limit senescent cell burden or activity<sup>115</sup>. Nonetheless, proteomic analyses from the New England Centenarian Study detected persistent SASP signatures in centenarians<sup>116</sup>, suggesting that senescence-mitigating mechanisms are not universally preserved.

The concept of anti-inflammaging, originally proposed as a systemic network of anti-inflammatory mediators counterbalancing chronic low-grade inflammation<sup>117</sup>, offers a useful framework to integrate these observations. According to this model, compensatory regulatory pathways are co-activated to restrain tissue damage and preserve physiological function despite persistent immune activation<sup>117</sup>. In line with this view, cell-free DNA profiling shows greater similarity between young individuals and healthy centenarians than between young individuals and unhealthy centenarians, suggesting that this biomarker reflects the cumulative burden and downstream biological impact of inflammation – including cell turnover, tissue damage and immune-mediated stress – rather than chronological age per se<sup>118</sup>. Circulating miRNAs further support this concept. Small RNA sequencing identified 79 differentially expressed circulating miRNAs across young controls (30 years, on average), older adults (71 years) and healthy versus unhealthy centenarians, with miR-19a-3p and miR-19b-3p emerging as discriminators of healthy ageing trajectories at extreme ages<sup>119</sup>. These miRNAs, known regulators of inflammaging and components of SASP, converge on FOXO-related signalling pathways, including *SMAD4*, *PTEN* and *BCL2L1*, thereby linking epigenetic regulation to the modulation of inflammatory and stress-response pathways<sup>119</sup>. Together, these molecular signatures are consistent with the cellular and cytokine-level regulatory mechanisms described above – including preserved T<sub>reg</sub> cell function and sustained anti-inflammatory signalling – and support a model in which anti-inflammaging networks, captured by integrative biomarkers such as cell-free DNA and circulating miRNAs, underlie clinically relevant heterogeneity and resilience to inflammation-driven pathology in centenarians.

**Inflammaging clocks.** Given the pronounced heterogeneity of inflammaging, composite metrics have been developed to quantify inflammaging age. A guided autoencoder deep learning model constructed an inflammatory ageing clock (iAge) from 50 cytokines, chemokines and growth factors, achieving a mean absolute error of 15.2 years and identifying CXCL9 as the most informative feature<sup>120</sup>. iAge tracked multimorbidity, immunosenescence, frailty and cardiovascular ageing, with centenarians over-represented in a low iAge index (protective) group compared with controls aged 50–79 years<sup>120</sup>.

Beyond individual biomarkers, the construct validity of inflammaging clocks reflects underlying network behaviour. For example, iAge correlated with changes in STAT1, STAT3 and STAT5 phosphorylation in cytokine-stimulated immune cells, consistent with a bow-tie architecture in which diverse inflammatory inputs converge on central signalling hubs, notably the JAK–STAT pathway, to generate context-dependent outputs<sup>120</sup>. This network logic helps to explain the absence of a universal inflammaging metric, as inflammatory trajectories are context-dependent and shaped by local exposomes; accordingly, axes derived from industrialised populations may not generalize to non-industrialised settings<sup>121</sup>. A complementary small immunological clock (SI-mAge), initially derived from 46 immunological

parameters, also identified CXCL9 as the top-ranked contributor, whereas the composition and relative importance of downstream markers differed from those defining iAge<sup>122</sup>. Extending this approach, an explainable deep learning framework integrating epigenetic and inflammatory markers (EpInflammAge) generated a disease-associated biological ageing measure sensitive to pathological states<sup>123</sup>.

Together, these multimodal clocks reinforce the notion that integrative indices capture systemic inflammation and disease resistance more robustly than isolated biomarkers. They also provide insight into how immune homeostasis may be maintained through coordinated regulation of inflammatory signalling, cellular senescence and epigenetic buffering.

In summary, resistance to age-related disease in centenarians does not arise from a single pathway but reflects diverse immune trajectories, some characterized by the ability to tolerate and buffer inflammation and others by mechanisms that limit its development altogether.

## The immunome of centenarians

Next-generation sequencing technologies have enabled comprehensive, multilayered analysis of the immunome, spanning the epigenome and transcriptome<sup>124</sup>. These approaches have uncovered molecular features that may contribute to immune competence and resilience in extreme human longevity (Fig. 3).

### Epigenome

Epigenetic regulation, particularly DNA methylation, appears to influence immune ageing<sup>125</sup>. In a Japanese cohort of centenarians and supercentenarians, DNA methylation profiles at 557 CpG sites enriched in cancer-related and neuropsychiatric-related genes resembled those of non-centenarians<sup>126</sup>. By contrast, centenarians and supercentenarians exhibited 140 CpG sites with an 'older' methylation pattern (characterized by advanced demethylation), enriched in immune-related genes, including those involved in TGFβ signalling<sup>126</sup>. Complementary evidence comes from a study of Italian centenarians' offspring, who display higher global DNA methylation levels in peripheral leukocytes than offspring of non-long-lived parents<sup>127</sup>. This epigenetic trait is consistent with enhanced genomic stability and a delayed age-related loss of DNA methylation, features that have been linked to healthier ageing trajectories and a reduced burden of age-associated diseases<sup>127</sup>.

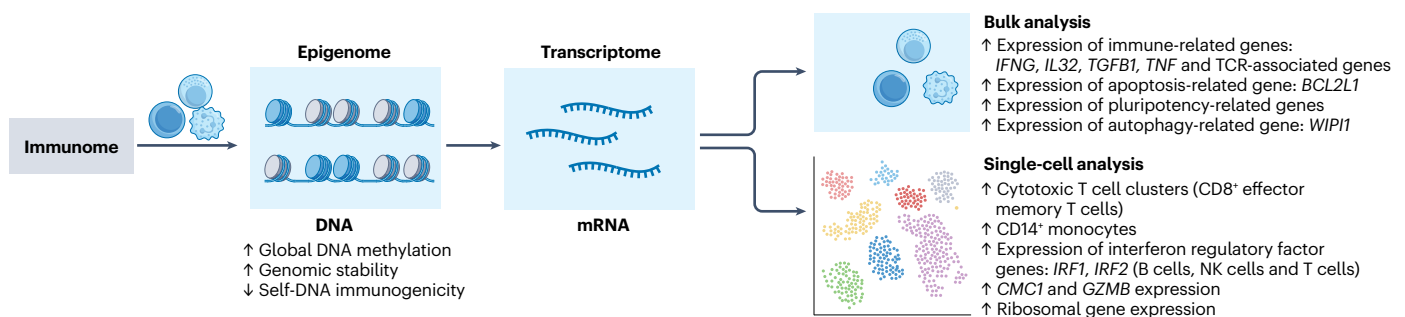
Conversely, global DNA hypomethylation has been linked to increased immunogenicity of self-DNA, enhancing innate immune activation and type I IFN responses, and thereby potentially favouring chronic inflammation, autoimmunity and cancer<sup>128</sup>.

### Transcriptome

**Bulk analyses.** Bulk transcriptomic profiling of immune cells from centenarians has revealed a wide array of differentially expressed genes<sup>65,78,129–132</sup>. For example, more than 1,700 immune-related genes were differentially expressed in peripheral blood mononuclear cells (PBMCs) of Spanish centenarians compared with septuagenarians and young adults<sup>65</sup>. Network analyses further showed that key immune-related genes (including *IFNG*, *IL32*, *TGFB*, *TNF* and genes involved in T cell receptor signalling) were similarly upregulated in centenarians and young adults, but not in septuagenarians<sup>65</sup>. These genes were also interconnected with apoptotic genes (*BCL2L1*, *FAS* and *FASL*)<sup>65</sup>.

The *BCL2L1* gene, which encodes the mitochondrial anti-apoptotic protein BCL-xL, has emerged as a candidate gene for exceptional longevity<sup>65</sup>. Supporting evidence includes: first, its selective upregulation in centenarians relative to septuagenarians; second, its ability to reduce senescence-associated markers when overexpressed in lymphocytes from septuagenarians; and third, the finding that a gain-of-function mutation in its *Caenorhabditis elegans* orthologue, *ced-9*, significantly extended both mean and maximal lifespan<sup>65</sup>. Interestingly, another transcriptomic study reported upregulation of pluripotency-associated genes, including those encoding a subset of the Yamanaka factors (c-MYC, OCT3/4 and SOX2), together with increased expression of genes encoding stemness-related surface markers (*BMP4*, *BMPR2*, *NCAM* and *VIM*), in PBMCs from Spanish centenarians compared with octogenarians<sup>130</sup>. Moreover, transduction of lymphocytes from octogenarians with *BCL2L1* induced increased expression of genes encoding three Yamanaka factors (*MYC*, *KLF4* and *SOX2*)<sup>130</sup>, further implicating this anti-apoptotic gene in promoting cellular plasticity and delaying immune senescence. Taken together, these findings suggest that transcriptomic programmes favouring stemness, reduced cellular differentiation and resistance to apoptosis contribute to immune function preservation in extreme ageing.

Additional support for adaptive transcriptomic remodelling comes from RNA sequencing of PBMCs from Chinese centenarians,



**Fig. 3 | The immunome of centenarians.** Multi-omics profiling of centenarians reveals epigenomic and transcriptomic adaptations linked to immune function preservation. Epigenomes reveal higher global DNA methylation with greater genome stability and reduced self-DNA immunogenicity. Bulk transcriptomes show increased expression of immune-related genes (*IFNG*, *IL32*, *TGFB1*, *TNF* and genes involved in T cell receptor signalling), the apoptosis-regulatory gene *BCL2L1* (encoding the mitochondrial protein BCL-xL), pluripotency-related

genes and the autophagy gene *WIP1*. Transcriptomic analyses at the single-cell level show enrichment of cytotoxic T cell clusters (CD8<sup>+</sup> effector memory cells), increased CD14<sup>+</sup> monocytes, upregulation of interferon regulatory factor genes (*IRF1* and *IRF2*) across B cells, natural killer (NK) cells and T cells; *CMC1* and *GZMB*; and ribosomal genes. Collectively, these signatures are consistent with delayed immune ageing and preserved function in extreme longevity.

## Glossary

### $\alpha$ -diversity

A measure of microbiome diversity applicable to a single sample (that is, within a single person). One example is the Shannon diversity index (H or H'), which quantifies community diversity by considering species richness (the total number of different species) and species evenness (how similar species abundances are).

### Age-related immune phenotype

An age-related decrease in circulating naive T cells relative to the accumulation of memory T cells, which decreases protection against pathogens and response to vaccines. It has been associated with chronic diseases and mortality.

### Aggregated inflammation score

A comprehensive blood-derived score of chronic low-grade inflammation that incorporates C-reactive protein, white blood cell count, platelet count and the granulocyte-to-lymphocyte ratio.

### Mendelian randomization

A method using measured variation in genes (for example, single nucleotide polymorphisms) to examine the causal effect of an exposure on an outcome.

which revealed upregulation of several autophagy-related genes<sup>78</sup>. Notably, one such gene – *WIP1* – was shown to extend lifespan when expressed in transgenic flies<sup>78</sup>, highlighting the importance of autophagy as a longevity mechanism. In a separate study, RNA-seq of blood-derived lymphoblastoid cell lines from centenarian women of Ashkenazi Jewish descent showed expression levels of inflammation-related genes (*BID* and *CD99*) comparable to those of young women (20–35 years), whereas individuals aged 60–80 years exhibited a more pro-inflammatory expression profile<sup>131</sup>. These findings are consistent with other reports reinforcing the notion that centenarians maintain a transcriptional state associated with inflammation resistance and immune youthfulness<sup>65,129,133</sup>.

**Single-cell studies.** scRNA-seq has provided unprecedented resolution of immune ageing by revealing cell-type-specific cellular and transcriptional changes. Multiple studies profiling immune cells from centenarians and supercentenarians have identified distinctive features in both immune composition and gene expression<sup>63,70,134–137</sup>. In one study analysing over 61,000 PBMCs from Japanese supercentenarians, an expansion of cytotoxic CD4<sup>+</sup> T cells was observed<sup>136</sup>.

### Progeroid mouse models

Mouse models that recapitulate features of accelerated ageing, often driven by mutations in genes involved in genome maintenance or nuclear architecture.

### Senescence-associated secretory phenotype

(SASP). A phenotype of senescent cells wherein those cells secrete high levels of pro-inflammatory cytokines, immune modulators, growth factors and proteases. The SASP may also include exosomes or ectosomes containing enzymes, microRNAs, DNA fragments, chemokines and other bioactive factors.

### Systemic inflammation response index

An index of systemic inflammation based on blood neutrophil, monocyte and lymphocyte counts.

### Yamanaka factors

A set of four transcription factors (*MYC*, *KLF4*, *OCT3/4* and *SOX2*) that are highly expressed in embryonic stem cells. Their overexpression can induce pluripotency in somatic cells, reprogramming them into induced pluripotent stem cells. These factors regulate the developmental signalling network necessary for ES cell pluripotency.

These cells produced IFN $\gamma$  and TNF after ex vivo stimulation and were significantly enriched relative to controls aged 50–80 years<sup>136</sup>. Similarly, a study covering the human lifespan – from children to supercentenarians – reported an expansion of CD4<sup>+</sup> cytotoxic T cells and GZMK<sup>+</sup>GZMB<sup>+</sup>CD8<sup>+</sup> T cells in supercentenarians compared with individuals aged 60–80 years<sup>137</sup>. Together, these findings suggest that the acquisition of cytotoxic function by CD4<sup>+</sup> T cells may represent an adaptive mechanism to maintain antiviral and antitumour immunity in extreme old age. An integrative analysis of more than 87,000 PBMCs from Chinese centenarians and supercentenarians further revealed an enrichment of CD8<sup>+</sup> effector memory T cells and terminally differentiated B cells, alongside a relative depletion of naive T cells and T<sub>reg</sub> cells<sup>63</sup>. Notably, CD14<sup>+</sup> monocytes exhibited enhanced capacity for antigen presentation, suggesting preserved innate immune surveillance in centenarians<sup>63</sup>. In parallel, IFN regulatory factor genes (*IRF1* and *IRF2*) were upregulated across B, NK and T cell subsets in centenarians and supercentenarians compared with controls, supporting enhanced antiviral competence<sup>63</sup>. This study also reported activation of the Hippo signalling pathway in CD8<sup>+</sup> effector memory T cells, involved in proliferation and apoptosis, which may contribute to immune robustness in extreme ageing<sup>63</sup>. scRNA-seq analyses of PBMCs from Chinese centenarians and their offspring identified both a quantitative expansion and functional reinforcement of cytotoxic T cells – particularly CD8<sup>+</sup> T cells expressing CX3CL1 and granzyme B<sup>135</sup>. Other analyses combining novel and publicly available scRNA-seq data identified a shift from CD4<sup>+</sup> T cell dominance towards B cell populations, alongside a broader increase in cytotoxic T cell subsets and reduction of naive and memory CD4<sup>+</sup> T cells<sup>134</sup>. Although early research reported reduced lymphocyte counts in centenarians<sup>67</sup>, these single-cell data emphasize qualitative and functional immune adaptation rather than a simple numerical decline.

At the transcriptional level, centenarians exhibited expression of age-associated genes, such as *STK17A*, involved in the DNA damage response, and immune-specific genes, such as *S100A4*, detected only in naive CD4<sup>+</sup> T cells from centenarians<sup>134</sup>. *S100A4* encodes a calcium-binding protein implicated in inflammation, metabolism and age-related disease, highlighting immune adaptation and inflammation control as potential contributors to exceptional longevity<sup>134</sup>. Notably, a recent scRNA-seq study estimated that the 'transcriptome age' of supercentenarians was approximately 65–76 years, substantially lower than their chronological age<sup>70</sup>. Contrary to model-predicted ageing trajectories, these individuals exhibited higher frequencies of naive CD8<sup>+</sup> T cells and lower proportions of cytotoxic CD8<sup>+</sup> T cells, memory CD4<sup>+</sup> T cells and megakaryocytes<sup>70</sup>. A striking molecular feature was elevated ribosomal gene expression across immune subsets, which Bayesian network inference identified as a central node that was inversely linked to inflammatory programmes and associated with slower biological ageing in supercentenarians<sup>70</sup>. Beyond protein synthesis, ribosomal proteins are increasingly recognized as regulators of inflammatory pathways<sup>138</sup>, reinforcing their potential role in preserving immune function in extreme ageing.

**Future methodological frameworks.** The development of single-cell and spatial transcriptomics has revolutionised our capacity to investigate cellular properties, functions and interactions in cellular and spatial contexts<sup>139</sup>. Yet these technologies generate complex, noisy and high-dimensional datasets often encompassing multiple modalities (gene expression, epigenetic modifications, metabolite levels and spatial locations). Limited availability of well-annotated reference

datasets and the complex correlations inherent to biological systems further complicate analysis<sup>139</sup>. Thus, deep learning methods, capable of handling high-dimensional data and automatically extracting meaningful patterns, have shown promise in overcoming these challenges<sup>139</sup>. Notable examples include: single-cell multiple reference annotator, which enables cross-dataset annotation while removing batch effects<sup>140</sup>; the single-cell deep contrastive clustering algorithm, which integrates denoising auto-encoders with contrastive learning for robust feature extraction and clustering<sup>141</sup>; or the scSMD model, which has a convolutional autoencoder-based framework<sup>142</sup>.

Beyond descriptive modelling, Mendelian randomization approaches combined with scRNA-seq have been used to infer causal relationships between genes and clinical conditions such as epilepsy<sup>143</sup> or polycystic ovary syndrome<sup>144</sup>. A large trans-omics Mendelian randomization study involving over one million parents identified proteins and metabolites causally linked to lifespan, notably, liver expression and plasma levels of haptoglobin<sup>145</sup>. Generative artificial intelligence is also emerging as a powerful tool in ageing research (for example, in the development of deep ageing clocks)<sup>146</sup> and holds promise for integrating single-cell and spatial omics data from centenarians and their offspring.

## The gut of centenarians

The gut has emerged as a central determinant of healthy ageing and immune regulation<sup>147</sup>. Its microbial ecosystem interacts intimately with host physiology, influencing not only metabolic and gastrointestinal functions but also systemic immunity and inflammation<sup>147</sup>. In centenarians, accumulating evidence suggests that a well-preserved gut-immune axis is a hallmark of exceptional longevity (Fig. 4).

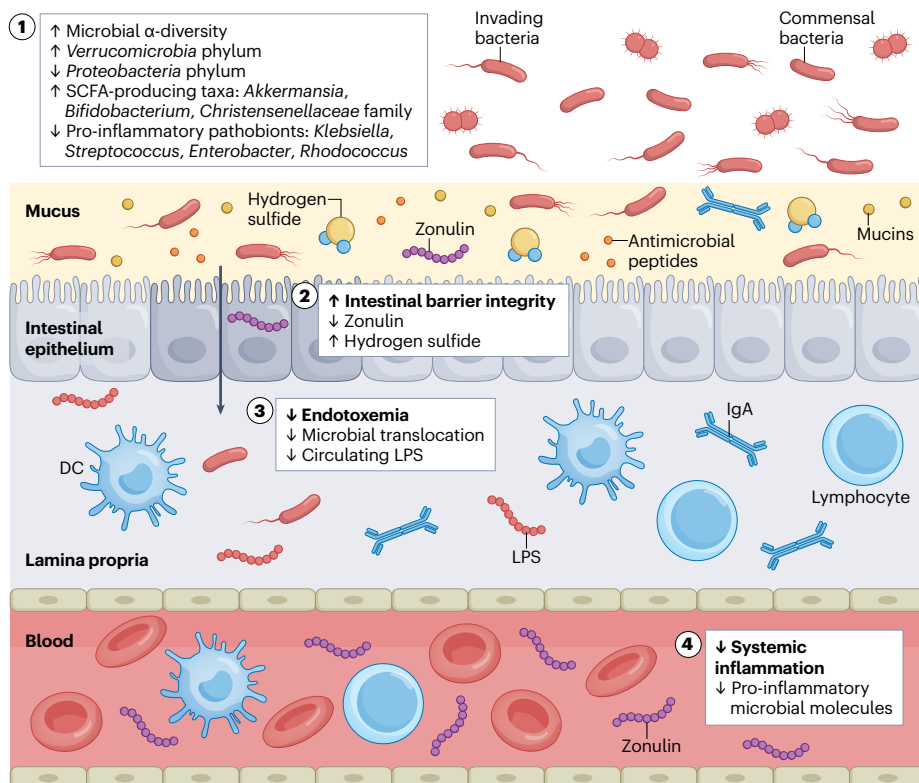
## The ageing gut microbiome

Age-related changes in the gut microbiome include reduced microbial richness, increased instability, a loss of beneficial taxa, such as Clostridiales and Bifidobacterium, and an over-representation of Proteobacteria, particularly pathobionts within the Enterobacteriaceae family<sup>147,148</sup>, including *Escherichia* and *Klebsiella* species<sup>149</sup>. These compositional changes are accompanied by functional losses, notably reduced capacity for short-chain fatty acid (SCFA) synthesis and diminished production of essential amino acids<sup>150</sup>. Collectively, these alterations contribute to a pro-inflammatory milieu and have been linked to immunosenescence, metabolic dysfunction and increased disease susceptibility<sup>147-150</sup>.

Experimental studies support a causal role for the microbiome in ageing. Depletion of gut microbiota in aged mice partially reversed age-associated inflammatory gene expression, whereas faecal microbiota transplantation from young mice restored intestinal barrier integrity and attenuated inflammation<sup>151</sup>. Evidence from progeroid mouse models further underscores this link: these animals exhibit profound intestinal dysbiosis, associated with increased intestinal expression of pro-inflammatory cytokines, expansion of Proteobacteria and Cyanobacteria, and depletion of Verrucomicrobia, including *Akkermansia* species<sup>152</sup>. Notably, oral supplementation of *Akkermansia muciniphila* extended the lifespan of these mice and improved gut barrier function<sup>152</sup>, while reducing immune and inflammatory gene expression in the colon of another mouse model of accelerated ageing<sup>153</sup>.

## The centenarian's gut microbiome

**Diet.** Diet is a major determinant of gut microbial composition, diversity and metabolite output<sup>154</sup>, and thus represents an important



**Fig. 4 | The gut-immune barrier in ageing versus centenarians.** With advancing age, the gut microbiome changes, featuring: reduced microbial α-diversity, loss of beneficial commensal bacterial taxa and enrichment with *Proteobacteria* and other pro-inflammatory pathobionts. These microbial shifts are associated with impaired metabolic output, weakened gut barrier function and greater lipopolysaccharide (LPS) and microbial translocation that can fuel systemic inflammation. By contrast, centenarians commonly show a contrasting pattern consistent with preserved gut health: (1) higher microbial α-diversity with enrichment of short-chain fatty acid (SCFA)-producing bacterial taxa (for example, *Akkermansia*, *Bifidobacterium* and *Christensenellaceae*) and depletion of pro-inflammatory pathobionts (for example, *Klebsiella*, *Streptococcus*, *Enterobacter* and *Rhodococcus*); (2) markers of more preserved barrier integrity (for example, lower serum zonulin) and physiological hydrogen sulfide levels; (3) reduced microbial translocation and lower circulating LPS levels; and (4) dampened pro-inflammatory microbial signals, aligning with lower systemic inflammatory tone. DC, dendritic cell.

contextual factor when interpreting centenarian microbiomes. Although data remain limited, studies that assessed dietary patterns in centenarians report associations between more diverse, plant-forward, less Westernised diets and microbial taxa linked to healthy ageing<sup>155–157</sup>. Consistent with this, centenarians exhibit microbial features resembling those observed under caloric restriction<sup>158</sup>. In Italian centenarians, lifelong exposure to non-obesogenic environments, regular small meals and absence of malnutrition have been described; these patterns may support circadian rhythmicity (including sleep) and promote an adaptive inflammaging profile<sup>158</sup>.

**Diversity.** Across different populations, including Italy<sup>159,160</sup>, China<sup>161–165</sup>, Kazakhstan<sup>166</sup> and Korea<sup>155</sup>, centenarians consistently display gut microbiomes that are distinct from the dysbiosis typical of ageing. Hallmarks include higher  $\alpha$ -diversity, greater species evenness and preservation of beneficial taxa such as *Akkermansia*, *Bifidobacterium* and *Christensenellaceae* (Table 2 and Supplementary Information Table 2), which have been linked to improved metabolic homeostasis, reduced inflammation and favourable immune modulation<sup>163,167–170</sup>. Evidence came from a seminal Italian study describing complex age-related changes, including rearrangement of *Firmicutes*, expansion of *Eubacterium limosum* and enrichment of facultative anaerobes (notably pathobionts) associated with peripheral inflammation<sup>171</sup>, findings that helped to frame later, larger cross-cohort analyses.

A large Chinese cohort study spanning ages 20–117 revealed that centenarians maintained a stable, *Bacteroides*-dominated enterotype, with lower pathobiont burden, resembling that of younger adults<sup>172</sup>. Although *Bacteroides* dominance in individuals over 80 years has been associated with reduced survival in the general population<sup>173</sup>, centenarians appear to be an exception, probably due to concomitant high diversity and enrichment of beneficial taxa<sup>172</sup>. Over longitudinal follow-up, centenarians retained youthful microbial features, including high evenness, low interindividual variation and stable *Bacteroides* abundance<sup>172</sup>. Notably, centenarians with lower microbial evenness showed greater microbiome instability and non-centenarian older adults showed higher abundance of pro-inflammatory taxa such as *Klebsiella*, *Streptococcus*, *Enterobacter* and *Rhodococcus*<sup>172</sup>, highlighting

a candidate microbial signature of exceptional longevity characterized not only by greater diversity and stability but also by selective depletion of potentially harmful taxa.

**Immune function.** Centenarian microbiomes show enhanced functional potential relevant to immune regulation. Metagenomic studies indicate increased capacity for SCFA production<sup>160,164</sup>, which may protect against inflammation and tumorigenesis via SCFA signalling in immune cells<sup>174</sup>. In addition, Japanese centenarians harbour microorganisms capable of producing unique secondary bile acids, including isoallothocholic acid, which exerts potent antimicrobial activity against multidrug-resistant Gram-positive pathogens<sup>175</sup>.

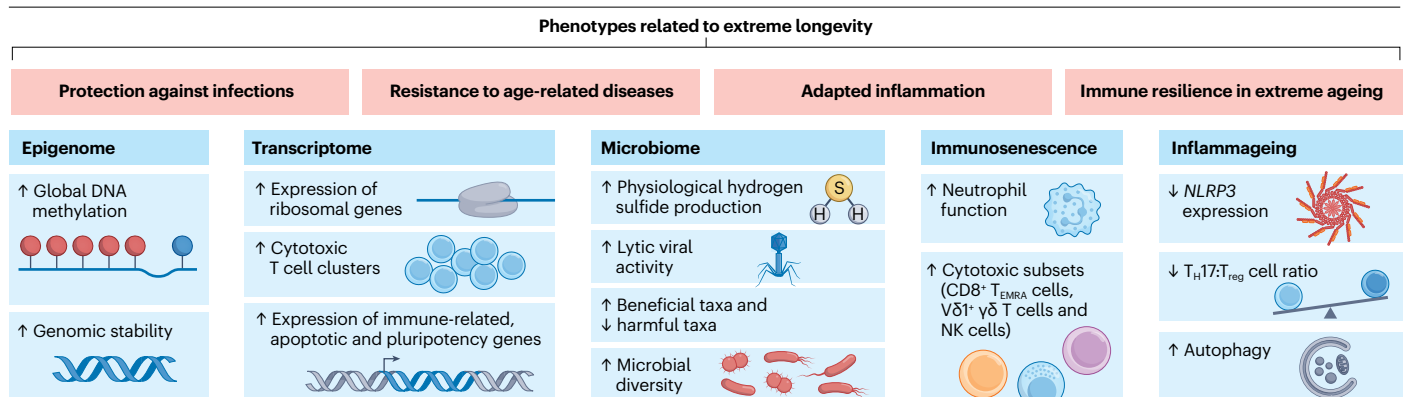
**Virome.** The human gut virome – comprising viruses that inhabit the intestinal environment – remains relatively understudied but may have an important role in immune regulation and ageing<sup>176</sup>. A metagenomic reanalysis of stool samples from centenarians in Japan and Sardinia identified more than 4,400 viral operational taxonomic units, with viral diversity increasing progressively with age<sup>177</sup>. Centenarians showed depletion of shared, core viral taxa and enrichment of rare, previously undescribed viruses<sup>177</sup>, alongside a shift from lysogenic to lytic viral activity. This shift may enhance microbial turnover and potentially ecological stability<sup>177</sup>. Notably, the centenarian virome was enriched in phage-encoded genes involved in sulfur metabolism, with potential implications for epithelial integrity and immune homeostasis<sup>177</sup>. Pre-clinical studies support a role for sulfides in maintaining gut immune function, as their depletion leads to loss of key commensals, such as *Lactobacillus* and segmented filamentous bacteria, and intestinal CD4<sup>+</sup> T cells – particularly T<sub>H</sub>1 cells<sup>178</sup>. Although the immunological functions of the virome remain incompletely understood, current evidence suggests it may contribute to mucosal barrier maintenance and immune regulation in extreme ageing.

### Intestinal barrier integrity

Ageing is associated with progressive intestinal barrier fragility, driven by alterations in tight junction composition, reduced mucus secretion and dysbiosis<sup>151,179–181</sup>. This ‘leaky gut’ facilitates the translocation

**Table 2 | Gut microbiome features associated with immune function in centenarians**

Microbiome functional domain	Core microbiome feature	Potential immune relevance	Key references
Microbiome diversity	Preserved or increased $\alpha$ -diversity and species evenness relative to older adults	Supports microbial ecosystem resilience and limits age-associated inflammatory drift	79,172
Enrichment of immunoregulatory taxa	Increased representation of <i>Akkermansia</i> , <i>Bifidobacterium</i> , <i>Alistipes</i> , <i>Christensenellaceae</i> and short-chain fatty acid-producing <i>Bacteroides</i> spp.	Promotes barrier integrity, immune tolerance and anti-inflammatory signalling	79,152,163,164
Attenuation of pro-inflammatory taxa	Reduced abundance of inflammation-associated pathobionts, including <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Streptococcus</i> and <i>Clostridium</i> spp.	May constrain chronic innate immune activation and systemic inflammaging	164,172
Microbial metabolic specialization	Enhanced microbial pathways involved in bile acid transformation, sulfur metabolism and short-chain fatty acid production	Microbial metabolites shape innate and adaptive immune function, including regulatory T cell and macrophage responses	164,175,177
Sex-specific microbiome signatures	Divergent microbial configurations in male and female centenarians (that is, healthier ageing in the latter)	Indicates sex-dependent microbiome–immune interactions in extreme longevity	165
Virome–microbiome interactions	Increased viral diversity and phage-associated metabolic potential with extreme age	Phage–bacteria dynamics may modulate microbial composition and immune exposure	177
Long-term microbiome stability	Maintenance of youth-associated microbial features across time or generations	Suggests durable microbiome configurations that support immune homeostasis	164,177



**Fig. 5 | Integrative immune and multi-omics features linked to exceptional longevity.** A summary of the traits that align with the phenotypes related to extreme longevity: protection against infection, resistance to age-related diseases, adapted inflammatory tone and preserved immune function. These traits reflect changes at the level of the epigenome, transcriptome

and microbiome, as well as an ability to mitigate immunosenescence and modulate inflammageing. NK, natural killer; T<sub>EMRA</sub>, terminally differentiated effector memory cells re-expressing CD45RA; T<sub>H</sub>17, T helper 17 cells; T<sub>reg</sub>, regulatory T cells.

of microbial products, particularly lipopolysaccharide (LPS), into the systemic circulation, where they activate innate immune pathways via Toll-like receptors and promote low-grade chronic inflammation<sup>182</sup>. Circulating zonulin, a biomarker associated with intestinal permeability<sup>183</sup>, is elevated in healthy ageing<sup>179</sup>, and serum concentrations of LPS-binding protein also increase with age<sup>180</sup>. LPS promotes a pro-inflammatory milieu that can contribute to plaque instability and thrombus formation<sup>182</sup>, and high circulating levels of zonulin and endotoxaemia-related markers (LPS and LPS-binding protein) have been associated with atherothrombosis<sup>182</sup> and CVD<sup>184</sup>. Interestingly, healthy Italian centenarians showed significantly lower serum zonulin and LPS levels compared with sex-matched young patients with acute myocardial infarction<sup>185</sup>, and even significantly lower serum LPS levels than healthy young controls<sup>185</sup>. Together, these findings suggest that centenarians may preserve, or adapt, intestinal barrier function in ways that limit systemic endotoxaemia and downstream immune activation.

Although it remains unclear whether improved intestinal barrier integrity is a driver or a result of healthy ageing, its apparent contribution to immune regulation and inflammation control in centenarians merits further investigation.

## Conclusion and perspectives

Centenarians exhibit distinct immune features that differentiate them from old people who do not achieve exceptional longevity (Fig. 5). These traits may contribute not only to an extremely long lifespan but also to extended healthspan. Particularly in semi-supercentenarians and supercentenarians, youthful features can include attenuated SASP, an apparent mitigation of inflammageing-related pathology, preservation of immune surveillance, sustained gut microbial diversity and relative maintenance of intestinal barrier integrity. In addition, circulating lymphocytes often display gene expression profiles reminiscent of much younger adults, including enhanced autophagy, enrichment of cytotoxic T cell and NK cell subsets and increased ribosomal activity.

Despite these insights, important questions remain. First, besides microbiome assessments most studies in centenarians have

reported peripheral blood analyses, which limits the generalizability of their results to the tissue or organ level. Although this limitation is understandable given feasibility constraints, the bulk of the evidence may not fully capture tissue-resident immune populations or local immune–stromal interactions that are central to ageing and disease processes. On the other hand, a central paradox is the coexistence of elevated circulating pro-inflammatory mediators with apparent protection from inflammation-driven diseases. This suggests that systemic inflammation in centenarians may be qualitatively distinct – less toxic, spatially compartmentalised or counterbalanced by anti-inflammageing mechanisms. Emerging candidates include the cGAS–STING pathway<sup>186,187</sup> and acyl-coenzyme A-binding protein<sup>81,188</sup>, the regulation of which in centenarians remains to be elucidated. Resolving this paradox will require prospective studies capturing individual immunobiographies, encompassing lifelong exposures to infections, vaccines, diet, microbiota and environmental stressors.

Another major gap is the paucity of longitudinal studies following individuals across successive stages of exceptional longevity. Most evidence derives from cross-sectional comparisons, leaving it unclear whether observed immune features represent causal drivers or correlates of survival. Tracking centenarians as they transition to semi-supercentenarian and supercentenarian status may reveal additional adaptations required for survival beyond 100 years and help to define the upper limits of human lifespan.

Finally, the marked heterogeneity among centenarians – ranging from healthy and functionally independent to frail and multimorbid – complicates the identification of universal biomarkers of healthy ageing. In this context, semi-supercentenarians and supercentenarians represent particularly valuable models of disease resistance. Integrating single-cell multi-omics, longitudinal clinical data and environmental exposures, supported by artificial intelligence, will be essential to unravel the complexity of immune ageing. Insights from these exceptional individuals may ultimately guide interventions that not only extend lifespan but also, more importantly, enhance healthspan in ageing populations worldwide.

Published online: 23 April 2026

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## Acknowledgements

A.P.-F. and S.R.A. are supported by US National Institutes of Health grant no. U01 TRO02004 (REACH project). Research by C.F.L. is funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union through project nos. P120/O0645, P123/O0396 and FORT23/O0023, and by the MCIN/AEI/10.13039/501100011033 and «Next Generation EU»/PRTR (project no. CNS2023-149 144144). Research by A.L. and C.F.-L. is funded by the Wereld Kanker Onderzoek Fonds, as part of the World Cancer Research Fund International grant programme (grant no. IIG\_FULL\_2021\_007).

## Author contributions

A.L. and P.C.-B. wrote the first manuscript draft with the help of A.P.-F. All authors researched data for the article, contributed to the discussion of content and also reviewed and edited the article in depth before submission. I.P.-P. created the original versions of the figures. A.P.-F. and P.C.-B. contributed equally. A.L.-S., C.L.-O. and A.L. share senior authorship.

## Competing interests

The authors declare no competing interests.

## Additional information

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41577-026-01291-5>.

**Peer review information** *Nature Reviews Immunology* thanks David Furman and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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