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Toward precision interventions and metrics of inflammaging

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Inflammaging describes a chronic, systemic, low-grade inflammatory state that is recognized as a major risk factor for age-related diseases (ARDs) and a pivotal convergence point of multiple biological mechanisms involved in aging. Here, we discuss the heterogeneity of inflammaging, proposing that it emerges as a consequence of each individual's lifelong exposures to inflammatory stimuli, shaped by a unique combination of genetics, lifestyle, socioeconomic conditions and environmental factors such as infections and pollution. Through this lens, we then discuss measuring inflammaging, describing the development of inflammatory clocks that quantify inflammatory age and show strong associations with ARD incidence as well as how other aging clocks intersect with inflammaging. Finally, we consider interventions that may counteract inflammaging, including nutritional interventions, physical activity and gerotherapies such as senolytics. We propose that deepening our knowledge of the individual nature of inflammaging stands to enhance our understanding of personalized aging trajectories and inform precision interventions.

The concept of inflammaging, that is, chronic, low-grade inflammation that occurs even in the absence of any infection or chronic conditions and is deeply involved in aging and ARDs, has evolved substantially since its inception 25 years ago[1]. The variety of stimuli responsible for and the complexity of the mechanisms underpinning inflammaging are illustrated in Fig. 1. Inflammaging underscores the intricate interplay between aging, metabolism and the immune system[2,3] and can be described as a continuous, dynamic remodeling of the immune system, intimately tied to the concept of immunosenescence, the gradual decline in immune function that occurs with age[4]. A possible conceptualization of this complex scenario (the intriguing relationship between inflammaging and the aging of the immune system) would suggest that they are likely to start as two distinct phenomena that eventually interact with, deeply influence and drive each other, positively or negatively[5,6]. A detailed discussion of key features of immunosenescence and inflammaging is beyond the purpose of this Review, but we like to emphasize that, in each person, a different, specific and personal combination of these two phenomena and mechanisms is involved. Inflammaging is a lifelong process that is suggested to begin in utero[7] and continue through infancy, adulthood and into old age[8], which can preferably be viewed as an adaptive, rather than a solely detrimental process[9]. Thus, aging is not merely a universal process but also an intensely individual experience. Indeed, no two individuals age in precisely the same way, including monozygotic twins[10]. The related concept of immunobiography, which tracks lifelong interactions between an individual's immune system and his or her historical, geographical and socioeconomic status (SES), emphasizes that this interplay is unique to each person[11]. Drawing on the 'Principium Individuationis' (ref. 12) and the concept of immunobiography, data suggest that a major characteristic of the immune system is its largely adaptive nature, which is at the basis of the individual patterns of immunological aging[13,14]. A plethora of individually unique internal and external sources of inflammaging have been identified[3,15,16] (Fig. 1). The accumulation with age, in most organs and systems, of senescent cells with their

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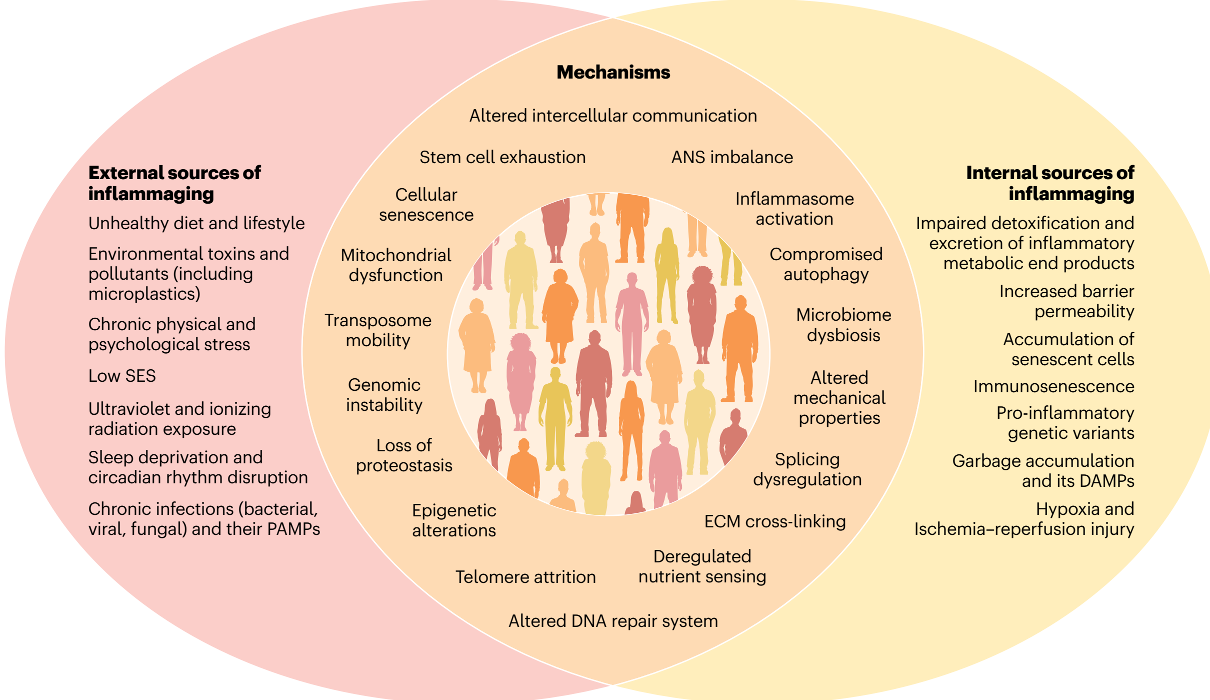

Fig. 1 | Main sources and mechanisms underlying personalized inflammaging. A systematic representation of the main internal and external sources that fuel inflammaging and of the main mechanisms and pathways that underlie personalized inflammaging. ANS, autonomous nervous system; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; PAMPs, pathogen-associated molecular patterns.

senescence-associated secretory phenotype (SASP) is considered a major source of inflammatory stimuli. Senescent cells have a highly heterogeneous distribution and phenotype[17], but their characterization at the individual level is still lacking. Another major role in inflammaging is played by SES. Several studies have shown inverse associations between SES and biomarkers such as C-reactive protein (CRP) and interleukin (IL)-6 (ref. 18). SES deprivation is associated throughout life with abnormal immune and neuroendocrine activity, depending on individual compositional factors[19]. A recent study showed that individuals experiencing social disadvantage had an increased risk of 66 ARDs and that the main enriched pathway involved upregulation of the pro-inflammatory regulator NF-κB and its downstream factor IL-8 (ref. 20). Early life appears to be a sensitive period during which low SES shapes the inflammatory phenotype in adulthood[21]. Growing evidence suggests that SES inequalities in midlife contribute to the prevalence of cardiovascular, metabolic and neurocognitive disorders in later life[22]. Additionally, lower SES and neighborhood SES conditions have been linked to increased exposure to infections and immunosenescence[23,24]. Addressing inflammaging through SES interventions could improve public health and reduce healthcare costs[25]. Future research must explore how SES disadvantage shapes inflammaging across the lifespan. Accordingly, in this Review, we pursue the concept of 'individualized inflammaging' within the framework of 'personalized medicine', emphasizing how a unique combination of exposures can drive individual trajectories of inflammaging and that we are starting to have tools to quantify and modulate the heterogeneous processes of inflammaging at a personal level.

Garbaging and anti-inflammaging

The age-related decrease in physiological barrier integrity[26] and lifelong exposure to damage entail an increase in internal 'garbage' such as endogenous, misplaced or altered molecules resulting from damaged and/or dead cells and organelles (cell debris) and loss of gut intestinal barrier integrity[27]. This 'garbage' represents a major source of inflammatory stimuli, resulting in the expression of inflammaging factors, notably pro-inflammatory cytokines, which gradually accumulate and lead to tissue damage and systemic inflammation[27]. Moreover, since 2000, a number of observations have suggested that inflammaging may be continuously buffered by a variety of emerging, still largely unexplored (particularly at the individual level) compensatory anti-inflammatory mechanisms, which are likely to reflect the ongoing adaptation of the body to the gradual increase in inflammatory stimuli with aging[28]. Thus, pro-inflammatory mediators such as cytokines accumulate over time, leading to tissue damage and systemic inflammation, but anti-inflammatory molecules are also concomitantly produced as a likely compensatory mechanism, suggesting that the body is actively engaged in preserving its functionality[29]. Within this adaptive framework, inflammaging can be seen as both a driver of ARDs[30] and an attempt by the body to maintain homeostasis[31], where inflammation acts as both a friend and a foe. Indeed, healthy centenarians largely free from ARDs exhibit mild inflammaging counteracted by consistent anti-inflammaging[28,32,33]. In summary, a major issue is the lack of longitudinal studies to confirm the cause-and-effect relationship between inflammaging levels and healthy longevity.

Inflammaging in men and women

Men and women differ regarding a variety of features that might potentially influence inflammaging, primarily differences in immune function[4,34,35]. Men exhibit higher inflammatory status and a weaker response against acute stimuli as well as a higher production of reactive oxygen species and less-efficient antioxidant mechanisms[36]. Women generally exhibit lower infection rates than men for various pathogens but face up to a fourfold higher risk of autoimmune diseases, especially during reproductive life[37]. Longitudinal studies revealed that higher IL-6 levels are associated with a faster decline in intrinsic capacity, defined as the physical and mental capacities that an individual can draw on at any point in time, for men but not for women[37,38]. Men and women differ in the rate at which they produce or clear senescent

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BOX 1

XAI

Advanced AI models show much promise in biomedical research and clinical practice but are often poorly interpretable and act as 'black boxes' that undermine the contestability of AI decisions, the possibility to identify and correct mistakes and, after all, the trustworthiness and security of deployment. These concerns led to the development of XAI, which aims to disclose the grounds beyond AI decision-making and to build logically interpretable solutions, despite the nonlinearity and complex architectures of deep models[168]. Global explainability methods disclose the contribution of each feature to the model output in general ('on average'), whereas local explainability disentangles specific decisions of AI. Both issues present major challenges for AI-based biological clocks to meet the needs of (1) understanding the general mechanisms and processes behind age acceleration and (2) delivering personalized reports on the patient's aging profile and associated risk factors. Approaches such as SHAP and GNNExplainer can be adapted to almost any type of input data (tables, images, time series) and different AI models and provide both global and local explainability, thus having the potential to become a gold-standard use in AI-based biological clocks[47].

cells, resulting the accumulation of senescent cells at different rates in various tissues[29,39]. Vasculature is an important target of inflammaging that exhibits notable sex differences, influencing how aging-related pathologies (cardiovascular, metabolic and cerebrovascular diseases) develop and respond to treatment differently in men and women[40,41]. In general, women live longer than men but are more prone to frailty and have worse health at the end of life. This apparent paradox can be largely explained by different age-related trends of inflammaging observed in men and women, fueled by complex interactions between sex-related differences in genetic factors, including maternally inherited mitochondrial DNA genetic variants, age-related X chromosome inactivation skewing, hormonal changes (menstrual cycle, pregnancy, menopause), specific environmental exposure and the microbiome, among others[35,37].

In summary, we suggest that it is important to go further regarding the expected large individuality of inflammaging within each sex or gender[42], taking into account that the limited number of available studies are largely non-longitudinal and therefore likely to be noisy.

How to measure inflammaging

The development of clocks

Inflammaging was first quantified using a cross-sectional limited number of inflammatory factors such as IL-6, IL-1, tumor necrosis factor (TNF) and CRP in peripheral blood[43]. It became increasingly clear that this limited set of markers is insufficient to capture the complexity of inflammaging, so new soluble proteins are emerging as reliable biomarkers. However, translating the biomarkers of inflammaging into clinical settings raises challenges related to repeatability and consistency among different laboratories and times. Methylation markers are more stable, but specific expertise is required to translate methylation analysis into a clinical context. As inflammaging is associated with the development of ARDs, developing biological clocks, built from a larger and possibly longitudinal pool of inflammaging factors, could provide personalized insights into immune aging and disease risk and be used to monitor the efficacy of interventions. In this area, machine learning and artificial intelligence (AI) tools are proving useful in the construction of clocks, and explainable AI (XAI; Box 1) approaches offer the possibility of unveiling, in each person, the contribution of each inflammaging factor to his or her predicted inflammatory age[44]. In summary, we note the consensus on using multidimensional data for clocks and the dichotomy of the choice of data and the ease of measurement (even at the bedside) confronting the stability of measured signals.

Inflammatory clocks and their explainability

An immune aging score correlated with age and predictive of all-cause mortality was proposed in ref. 45. Unlike the majority of clock models regressed on chronological age, it used longitudinal immune cell composition and cytokine profiling to build a nonbranched multidimensional trajectory that described the change of the immune system over time. The longitudinal approach aided noise buffering. Next, a guided autoencoder deep learning network was used to build the iAge clock based on 50 cytokines, chemokines and growth factors with a mean average error (MAE, the performance metrics of clocks) of 15.2 years[33]. Remarkably, C–X–C motif chemokine ligand 9 (CXCL9), a chemokine that modulates multiple genes implicated in inflammation, cellular senescence and vascular aging, manifested the most significant age association iAge and displayed association with multimorbidity, frailty and longevity. The age prediction accuracy of the next inflammatory clocks, named ipAge, was modified and improved regarding two characteristics[46], based on another lineage of 38 chemokine and cytokine markers and a linear regression model. CXCL9 remained the top significant marker, although the next significant markers of ipAge were different. Furthermore, the SImAge clock, based on the deep learning FT-Transformer model, reduced the number of required inflammatory markers to ten and the MAE to 6.94 years[47]. The 'black box' of the SImAge neural network was disclosed by the SHAP value XAI method, providing explainability for the model in general and for each particular participant[47] (Fig. 2). Another cytokine clock (CyClo), based on LASSO regression and the concentration of 24 blood immune proteins, predicted age with a MAE of 6 years and exhibited significant correlation with the default mode, limbic and dorsal attention networks assessed by magnetic resonance imaging[48]. Intersection between the top biomarkers of iAge, SImAge and CyClo clocks is very limited: iAge and SImAge have only CXCL9 in common (Table 1), iAge and CyClo share eotaxin, and SImAge and CyClo overlap in vascular endothelial growth factor (VEGFA), IL-6 and CXCL10. This could be both due to the moderate overlap of the markers assessed by different panels used in the studies and the limited cohort sizes (several hundred to a thousand) and geographical diversity (US and Russia). Developing an inclusive and expectantly more informative panel for inflammatory clocks remains a clear challenge. In any case, as the different clocks appear to work well despite including different sets of inflammatory biomarkers; these results suggest that the components of inflammaging are much more numerous and their interaction is more complex than previously thought. It will be crucial to disentangle the informative importance of the single components of these clocks for the purpose of the personalized approach to inflammaging. Efforts have to be undertaken to ensure worldwide coverage and a more balanced representation of included individuals, with respect to ethnicity, climate, SES and other environmental factors. Addressing the issue, SImAge was used to study inflammatory profiles in the Yakutian population, living in an extremely cold climate[47]. Although a statistically significant SImAge acceleration in comparison with the Central Russia population was not detected, more than a half of its entries demonstrated a significant difference, suggesting a trend toward increased inflammaging in Yakuts. Expanding the factors on which inflammatory clocks are built may also yield improvements; for example, including IL-11 on the basis of its role as a regulatory hub of inflammaging[49]. In summary, it is already possible to estimate the inflammatory age of a person even if the current iAge, SImAge and CyClo clocks show little overlap, probably owing to current limitations of different assays measuring only several dozen inflammatory markers, the cross-sectional nature of data, cohort sizes and

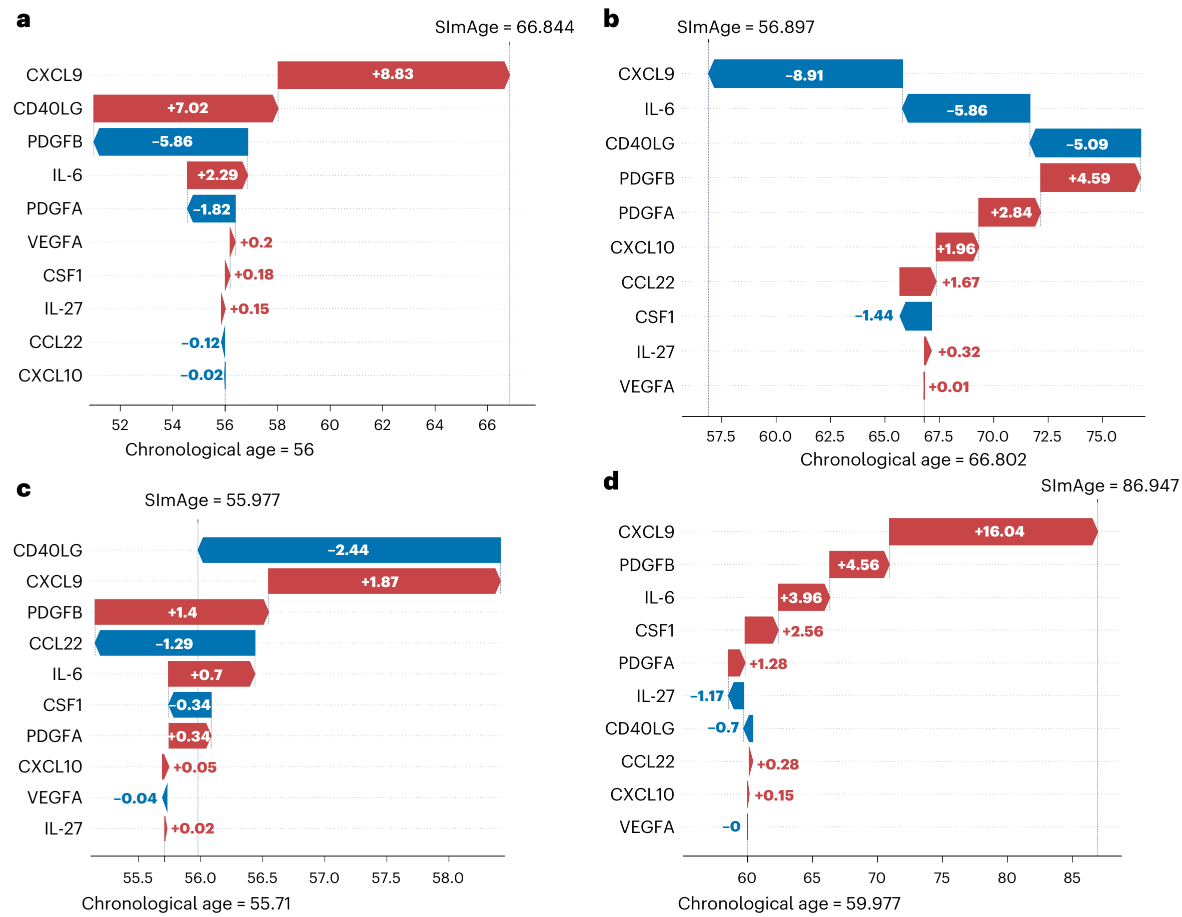

Fig. 2 | Local explainability of AI-based SImAge clock illustrated by waterfall plots. Plots are visualizations of the results[167] of SHAP values in year units and provide specific contributions of inflammatory clock variables to individual age acceleration. **a**–**d**, Data for participants from the control group with positive (chronological age, 66.8 years; inflammatory age, 56.9 years) (**a**), negative (chronological age, 56.0 years; inflammatory age, 66.8 years) (**b**) and negligible (chronological age, 55.7 years; inflammatory age, 56.0 years) (**c**) age acceleration and a patient with end-stage renal disease (chronological age, 60.0 years; inflammatory age, 86.9 years) (**d**), exemplifying high and low inflammation, balanced and pathological individual profiles. For a description of markers, please see Table 1.

geographical diversity. We envisage that this approach, which can be applied early even to adults before clinical manifestation of increased inflammatory age, can help to increase the healthspan of older adults, which is lagging compared to the lifespan.

The contribution of aging clocks to the inflammaging signature

Broader screening of the plasma proteome produced a number of promising, albeit not inflammaging-specific, proteomic clocks. In particular, both linear and nonlinear age dependencies were identified in the levels of 529 plasma proteins[50] as the base for a set of clocks produced by LASSO regression[51]. The recently proposed ProtAge clock, based on the gradient-boosting LightGBM AI model, makes use of the levels of 204 proteins, has a MAE of 4.1 years and is associated with the incidence of 18 major chronic diseases, multimorbidity and all-cause mortality risk[52]. Instructively, inflammation-related CXCL9, growth differentiation factor 15 (GDF15) and CXCL17 are among the top important markers identified by XAI SHAP. Finally, AI can accurately predict Parkinson's disease at up to 7 years to the onset of the motor phase based on just eight inflammation-related proteins[53].

Despite the plethora of epigenetic clocks and the known disagreement between them, they exhibit sensitivity to various pathologies, including those related to the immune system[54–56]. The lack of their specificity to inflammation can be addressed by inferring the levels of circulating proteins by means of DNA methylation (DNAm) data. In particular[57], associations of DNAm were identified with some key proteins of the immune system, such as CD48, CD163, CXCL10, CXCL11, LAG3, FCGR3B and B2M. Stevenson et al.[58,59] built DNAm scores that estimate the levels of CRP and IL-6 and demonstrated their sensitivity to cognitive abilities, in contrast to their original protein counterparts. Later, EpiScores, elastic net-based DNAm estimators for 109 plasma proteins, were developed[60]. The selected list proved to be enriched for immune system pathways and therefore appears promising for characterizing inflammation-related morbidities. GrimAge and EpiScore composite variables were incorporated to construct epigenetic chronological and biological age estimators by elastic net with a MAE of 2.3 years[61]. All these proteomic and hybrid proteomic–epigenetic clocks have the potential to measure aging and inflammaging[62] and thus to identify different types of aging patterns in different individuals, a phenomenon defined as the 'ageotype'[63,64].

Recently, it was demonstrated that it is possible to generate a biological clock using microRNA (miRNA) profiles to predict biological age related to human blood[65,66] or skin[67]. Several settings of miRNAs have been proposed as potential biomarkers of inflammaging, even if an inflammatory-related miRNA-specific clock has not been developed yet. In summary, we stress that the major aim of inflammatory clocks is not to predict chronological age but to quantify the possible difference between the chronological age of a person (assumed an objective reference point) and their inflammatory age and even more in the specific composition and ranking of their personal inflammatory clock.

Table 1 | SImAge and iAge markers of inflammaging according to their relevance to chronic diseases and cost

Marker	Relevance to ARDs	Cost[a]	Routine blood test
IL-6	Key pro-inflammatory cytokine, associated with multiple ARDs and mortality	Moderate	Yes
IL-1β	Pro-inflammatory cytokine, linked to systemic inflammation	Moderate	Yes
Leptin	Adipokine, associated with metabolic disorders and inflammation	Moderate	No
PAI1	Fibrinolysis regulator, linked to thrombosis and aging	Moderate	No
CSF1	Macrophage regulator, linked to inflammation and metabolic disorders	High	No
PDGFA	Growth factor, associated with fibrosis and vascular disorders	High	No
CXCL10	Chemokine, marker of immune activation and inflammation	High	No
CXCL9	Chemokine, reflects T cell activation and chronic inflammation	High	No
CCL22	Chemokine, linked to immune regulation and inflammation	High	No
PDGFB	Growth factor, involved in tissue remodeling and fibrosis	High	No
VEGFA	Vascular growth factor, associated with angiogenesis and inflammation	High	No
Eotaxin	Chemokine, linked to allergic inflammation and immune aging	High	No
MIP1α	Chemokine, reflects immune cell activation	High	No
IL-5	Cytokine, regulates eosinophils and allergic reactions	High	No
IFNα	Antiviral cytokine, associated with autoimmunity	High	No
IL-4	Regulatory cytokine, influences immune response	High	No
TRAIL	Cytokine, linked to cell death and inflammation	High	No
IFNγ	Pro-inflammatory cytokine, marker of T cell activation	High	No
CXCL1	Chemokine, attracts neutrophils during inflammation	High	No
IL-2	Cytokine, regulates T cell proliferation	High	No
TGFα	Growth factor, associated with tissue remodeling	High	No
LIF	Cytokine, influences cell differentiation and inflammation	High	No
IL-27	Cytokine, pro- and anti-inflammatory effects, regulates helper T cell development	High	No
CD40LG	Cytokine, expressed on the surface of T cells, regulates B cell function by engaging CD40 on the B cell surface	High	No

[a]Moderate cost estimated on current pricing: <$10; high cost, >$10.

How to treat inflammaging

Inflammaging is fueled by a complex interaction of genetic, lifestyle and environmental factors. Research has increasingly focused on ways to mitigate or delay inflammaging, with particular attention to interventions at relatively low cost and with great potential feasibility involving nutrition and lifestyle, such as the Mediterranean diet[68] and physical activity[69] (Fig. 3). These interventions not only have the capability to reduce inflammation, but also may foster healthy aging by improving gut microbiota composition, influencing gene expression and promoting epigenetic rejuvenation[70–72]. At the same time, a new class of drugs called geroprotectors, including senolytics, has emerged as compounds able to prolong the lifespan and healthspan of organisms by mitigating specific targets of inflammaging such as metabolism, oxidative stress and cell senescence[73]. Two major points emerge from the available literature related to such interventions: in general, individual variability regarding the effect of the intervention on inflammatory parameters is not reported, and longitudinal studies are lacking.

Inflammaging and nutrition

Nutrition represents a pervasive tool able to finely modulate the pro-inflammaging and anti-inflammaging balance and thus the phenotype throughout life[74]. A diet rich in anti-inflammatory compounds can help to lower the risk of chronic diseases, improve immune function and potentially decelerate the aging process[75]. Processed foods that are high in sugar and saturated fats are known to trigger inflammatory pathways, whereas whole foods, which are abundant in vitamins, minerals and antioxidants, help to counteract these effects[76]. Over the past decade, nutritional science has highlighted several promising dietary strategies for extending healthspan and addressing the aging process[77]. Caloric restriction, intermittent fasting and time-restricted eating[78] have demonstrated significant effects on metabolic health, inflammation and lifespan across various species[79], although their relevance to humans is still under investigation[80].

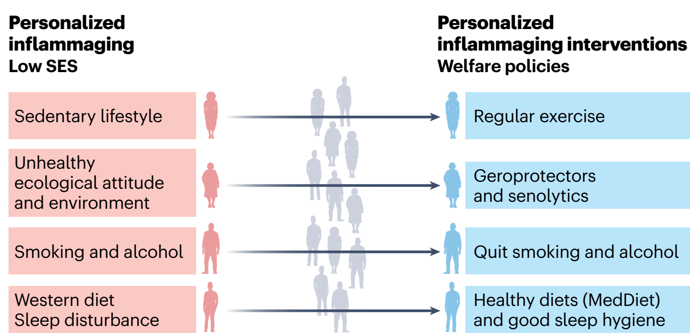

Fig. 3 | Personalized anti-inflammaging treatments. The main strategies to mitigate or delay inflammaging in a single individual are illustrated. Particular attention is paid to general feasibility and low cost. MedDiet, Mediterranean diet.

Recent clinical trials have positioned the Mediterranean diet as a promising dietary intervention to modulate inflammaging[81,82].

Mediterranean diet and anti-inflammaging. The Mediterranean diet has been associated with a reduced risk of chronic diseases and improved metabolic health[83], although its direct impact on longevity remains to be fully elucidated. It has also been suggested as a potential anti-inflammaging strategy owing to its anti-inflammatory dietary profile[84], although evidence from clinical trials, such as the PREDIMED study, relies on a limited set of inflammatory markers (for example, CRP and IL-6). In clinical settings, the Mediterranean diet is typically defined by a high intake of plant-based foods (vegetables, fruits, legumes, nuts and whole grains), frequent use of extra virgin olive oil as the main fat source, moderate consumption of fish, poultry, dairy and red wine[68] and limited intake of red meat, processed foods and sweets, while also acknowledging that variations in dietary patterns exist across different Mediterranean populations[85]. Key benefits of the Mediterranean diet include enhancement of satiety, reduced postprandial glycemia and controlled insulin secretion due to its focus on low-glycemic index carbohydrates and abundant dietary fiber. Although these features have been linked to improved health outcomes and reduced inflammation, their classification as anti-aging interventions remains speculative and subject to ongoing research. Our group coordinated the NU-AGE study (NCT01754012), a randomized controlled trial aimed at reducing inflammaging with a 1-year Mediterranean diet intervention[86] in a gender-balanced cohort of 1,200 participants over the age of 65 from five European countries[87]. Compared with a randomly chosen half of the participants who continued their habitual diet, people in the other half who consumed the Mediterranean diet rejuvenated their epigenetic age (measured by the DNAm clock)[70]. Moreover, high adherence to Mediterranean diet counseling significantly improved many other parameters such as intake of nutrients (macronutrients and micronutrients)[88,89], cognitive status[90], osteoporosis and frailty[91,92]. Of particular interest is that the Mediterranean diet induced health and inflammatory improvement (decrease in CRP and IL-17 levels) while increasing the abundance of specific gut microbiome taxa that are negatively associated with pro-inflammatory markers[72,93]. Indeed, inflammaging appears to be related to a specific signature of the gut microbiome in older adults[94]. Moreover, the gut microbiome regulates immunosenescence[95], being at the center of a functional network including many organs and systems such as brain, liver, kidney and muscle. Targeting the gut microbiome has therefore emerged as a promising strategy to counteract inflammaging. In particular, specific probiotic strains (for example, *Lactobacillus plantarum*, *Bifidobacterium longum*) have been shown to reduce systemic inflammation and modulate immune responses in aged mice and older adults[96,97]. Prebiotic interventions, such as inulin or fructooligosaccharides, have also been shown to enhance short-chain fatty acid production and reduce pro-inflammatory cytokine levels[98]. Clinical evidence from the ELDERMET and NU-AGE studies supports the link between gut microbial composition, diet and inflammatory status in older adults[72,99]. Additionally, early-phase trials on fecal microbiota transplantation in older adults have demonstrated feasibility and potential immunomodulatory effects[100,101], although further studies are needed. Interestingly, the NU-AGE trial revealed variations across participants from the five countries and between genders as well as a large heterogeneity of responsiveness to the Mediterranean diet at the individual level[102,103]. This heterogeneity highlights the importance of personalized nutritional approaches, as genetic factors, baseline inflammatory status and microbiome composition may all influence the individual's response to dietary interventions, paving the way for future personalized recommendations. On the whole, available data suggest that the Mediterranean diet can fine-tune the balance between pro-inflammaging and anti-inflammaging, delaying ARDs and probably acting as a form of chronic hormesis[31,68]. Hormesis assumes that extremely low doses of poisonous compounds, such as those present in most edible vegetables, can exert mild stress that in turn would enhance body cellular and molecular defense mechanisms. Indeed, the Mediterranean diet contains bioactive compounds or 'hormetins', such as resveratrol, quercetin and phenolic antioxidants, which activate pathways including NRF2, NF-κB, mTOR and sirtuins. Interestingly, certain hormetins are also considered geroprotectors and senolytics (see the sectons Geroprotectors targeting inflammaging and Senolytics targeting inflammaging). In summary, the Mediterranean diet can be considered an anti-inflammatory diet, but future trials are needed to evaluate its efficacy at the individual level.

Inflammaging and physical activity

Physical activity is a cornerstone for healthy aging, combating inflammaging and immunosenescence with systemic and cellular benefits[104]. Sarcopenia, which is strongly linked to frailty, is highly correlated with inflammaging[105]. The urgent need for a personalized approach regarding evidence-based exercise prescriptions that align with individual health profiles and conditions, moving beyond generic activity guidelines, has been stressed recently. Indeed, tailored and structured exercise prescription sequences for older adults are highly recommended[106]. Regular aerobic exercise reduces systemic inflammation, although its effectiveness depends on factors such as age, type, duration and intensity of training[69,107]. The efficacy of exercise in reducing inflammaging appears to be highly individual, influenced not only by sex differences but also by genetic factors, baseline inflammatory status, age of exercise initiation and pre-existing health conditions, which suggests the need for personalized exercise prescriptions integrating strategies that align dietary and exercise interventions to support healthy and active aging[108] Exercise initially induces pro-inflammatory cytokine production from muscle contraction but later triggers anti-inflammatory molecules, with systemic involvement of the immune system and other organs such as the liver, adipose tissue and gut, benefiting trained individuals through a long-term systemic effect. The anti-inflammatory effects of exercise are partly mediated by myokines (also known as 'exerkines'), such as IL-6, IL-10 and IL-15, which counteract inflammation by promoting anti-inflammatory molecules such as IL-1RA and IL-10 (refs. 109–112). In this regard, to explain why trained older adults show lower circulating IL-6 levels, our group hypothesized also in this case a hormetic effect, in which continuous, mild exercise is able to induce adaptive, beneficial responses[113]. Lifelong running has been shown to reduce inflammaging and extend healthspan in mice[114]. Human studies indicate that moderate aerobic exercise and high-intensity interval training lower IL-6 and CRP levels in older sedentary men[115]. Resistance training also reduces muscle TNF expression in older adults, further decreasing inflammation[69,116]. Regular exercise can also modify body composition and respiratory fitness, improving muscle mass, reducing visceral fat tissue (a source of pro-inflammatory signals)[117–119] and enhancing antioxidant defense mechanisms[117]. However, sex differences exist, with women experiencing less-pronounced anti-inflammatory benefits from lifelong aerobic exercise than men[120,121]. Finally, exercise has been found to interact with gut microbiota, highlighting a bidirectional link between skeletal muscle and gut microbiota: the muscle–gut axis. Exercise fosters beneficial microbial species, while gut-derived metabolites such as short-chain fatty acids enhance muscle metabolism and reduce inflammation. On the other hand, dysbiosis contributes to muscle atrophy and metabolic dysfunction[122], while increased abundance of Christensenellaceae, Porphyromonadaceae and Rikenellaceae correlates with lower visceral adiposity[123]. Interestingly, protein supplementation with exercise further reduces inflammation[124], and regular exercise paired with the Mediterranean diet supports cardiovascular health and mental well-being[125]. In summary, combining exercise with proper nutrition appears to amplify its benefits, providing a holistic strategy to combat inflammaging and promote healthy aging, reducing malnutrition and preserving muscle mass, cognitive function and quality of life.

Inflammaging and sleep quality

Emerging evidence highlights that sleep disturbances, such as insomnia and obstructive sleep apnea, exacerbate inflammaging. Sleep deprivation increases levels of pro-inflammatory cytokines and CRP, contributing to chronic conditions such as heart disease and diabetes[126]. Conversely, good sleep quality reduces age-related inflammation, and higher sleep efficiency correlates with lower IL-6 levels[127,128]. Sleep is crucial for clearing inflammatory stimuli or 'molecular garbage' produced by brain cells during normal activity[27,129]. In particular, microglial senescence, which is highly sensitive to aging, is a key driver of neurodegenerative progression and a promising therapeutic target[128]. Accumulating senescent microglia, which are essential for clearing cellular debris, accelerate brain aging, inflammaging and susceptibility to neurodegenerative diseases. Similarly, the glymphatic system, which is facilitated by aquaporin 4 (AQP4) on astrocyte endfeet, clears brain metabolites and maintains homeostasis. Dysfunction of this system leads to protein accumulation (amyloid-β and tau), neuroinflammation and ARDs, sharing features with aging, including mitochondrial dysfunction, oxidative stress and chronic inflammation[130]. A recent model predicted that insufficient sleep increases senescent glia accumulation, surpassing a critical inflammaging threshold. This progression becomes irreversible even with restored sleep, driving inflammaging further. Reversing this scenario requires reducing senescent glia below the threshold[131]. Tools such as the Cognitive Clock might reflect brain inflammaging levels and correlate with age acceleration[132]. This machine learning-based Cognitive Clock is indeed able to predict, with high accuracy, not only chronological age but also epigenetic and phenotypic ages[132]. The sleep–inflammation relationship is bidirectional and mediated by the gut–brain axis[122]. Chronic inflammation disrupts sleep patterns, creating a cycle that accelerates aging. Insomnia, which is common among middle-aged and older adults, worsens with age, impairing quality of life and increasing risks for heart failure and neurodegenerative and metabolic diseases[133]. Distinct gut microbiota profiles can help to stratify insomnia types, identify at-risk individuals and enable microbiota-based diagnostics and therapies[134,135].

In summary, prioritizing sleep hygiene and addressing sleep disorders are critical for reducing inflammation and promoting healthy aging.

Geroprotectors targeting inflammaging

Unlike nutraceuticals, which are dietary supplements that maintain physiological functions without necessarily affecting aging mechanisms, geroprotectors are compounds that target the fundamental causes of aging and ARDs, their primary criterion being to extend longevity while preserving physiological function and health-related quality of life[136]. Accordingly, we focus here on major geroprotectors and a few nutraceuticals that share characteristics with geroprotectors. Geroprotectors can be classified by their mechanisms of preventing macromolecular damage or slowing aging-related gene activity and work through multiple pathways including mTOR, NF-κB, stress response factors (FOXO3A, AMPK, NRF2, HIF1, HSF1), mitochondrial function improvement and epigenetic mechanisms[73], all of which are mechanistically linked to inflammation regulation (Table 2). Anti-inflammatory drugs such as aspirin and ibuprofen have shown life-extending properties in various organisms[137,138]. Natural geroprotectors such as vitamin D, curcumin, resveratrol, polyphenols and terpenoids influence inflammaging predominantly through indirect mechanisms rather than direct anti-inflammatory action[139–141]. These compounds primarily modulate upstream cellular pathways including NRF2, AMPK, SIRT1 and FOXO3 signaling, which subsequently leads to downregulation of inflammatory processes. This distinction is important when considering personalized approaches to inflammaging, as individual variations in these primary target pathways may account for the heterogeneous responses observed in clinical studies. Understanding these indirect mechanisms helps to explain why geroprotector efficacy may vary substantially among individuals and why biomarker profiles reflecting specific cellular pathway activity might better predict treatment response than general inflammatory markers alone. Transcriptomic data from major geroprotective interventions suggests inflammation reduction as a core anti-aging mechanism[142]. Currently, several clinical studies are underway in which the effectiveness of potential geroprotectors is studied using inflammaging markers. For example, metformin is used by the Targeting Aging with Metformin (TAME) trial with a comprehensive inflammaging biomarker panel, including classical inflammatory markers (IL-6, TNF receptor I or II, CRP) alongside novel anti-aging factors such as GDF15 (ref. 143). Both preclinical and clinical results indicate metformin's effectiveness in reducing IL-6 and CRP levels[144]. Rapamycin, an mTOR inhibitor, extends lifespan in *Drosophila melanogaster*[145] and mice[146]. In humans, clinical investigations of rapamycin have incorporated comprehensive immunological analyses, including assessment of immune cell senescence markers and inflammatory mediators in peripheral blood samples[147]. A randomized, double-blind multicenter trial of rapamycin (2 mg per m^2 per day or 1 mg per m^2 per day versus placebo) in 63 patients with amyotrophic lateral sclerosis[148] demonstrated anti-inflammatory effects through decreased IL-18 expression (both messenger RNA and protein levels) and beneficial changes in immune cell populations. Finally, spermidine ameliorates colitis via induction of anti-inflammatory macrophages and prevention of intestinal dysbiosis[149].

The effectiveness of geroprotectors is likely to vary between individuals owing to differences in their inflammaging mechanisms and baseline inflammatory profiles. Future research should focus on identifying biomarkers that can predict individual responsiveness to specific geroprotector compounds.

In summary, research on inflammaging-targeted geroprotectors has demonstrated their potential in delaying aging processes, promoting healthspan and reducing disease severity, and we suggest that future studies may benefit from using the inflammaging clocks discussed above. However, challenges such as the lack of a unified theory of aging, complex classifications, discrepancies in mechanisms and difficulties in translating findings to human applications need to be addressed. Further research and well-designed clinical trials are essential to fully realize the potential of these interventions in combating inflammaging and promoting healthy aging.

Senolytics targeting inflammaging

A vast and growing literature, using a variety of biological clocks and markers, suggests that aging is malleable and that the aging rate can be not only delayed but also reversed. The same considerations can be applied to inflammaging. Cellular reprogramming has demonstrated rejuvenating effects both ex vivo and in vivo, potentially by deactivating stress signals from damaged cells, which can reduce inflammation[150]. Heterochronic parabiosis, which involves the joining of circulatory systems between young and old organisms, can reduce systemic inflammation by diluting pro-inflammatory mediators in old blood or introducing youthful anti-inflammatory factors as well as by reducing the burden of senescent cells in the older organism[151]. Senolysis, the selective elimination of senescent cells through senolytic agents, reduces inflammaging, distinct from senomorphic compounds, which attenuate the SASP through modulation rather than removal of senescent cells[152]. Senolytics are synthetic or natural compounds that induce apoptotic cell death in senescent cells by affecting several prosurvival pathways[153]. This mechanism is crucial, because senescent cells, despite high levels of DNA damage, evade apoptosis and contribute to the pro-inflammatory environment characteristic of inflammaging[154]. As with other inflammaging interventions, individuals may respond differently to senolytic treatments depending on their unique senescent cell burden, tissue distribution and inflammatory signature, highlighting the importance of personalized approaches to senolytic therapy. Senolytics such as dasatinib, navitoclax and venetoclax have demonstrated anti-inflammatory effects, ameliorating chronic inflammation[155]. Clinical trials are currently underway to assess the therapeutic efficacy of senolytics in mitigating various age-related morbidities, including diabetes, idiopathic pulmonary fibrosis, Alzheimer's disease, COVID-19, osteoarthritis, osteoporosis, eye diseases, bone marrow transplant and conditions that affect survivors of childhood cancer[156]. Preliminary results from these trials are promising, suggesting that senolytics can

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Table 2 | Geroprotectors and senolytics targeting inflammation

Geroprotector	Model organism	Health condition	Readouts and endpoints	Key findings	Reference
Rapamycin	Mice	Genetically heterogeneous healthy aging	Lifespan, age-related pathologies	Extended lifespan even when administered late in life	146
	D. melanogaster	Healthy	Survival	Improved survival	145
	Humans	Amyotrophic lateral sclerosis	IL-18 expression, immune cell populations	Decreased IL-18 expression, beneficial changes in immune cell populations	148
	Humans	Healthy adults	Immune cell senescence markers, inflammatory mediators	Results pending (referenced as ongoing clinical investigation)	147
Metformin	Humans	Polycystic ovary syndrome	Serum CRP and IL-6 levels	Reduction in inflammatory markers	144
	Humans	Various (TAME trial)	Multiple inflammaging biomarkers including IL-6, TNF receptor, CRP, GDF15	Trial in progress	143
Ibuprofen	Yeast	Healthy	Longevity, tryptophan import	Enhanced longevity through inhibition of tryptophan import	137
	D. melanogaster	Healthy	Longevity	Extended lifespan	138
Acarbose	Humans	Adults (meta-analysis of RCTs)	Inflammatory cytokines and adipokines	Reduction in inflammatory markers	165
Spermidine	Mice	Colitis model	Macrophage phenotype, intestinal microbiota	Ameliorated colitis via induction of anti-inflammatory macrophages and prevention of intestinal dysbiosis	149
Terpenoids (natural geroprotectors)	Various (review paper)	Healthy and disease models	NRF2, AMPK, SIRT1 activation	Potential geroprotective effects through multiple pathways	141
Polyphenols (natural geroprotectors)	Various (review paper)	Healthy and disease models	NRF2, AMPK, SIRT1, FOXO3 activation	Potential geroprotective effects through multiple pathways	140
Dasatinib+quercetin (senolytics)	Aged rats	Normal aging	Cognitive abilities, inflammation, hippocampal synaptic plasticity, histone H3 methylation	Improved cognitive abilities, alleviated inflammation, changes in hippocampal synaptic plasticity and histone methylation profile	153
	Humans	Diabetic kidney disease	Circulating SASP factors (IL-1α, IL-6, MMP9, MMP12)	Reduction in SASP factors	157
	Mice	Aging model	Adipose tissue inflammation, metabolic function	Attenuated adipose tissue inflammation, improved metabolic function	166
Navitoclax and venetoclax (senolytics)	Zebrafish	Chronic inflammation models	Anti-inflammatory effects	Senescence-independent anti-inflammatory activity	155

RCT, randomized controlled trial.

decrease senescent cell numbers, reduce inflammation and alleviate frailty[156]. A clinical trial of dasatinib plus quercetin in individuals with diabetic kidney disease showed a reduction in circulating SASP factors including IL-1α, IL-6 and the metalloproteinases MMP9 and MMP12 (ref. 157).

On the whole, senolytics have been shown to delay, prevent or alleviate various age-related conditions, including frailty, cancers, and cardiovascular, neuropsychiatric, liver, kidney, musculoskeletal, lung, eye, hematological, metabolic and skin disorders. Despite these encouraging findings, the use of senolytics is not without risks. A primary concern is the potential for off-target effects, as senolytics target pathways that are also present in non-senescent cells. For example, inhibition of B cell lymphoma 2 (BCL2) family proteins can lead to unintended apoptosis in healthy cells, potentially causing adverse effects[158]. Furthermore, the long-term effects of senolytic therapy remain unclear, necessitating further extensive clinical trials to thoroughly evaluate the safety and efficacy of these agents. Targeting inflammaging is complex, as immune responses must be carefully modulated to avoid exacerbating inflammation or causing further tissue damage[105].

In conclusion, senolytics represent a promising avenue for treating age-related dysfunctions and diseases by targeting and eliminating senescent cells, potentially improving healthspan and lifespan. However, thorough investigation into the long-term safety and efficacy of these drugs is imperative to ensure their safe application in humans. Moreover, the possible predicted marked heterogeneity in individual burden and distribution of senescent cells and response to senolytics underscores the need for personalized approaches to such anti-inflammaging treatment (Fig. 3).

Conclusions and perspectives

The present Review suggests that inflammaging appears to be highly individualized, particularly in humans, owing to the complexity and intricacy of factors that characterize the aging of *Homo sapiens*, and that emerging approaches, such as the use of inflammaging-specific biological clocks, could enable more personalized strategies for managing inflammaging in the future. Indeed, the results of inflammatory clocks, and particularly of the one using XAI, show that (1) inflammaging is different among individuals, being the stratification of the components specific to each person; and (2) inflammatory age can be poorly related to chronological age, as is the case for many other biological clocks, being rather a function of exposure to a 'personal inflammatory load'. Thus, cross-sectional inflammaging data should be considered

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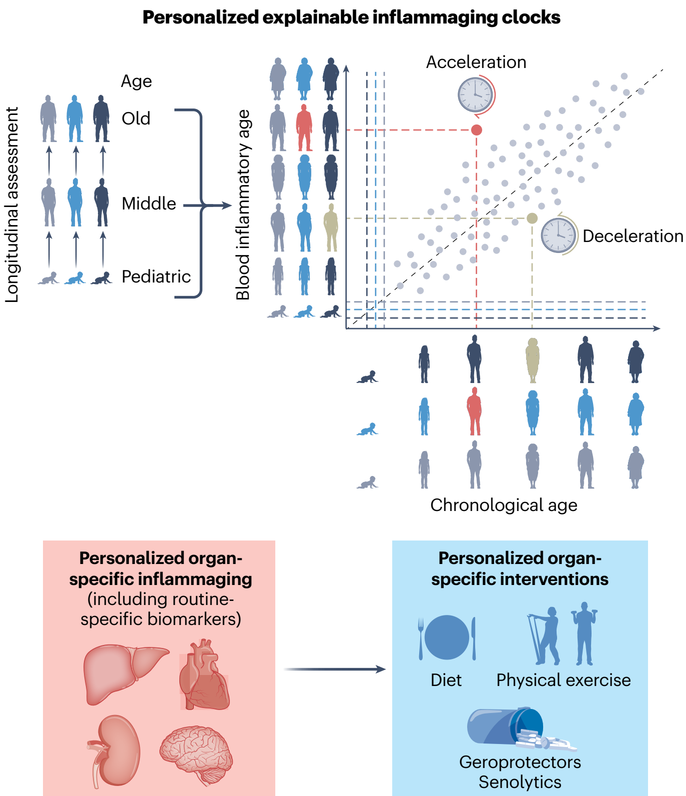

Fig. 4 | Personalized explainable inflammaging clocks. Recent progress in the field makes it desirable and feasible to conduct large, individualized, longitudinal studies in which inflammaging clocks, possibly organ specific, are measured in the same person at different time points in the lifespan. Measurement of blood-based inflammaging clocks in the same individual and routine parameters aided by the latest generation of epigenetic clocks should improve the early quantification of the aging rate at the individual level.

preliminary owing to their possible high noise, and longitudinal studies in the same person are urgently needed to check their temporal reliability (Fig. 4). Another related factor to consider is that soluble proteins such as those measured in inflammatory clocks are technically easy to measure, even in a clinical setting, but their biological stability shows high fluctuation.

There is an urgent need to address the heterogeneity of inflammaging, particularly as it may vary across different populations, especially those outside affluent, high-income groups. Geographic and demographic evidence suggests that aging and longevity are influenced by a complex interplay of genetics, environment and chance, and these factors differ substantially across regions and time. Therefore, we can expect inflammaging to manifest in specific ways in different populations, underscoring the need for studies that include diverse ethnic and environmental backgrounds. This is especially important for indigenous populations such as, for example, those in Brazil[159], Yakutia[44], Bolivia and Malaysia[160], where distinct patterns of inflammaging are emerging and warrant closer investigations[47,159].

Another key point is that the majority of current data on inflammaging in older individuals, including centenarians, lacks personalized information, as most studies report aggregated data that do not account for individual differences. This limits the potential for tailored interventions. In particular, it remains largely unknown how particular interventions such as diet, exercise, geroprotectors and senolytics will intersect with the individualized factors that drive inflammaging to modulate its phenotype. Looking ahead, it will be crucial to quantify inflammaging at system and organ levels, providing essential information for physicians to implement more targeted, early and personalized interventions. As the degenerative diseases of aging start years before they manifest clinically[161], it could be worthwhile to measure inflammaging in adults who are still seemingly healthy to identify individuals at risk for these conditions. In this regard, a substantial challenge remains the lack of methodologies to quantify the number, anatomical distribution and type of senescent cells in individuals, as these cells are considered a major source of inflammaging. Understanding the role of senescent cells in inflammaging across different organs and time points is a crucial area for future research.

The use of anti-inflammatory monoclonal antibodies alone or in combination could be envisaged to counteract inflammaging at the individual level on the basis of the results of the personalized inflammatory profile[162]. Nevertheless, the long-term safety, immunosenescence risk and economic viability of such interventions remain critical areas for further investigation. From a short-term perspective, there is an urgent need to establish a consensus on a standardized set of inflammaging markers for first-line screening, which could be used routinely in large populations of adults and older individuals. This strategy could eventually be followed by more specific and expensive assessments, if needed. Such an approach would complement initiatives such as the transdisciplinary Clin-STAR group on inflammaging[163], fostering a broader, more inclusive approach to understanding and addressing inflammaging. This two-step strategy could also be instrumental in exploring new, previously unrecognized situations in which inflammaging plays a role, expanding our knowledge of its impact and potential interventions[164].

From a longer-term perspective, a pervasive application of personalized and possibly organ-specific inflammaging clocks could offer a cost-effective, preventative public health strategy. Moreover, by integrating these tools with other clocks, such as brain clocks and the most advanced epigenetic clocks, it should be possible to reach a remarkable level of precision in quantifying the individual risk of specific ARDs, paving the way to early targeted interventions. Ultimately, we envision large, individualized, longitudinal studies in which inflammaging clocks, possibly tailored to specific organs and combined with other clocks, are measured at multiple time points across a person's lifespan, offering an unprecedented level of precision in aging research.

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Author contributions

C.F. and A.S. conceived the Review and wrote the first draft of the manuscript. F.O., A.M. and M.I. provided constructive input and wrote additional sections in subsequent revisions of the manuscript. All authors approved the final version of the Review and its tables, box and figures.

Competing interests

The authors declare no competing interests.

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