Aging and Inflammation

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Aging can be conceptualized as the progressive disequilibrium between stochastic damage accumulation and resilience mechanisms that continuously repair that damage, which eventually cause the development of chronic disease, frailty, and death. The immune system is at the forefront of these resilience mechanisms. Indeed, aging is associated with persistent activation of the immune system, witnessed by a high circulating level of inflammatory markers and activation of immune cells in the circulation and in tissue, a condition called "inflammaging." Like aging, inflammaging is associated with increased risk of many age-related pathologies and disabilities, as well as frailty and death. Herein we discuss recent advances in the understanding of the mechanisms leading to inflammaging and the intrinsic dysregulation of the immune function that occurs with aging. We focus on the underlying mechanisms of chronic inflammation, in particular the role of NF-κB and recent studies targeting proinflammatory mediators. We further explore the dysregulation of the immune response with age and immunosenescence as an important mechanistic immune response to acute stressors. We examine the role of the gastrointestinal microbiome, age-related dysbiosis, and the integrated stress response in modulating the inflammatory "response" to damage accumulation and stress. We conclude by focusing on the seminal question of whether reducing inflammation is useful and the results of related clinical trials. In summary, we propose that inflammation may be viewed both as a clinical biomarker of the failure of resilience mechanisms and as a causal factor in the rising burden of disease and disabilities with aging. The fact that inflammation can be reduced through nonpharmacological interventions such as diet and exercise suggests that a life course approach based on education may be a successful strategy to increase the health span with few adverse consequences.

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AGING AND THE RISE OF INFLAMMATION

Aging—the complex array of phenotypic and functional manifestations that eventually lead to the death of the individual—occurs in all living species with only a few rare exceptions. Much has been written about the biological significance of aging and why individual mortality exists, with many theories coming back to the idea that, for the good of the population, there is an evolutionary advantage to "eliminate" aged organisms, particularly when past reproductive prime, because they consume significant resources and present a burden on the community (Cleveland and Jacobs 1999). At the beginning of life, a magnificent, extremely robust, and redundant program encoded by the genome aims to create an organism that is fully functional and in perfect homeostatic equilibrium within its environment. This status of perfect molecular order though cannot escape the second law of thermodynamics. To counteract the trend toward a higher level of entropy and facilitate a longer life span, a cadre of compensatory mechanisms have evolved that continuously surveil the integrity and functionality of molecules, organelles, cells, tissues, and organs, repairing or recycling and replacing severely damaged structures when needed (Alzeer 2022). These mechanisms are initially so effective that the progression of entropy is almost imperceptible. However, over time, the efficiency of these resilience mechanisms declines because their core molecular components become damaged through entropy, and because cumulative internal and external stressors impose an increasing burden beyond the level at which these systems can fully cope. Intrinsic to this model, as organisms age, resilience mechanisms shift from intermittent activation (e.g., during acute infection) to a chronic state of activation that is more typical of chronic disease. The immune system is a prototypical example of a resilience system.

An optimally functioning immune system protects against danger signals. Easily recognizable environmental danger signals include infection by pathogenic viruses or bacteria. The immune system is also a surveillance mechanism that maintains tissue homeostasis by repairing damage induced by extrinsic (UV radiation, oxygen deprivation, etc.) and intrinsic (protein aggregates, mitochondrial respiration, uric acid crystals, etc.) sources. The cardinal components of immunity are the inherent mechanisms that accurately tune the response to the need. Excessive and uncontrolled immunity leads to autoimmunity and hyperinflammatory syndromes (such as rheumatoid arthritis, intestinal bowel disease, and acute phase responses), whereas suboptimal responses result in immune deficiencies. Because the immune system is at the heart of all resilience mechanisms, it is not surprising that activation of the immune system, as indicated by high circulating levels of inflammatory markers and a state of active immune responses in multiple tissues, has been considered as one of the "pillars" of aging, now known as "inflammaging" (Ferrucci and Fabbri 2018).

In this article, after introducing the evidence that supports the concept of inflammaging, we explore some of the mechanisms that may be at the root of this chronic inflammatory state. Figure 1 provides a comprehensive view of the many causes and consequences of inflammaging proposed in the literature. However, rather than going through this long list, we will limit our discussion to a few topics that are receiving considerable attention at present. We describe instances where inflammation is mostly interpreted as a "response" to damage accumulation or stress, focusing on the role of the microbiome and the integrated stress response (ISR). We approach the literature on inflammaging from a mechanistic perspective. Next, we explore the existing evidence that inflammaging is driven by age-related intrinsic dysregulation. Finally, we review the literature on the available evidence that interventions aimed at reducing inflammation prevent or slow down the adverse phenotypic and functional effects of aging.

INFLAMMAGING AND UNDERLYING MECHANISMS

Several articles have described the characteristics of inflammaging, initially from the prospective of circulating biomarkers and more recently as the infiltration and activation of immune cells in

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Figure 1. (*See following page for legend.*)

multiple tissues. Studies have found that circulating levels of interleukin 6 (IL)-6, tumor necrosis factor (TNF)-α, IL-1, and other proinflammatory markers increase with aging, even in individuals who are deemed to be extremely healthy (Furman et al. 2019). In addition, high levels of inflammatory markers have been associated with, and in some cases predictive of, a large variety of age-related adverse health outcomes or conditions, including major chronic diseases (e.g., diabetes, atherosclerosis, dementia), viral infections (COVID-19 and flu), disability, frailty, nursing home admission, and death. Although a mechanistic understanding of the connection between inflammaging and adverse outcomes is still lacking, many authors have hypothesized that these pathologies are directly caused by the endocrine and metabolic effects of inflammatory mediators. For example, the shift toward catabolism and insulin resistance induced by inflammation may play a role in sarcopenia and neurodegenerative diseases. Nevertheless, other hypotheses should be considered.

Chronic inflammation that does not resolve, such as seen in inflammaging, could be a normal response to a persistent proinflammatory stimulus and most certainly involves a number of contributory mechanisms. For instance, aging is associated with changes in the gut microbiome due to the leakage of pathogen-associated molecular patterns (PAMPs), which are recognized by pattern-recognition receptors (PRRs) and trigger innate immunity (Conway and Duggal 2021). Moreover, there is evidence that mitochondrial function declines with aging, and it has been recently recognized that mitochondrial stress can trigger an inflammatory response through the release of oxidated mitochondrial DNA (mtDNA) and oxidated cardiolipin (also called damage-associated molecular patterns [DAMPs]), triggering the NLRP3 inflammasome, NF-κB, and the cGAS-STING pathway (Walker et al. 2022). Of note, dysfunctional mitochondria are physiologically removed by mitophagy, and the persistence of damaged mitochondria with age is at least in part explained by defective mitophagy (Kaushik et al. 2021). Finally, aging is associated with the accumulation of senescent cells that assume a senescent-associated inflammatory phenotype (SASP) and produce a large variety of bioactive molecules, including a collection of cytokines and chemokines (Walker et al. 2022). As the integrity and functionality of the immune system itself is progressively challenged by damage accumulation, an important question is whether a primary defect in the immune system contributes to the rise of inflammaging. Despite the strong rationale, the evidence for this hypothesis is still weak and limited to animal models.

Figure 1. Inflammaging, homeostasis, and resilience mechanisms. The rate of aging and progressive systemic entropy can be viewed as a continuing dynamic equilibrium between the forces of inflammaging and its consequences and counteractive mechanisms to maintain homeostasis. Affecting these opposing influences on the human body and the rate of biological aging are members of the gastrointestinal (GI) microbiome, including the positive effects of commensals and anti-inflammatory metabolites on the one hand and pathobionts and proinflammatory metabolites on the other. Many causes of inflammaging have been proposed (large blue circle) and, to name a few, include stress, injury, malnutrition, a sedentary state, intestinal dysbiosis, integrated stress response (ISR) activation, hypoxia, mitochondrial dysfunction, obesity, metabolic syndrome, chronic inflammation, the unfolded protein response, nutrient deprivation, cellular senescence, iron excess or deficiency, impaired autophagy, genomic instability, dysregulated nutrient sensing, protein precipitation, chronic infections, and dehydration. The possible consequences of inflammaging are numerous and are hypothesized to lead to age-related disorders including neurodegenerative disease, cancer, atherosclerosis, and impaired tissue renewal. Countering the effects of inflammaging are many proposed mechanisms and resilience strategies that maintain homeostasis (large pink circle) and include autophagy, mitophagy, DNA repair, exercise, epigenetic adaptation, ISR reprogramming, the heat shock response, diets such as the Mediterranean diet, tissue renewal, calorie restriction, chaperone-mediated proteostasis, mitochondrial bioenergetics, and metabolic homeostasis. Inflammaging, pathobionts, and proinflammatory metabolites will favor increasing age and an aging body (small blue circle), whereas homeostasis and resilience mechanisms and microbiome diversity, commensals, and anti-inflammatory metabolites may favor slower biological aging (small pink circle).

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The above age-related biological phenomena are far from being an exhaustive list of the persistent outcomes that likely drive inflammaging (see Fig. 1) yet highlight the important role of chronic inflammation in aging. The described outcomes also raise two opposite and complex questions of (1) whether inflammaging is contributing to pathology, or (2) whether inflammaging is a resilience mechanism itself and its absence would lead to an even more severe accumulation of damage. Assuming the latter, chronic inflammation would signify the presence of persistent, unresolved pathology and, thus, it is not surprising that inflammaging is associated with adverse health outcomes. From a more general prospective, the emergence of chronic inflammation with aging may designate the time when resilience mechanisms no longer match the rise in entropy and damage accumulation, suggesting that in chronic disease and frailty, inflammaging may be both a biomarker of resilience exhaustion and a causal factor.

One of the most popular theories about the origin of inflammaging is that the up-regulation of inflammation is linked to the effect of aging on endocrine regulation and metabolism. Supporting this concept are observations that chronic inflammation is significantly more prevalent and severe in older individuals with visceral obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease, and neurodegenerative disorders (Furman et al. 2019; Bektas et al. 2020). These conditions are caused by a combination of genetic predisposition and lifestyle or environmental stressors, such as pollution, smoking, sedentary behavior, and an unhealthy diet, as well as social and psychological stress, just to name a few (Bektas et al. 2020). Mechanistically, exogenous compounds, such as bacteria or viral fragments and certain microbiota elements, act as PAMPs, whereas endogenous processes generate DAMPs. PAMPs and DAMPs interact with sensors present on the cell surface or in the cytoplasm that in combination trigger inflammatory responses and proinflammatory cytokine secretion, which are hallmarks of inflammaging (Franceschi et al. 2018). Indeed, studies have underlined the role of immunobiography (the cumulative history of exposure to certain microorganisms (e.g., HIV and CMV) or antigens in causing chronic inflammation via the modulation of inflammatory responses (Franceschi et al. 2017, 2018; Ferrucci and Fabbri 2018; Fulop et al. 2018).

INFLAMMAGING AS A CAUSE OF PATHOLOGY AND ACCELERATED AGING

The prediction of the inflammaging hypothesis would be that suppression of age-associated chronic inflammation will coordinately attenuate multiple aging phenotypes and improve overall health and longevity. The immense implications for extending human health span via this strategy motivates rigorous tests of the hypothesis to identify nodes that can be therapeutically manipulated to meet this goal. Causal connections between two observables can be established by either activating or down-regulating one and assessing the effects on the other. In the case of inflammaging, this means (1) inducing chronic inflammation and assaying the development of aging phenotypes, or (2) attenuating chronic inflammation and exploring the health consequences. Major hurdles in experimentally testing this are (1) molecular characteristics (known as markers) of chronic inflammation, especially those instrumental in causing aging phenotypes, remain unclear, and (2) inducing inflammation for a long period of time is probably harmful. Thus, challenges to the inflammaging hypothesis usually entail studying the effects of increasing inflammation in animal models and reducing inflammation in both animal and human experiments. In this section, we highlight recent studies that exemplify both approaches.

Inducing Inflammation

One consistent theme in inflammation is the essential role of the transcription factor NF-κB (Taniguchi and Karin 2018). NF-κB, a heterodimer comprised of p50 and p65 components, is a well-known universal stress sensor, which when activated by different types of stimuli up-regulates the transcription of inflammatory cytokines, chemokines, and adhesion molecules, thereby causing inflammation. Additionally,

NF-κB induces the expression of transcripts that encode for proteins that regulate cell proliferation, apoptosis, morphogenesis, and differentiation. Moreover, NF-κB is activated in response to DNA damage (via ATM/ATR activation), mitochondrial dysfunction (via generation of reactive oxygen species) or proinflammatory cytokines in the milieu. Whether we consider the proinflammatory cytokines associated with human aging (such as IL-1, IL-6 or TNF-α) or the proinflammatory components of the SASP (widely believed to be a major cause of inflammaging), there is the unifying theme that many of the genes involved in these outcomes are regulated by NF-κB. Thus, it is not surprising that NF-κB is implicated in inflammaging and many of the hallmarks of aging (Songkiatisak et al. 2022). However, it is important to note that NF-κB responses are inducer- and cell-specific and have a strong kinetic dimension (Sen and Smale 2010), which makes it difficult to formulate a simple model for its contribution to age-associated chronic inflammation. Two kinds of observations provide causal connections between NF-κB and aging.

First, mice that lack NFKB1, the p50 component of NF-κB, manifest several characteristics of premature aging (Jurk et al. 2014). These include high systemic IL-6 levels and immune cell infiltration in the liver. Regeneration capacity of both liver and gut is also significantly reduced, and telomere-dysfunctional senescent cells accumulate in various tissues. Furthermore, the frequency of senescent cells in the liver or intestinal crypts correlates with mean and maximum life span of *NFKB1* knockout animals. Although accelerated aging in mice that lack an NF-κB component may appear counter to the hypothesis (i.e., that NF-κB supports a major protective response), one plausible explanation is that p50 homodimers have been previously suggested to dampen NF-κB-dependent responses. That is, p50 homodimers act as functional repressors of NF-κB-dependent gene expression in some circumstances (Cartwright et al. 2018). Thus, the absence of p50 may accentuate NF-κB activity resulting in chronic inflammation. A specific role for inflammation in the aging phenotypes of NFKB1-deficient mice is supported by the observation that treatment with the nonsteroidal anti-inflammatory ibuprofen ameliorates cognitive defects in these animals (Fielder et al. 2020). Interestingly, rapamycin treatment also improved aging phenotypes in NFKB1-deficient mice (Correia-Melo et al. 2019). Because low-dose rapamycin has been hailed as one of the most robust anti-aging treatments (Selvarani et al. 2021), the positive effects in NFKB1-deficient mice supports the idea that aging phenotypes in this model recapitulate features of normal aging.

Second, down-modulation of NF-κB activity via genetic deletion of one allele of RelA, the p65 component of NF-κB, has been shown to overcome aging in mouse models (Tilstra et al. 2012; García-García et al. 2021). These observations were extended recently with the use of a selective inhibitor of NF-κB activation. Zhang et al. (2021) showed that treatment of the *Ercc1*$^{-/\Delta}$ mouse model of accelerated aging (see more below) with SR12343, an agent that blocks IKK/NF-κB activation by disrupting the association between IKKβ and NEMO, two key NF-κB signaling proteins, reduced aging phenotypes such as elevated levels of senescent cells in tissues, expression of p16, and muscle pathologies. Concurrently, NF-κB activation, as measured by phosphorylation of RelA and expression of NF-κB target genes (e.g., *Tnfa*, *Cox2*, and *Mcp1*), was reduced following SR12343 administration. Thus, targeting NF-κB activation has therapeutic potential in ameliorating certain aging phenotypes. However, a caveat that must be considered is that NF-κB activation serves important physiological functions in most tissues via control of cell adhesion, cell viability, and cell cycle, among many others. The challenge will therefore be to find the "sweet spot" whereby effects against persistent activation that lead to sustained expression of inflammatory markers during aging are maximized, while minimally affecting acute activation in response to environmental or pathogenic stress.

Attenuating Chronic Inflammation

The geroscience hypothesis posits that manipulating underlying causes of aging has the potential to simultaneously alleviate multiple physiological characteristics of aging. As discussed,

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inflammaging has emerged as one of the most robust "underlying causes" of the phenotypes of aging. Several ongoing clinical trials have therefore explored the use of rapamycin and metformin, two compounds with immunosuppressive activity, to alleviate inflammaging and, thereby, age-associated comorbidities. The molecular targets and benefits of these compounds have been previously discussed and will not be further considered here (Selvarani et al. 2021). Instead, we will focus on recent studies in which select proinflammatory mediators were targeted, because specific mediators of inflammaging are less likely to have broad spectrum effects. Selective intervention may prove to be more effective, with fewer side effects, and more in line with the coming era of individualized medicine. Moreover, because inflammaging is a classic example of pleiotropic antagonism, long-term suppression of inflammatory responses may have detrimental consequences that are yet to be fully defined, again pointing to the need for more directed therapies beyond generalized anti-inflammatory treatments.

IL-6 and TNF-α are frequently associated with inflammaging, and biologics against these cytokines have proven to be effective in situations of acute inflammation, such as in psoriatic arthritis (using anti-IL-6 receptor) and rheumatoid arthritis (using therapies directed against TNF-α). Several recent examples indicate that interfering with TNF-α function can also overcome certain aging phenotypes. Davison-Castillo et al. (2019) showed that skewed hematopoiesis during aging results in the generation of hyperactive platelets that may contribute to increased thrombotic risk. Defective platelet generation in old mice was reduced by depleting TNF-α with anti-TNF antibodies, reducing predisposition to thrombosis. Perturbations of hematopoietic stem cells (HSCs) also underlies myeloid-biased hematopoiesis and an increased incidence of myeloid malignancies with age (Pang et al. 2017). This adverse phenotype was partially reversed by suppressing TNF-α signaling (Davizon-Castillo et al. 2019). At the functional level, in a mouse model of pneumococcal infection, the susceptibility of old mice to bacterial colonization was circumvented by pharmacological reduction of TNF-α or removal of a subset of proinflammatory monocytes (Puchta et al. 2016). Finally, a synthetic derivative of myosmine that suppresses TNF-α production ameliorated several phenotypes in aging mice, including muscle loss and frailty (Sabini et al. 2023). In these examples, neutralizing one inflammatory cytokine appears to have substantial beneficial effects. This may be because, unlike many other age-associated proinflammatory markers, TNF-α is an activator of NF-κB. Thus, its specific inhibition has the potential to mitigate proinflammatory NF-κB-dependent gene expression. One such NF-κB target is the *IL6* gene. Neutralizing IL-6/IL-6R signaling has recently been shown to overcome accelerated aging features in a mouse model of Hutchinson–Gilford progeria syndrome (Squarzoni et al. 2021). IL-6 has also been implicated in HSC dysfunction with age via the micro-RNA, miR146a (Grants et al. 2020). Unlike TNF-α, however, IL-6 cannot perpetuate NF-κB activity, resulting in more restricted outcomes.

A somewhat new player in the inflammaging cytokine milieu is IL-17, which is associated with inflammatory immune diseases such as rheumatoid arthritis, psoriasis, and multiple sclerosis (Mills 2023). Solá et al. (2023) found that IL-17 producing innate lymphoid cells and a subset of T cells increase with age in mouse skin and that neutralizing IL-17 delayed many symptoms of skin aging. Increased IL-17 production was also observed in human $CD4^+$ T cells from older compared to younger individuals. Expression of this inflammatory cytokine was connected to defective autophagy and disrupted the redox balance in old $CD4^+$ T cells, outcomes that were reversed by metformin treatment ex vivo (Bharath et al. 2020). It is possible that IL-17 has not been featured prominently as an inflammaging cytokine so far, because its production and function may be localized in specific tissue environments.

Overall, a review of this literature suggests that the chronic proinflammatory state observed in many older persons is causally linked with age-associated chronic disease and other aging phenotypes and that inflammation is an important target for interventions aimed at improving health span and longevity.

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INFLAMMAGING AND IMMUNOSENESCENCE

Dysregulation of immune responses during aging accentuates the deleterious rather than the protective immune responses, a phenomenon termed immunosenescence (Walford 1969; Franceschi et al. 2000). The varied and complex phenotypes associated with immunosenescence, presumably due to the involvement of multiple cell types and their interactions with various tissues (Fig. 2), is distinct from the phenomenon of cellular senescence (Sharma 2021; Lee et al. 2022). Because both inflammaging and immunity have essential inflammatory components, it is sometimes considered paradoxical that functional immunity declines with age as chronic low-grade inflammation increases. The key distinction is that optimal immunity requires regulated control of inflammation, both increased and decreased depending on need, a balance that is upset during aging. Accordingly, elderly people are more susceptible to infectious diseases, more prone to autoimmune diseases and cancer, and less responsive to vaccination (Goronzy and Weyand 2012, 2013). These facts, as well as the negative consequences of rampant and uncontrolled inflammation, have been highlighted during the COVID-19 pandemic (Demaret et al. 2021; Levin et al. 2021).

Immunity is broadly subclassified into innate or adaptive responses. Innate immunity is mediated by many different cell types, including monocytes/macrophages, granulocytes, natural killer (NK) cells, and innate lymphoid cells. These cells are first responders to danger signals and eliminate pathogens by mechanisms such as phagocytosis, NETosis, and the production of toxic reactive oxygen species (Ogawa et al. 2008; Simell et al. 2011; Brubaker et al. 2013; Hazeldine et al. 2014). They are also classic inflammatory cells in that they produce chemokines and cytokines that result in systemic inflammation. Although slower than innate responses, adaptive immunity features the generation of memory in B and T lymphocytes and natural killer T (NKT) cells. These so-called memory cells carry receptors that are selected for during an immune response to target and destroy specific pathogens. Adaptive immune memory permits more rapid and effective responses to reinfection with the same (or closely related) pathogens and is the basis of all vaccinations. $CD4^+$ T cells are required to generate optimal B-cell responses and, along with NKT cells, produce inflammatory cytokines, such as TNF-α, IFN-γ, and IL-17, which have been implicated in rheumatoid arthritis and psoriasis (Chemin et al. 2019; Povoleri et al. 2020; Nussbaum et al. 2021; Hu et al. 2022). Finally, $CD8^+$ T cells kill cells that have been infected with intracellular pathogens such as viruses. Recently a form of memory has been identified in innate cells as well and is referred to as trained immunity (Netea et al. 2011; Brueggeman et al. 2022). This form of memory is relatively short-lived and not pathogen specific.

Virtually all aspects of immunity are affected with age (reviewed recently and comprehensively in Goronzy and Weyand 2013; Nikolich-Žugich 2018; Nikolich-Zugich et al. 2020; Santoro et al. 2021; Shive and Pandiyan 2022; Teissier et al. 2022; Fulop et al. 2023). Key new developments are summarized in Table 1. The complexities of age-associated immunosenescence can be divided into three elements.

First, immune cell populations change with age. For adaptive immune cells, this change entails a decreased proportion of naïve (antigen inexperienced) cells and an increased proportion of memory cells (resulting from prior infections and vaccinations) in both B and T lymphocyte compartments (Listì et al. 2006; Britanova et al. 2014). The impact of trained immunity on age-associated immune dysregulation remains to be determined. Additionally, the aging immune system features the emergence of cells that are barely detectable in early life. Prominent among such cells are the exhausted T cells, marked by the absence of the cell-surface marker CD28. Exhausted T cells do not participate in effective immune responses and may constitute one major cause of reduced immunity with age (Boucher et al. 1998; Weng et al. 2009). These cells exhibit features of classic cellular senescence and may, thus, contribute to inflammaging via proinflammatory cytokine and chemokine expression (Lee and Lee 2016; Coleman et al. 2021). Moreover, recent single-cell RNA sequencing studies identified aging-related increased proportions of cy-

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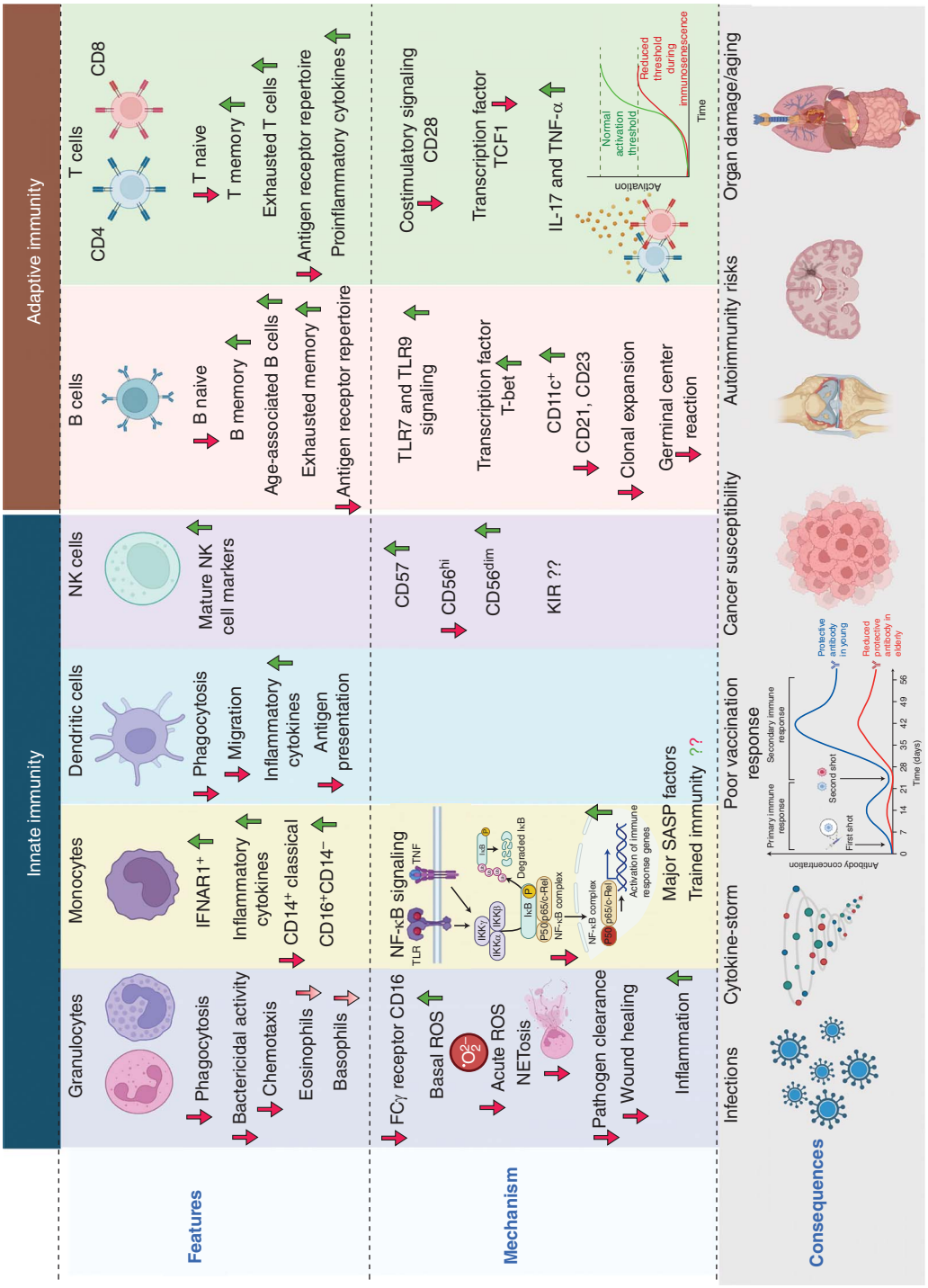

Figure 2. (*See following page for legend.*)

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totoxic and regulatory subsets of $CD4^+$ T cells with marked pro- and anti-inflammatory patterns of gene expression (Elyahu et al. 2019; Hashimoto et al. 2019; Cano-Gamez et al. 2020; Mogilenko et al. 2022). In the B-cell compartment, a subset of cells, named age-associated B cells (ABCs), increases with age in mice (Hao et al. 2011; Cortegano et al. 2017). ABCs were independently defined by different cell-surface markers by Hao et al. (2011) and Rubtsov et al. (2011) and are commonly associated with microbial immune responses and B-cell memory (Chang et al. 2017; Knox et al. 2017). These cells express the transcription factor T-bet, require Toll-like receptor (TLR)7 and 9 signaling for their generation (Naradikian et al. 2016), and are metabolically active (Frasca et al. 2021). $CD11c^+$ B cells have also been reported in humans, where they are primarily associated with autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis (Rubtsov et al. 2011; Wang et al. 2018). Another subset of B cells in old mice are exhausted memory B cells (Ehrhardt et al. 2008; Rubtsova et al. 2015). ABCs and exhausted memory B cells share some cell-surface characteristics, such as low levels of CD21 and CD23 markers, but further relationships remain to be defined. Whether and how ABCs contribute to age-associated decline in humoral responses is an active area of investigation. Thus, aging is associated with the emergence of new cell subpopulations that alter immune homeostasis toward proinflammatory phenotypes that can reduce effective immunity while exaggerating inflammaging.

Second, properties of immune cells change with age. One such change is in the antigen receptor repertoires of naive B and T cells. Reduced diversity of antigen recognition specificities with age has been proposed to contribute to reduced adaptive immunity during aging (Gibson et al. 2009; Tabibian-Keissar et al. 2016), presumably because the "right" pathogen-specific receptor is not present to trigger effective immunity. However, considerable antigen receptor diversity remains even in older individuals (Verma et al. 2012; Joseph et al. 2022), suggesting that other features must contribute to the overall decrease in immune responses as well. For example, age-associated changes in cel-

Figure 2. Effects of aging on innate and adaptive immunity—"multiple shades of immunosenescence." Immunosenescence with age is rooted in both innate and adaptive arms of immunity and its extent dictates the health status of a host. Immunosenescence in major innate immune cells is featured by either loss of normal function or by hyperresponsiveness. Reduction in functionality and associated mechanisms are denoted by downward facing red arrows, whereas up-regulated features are indicated by upward green arrows. Contradicting reports are represented by gradient-filled arrows, whereas still not reported events have "?" symbols. Innate immune cells reduce phagocytotic and chemotactic properties, which can be mediated by reduction in expression of Fcγ receptors or other chemokine receptors, respectively. In granulocytes, reactive oxygen species (ROS) levels are dysregulated, which leads to delayed pathogen clearance and wound healing, fostering chronic inflammation. Monocytes having interferon α-receptor1 (IFNAR1) are markedly increased in the lungs, whereas, systemically, classical monocytes (which are more responsive to lipopolysaccharide [LPS]) are reduced. NF-κB signaling dysregulation is a major culprit in age-related monocyte dysregulation (see text for p50 knockout studies). These cells further participate in generating major senescent-associated inflammatory phenotype (SASP) factors. Meanwhile, the emerging concept of "trained immunity" has not yet been linked with immunosenescence or aging. Adaptive immunity is globally characterized by a reduction in naive lymphocytes and up-regulation of memory and exhausted cells. These, in part, can be explained by selective Toll-like receptor (TLR) signaling in B cells and reduced expression of costimulatory CD28 on T cells. The antigen receptor repertoire is significantly hindered in lymphocytes. Transcription factor T-bet in B cells are overexpressed, whereas the T-cell factor 1 (TCF1) is down-regulated, leading to a loss in their optimal functionality. The inflammatory environment of interleukin (IL)-17 and tumor necrosis factor (TNF)-α reduces the activation threshold of T cells and leads them to be unnecessarily hyperactive with age, which can create an autoimmunity-like situation. Ultimately, interplay of these immunosenescence properties make the host susceptible to infections, cytokine-storm (after uncontrolled infections), poor outcome of vaccinations in the elderly, and increased susceptibility toward cancers and autoimmunity. Furthermore, immunosenescence can cause organ damage and accelerate aging of various organs. (Figure created using BioRender.com.)

Table 1. Age-associated immunosenescence features in main immune cell populations

Cell type	Effects of immunosenescence/effects with age	References
Adaptive immune cells		
B cells	Loss of naive IgD^+ B cells Decrease in IgM and IgG increases with age mostly in men Significant IgD^- memory B-cell increase Lack of clonotypic immune response Higher proportion of memory B cells in PBMC than bone marrow (BM) BM has fewer plasma cells in old age Loss of marginal zone B lymphocytes An enhancement of a $CD19^+CD45R^{lo}$ innate-like B-cell population (B1REL) and the so-called aged B-cell compartment (ABC, $D45R^+CD21^{lo}CD23^{lo}CD5^-CD11b^-$) in aged senescence-accelerated (SAMP8) mice but not in aged senescence-resistant (SAMR1) mice	Listì et al. 2006; Pritz et al. 2015; Cortegano et al. 2017
T cells	Decline in proportion of $CD28^+$ T cells Age-related diminution of T-cell responsiveness to mitogenic signals T-cell receptor (TCR)-β diversity decrease Decrease in naive and increase in memory cells with senescent phenotype Increased $CD57^+$ and $KLRG1^+$ (senescent markers) in terminally differentiated memory T cells The sestrin-driven senescence of $CD8^+$ T cells has recently been reported to lead to loss of TCR Expression together with the acquisition of natural killer (NK) features Increase of proinflammatory cytokines Decrease in telomere length Greater type I interferon (IFN), interleukin (IL)-2, but less IL-4 Gene-expression profile of T cells reveal up-regulation of immunosuppressive markers and immune checkpoints; aged CD4 memory T cells exhibited proapoptotic gene signatures, aged CD8 memory T cells expressed antiapoptotic genes Microenvironment in which $CD4^+$ T cells develop in older individuals may cause production of more cells committed to Th1 Accumulation of activated Tregs with anti-inflammatory features in mice; proinflammatory phenotype in cytotoxic CD4 cells in mice	Boucher et al. 1998; Sakata-Kaneko et al. 2000; Britanova et al. 2014; Elyahu et al. 2019; Pereira et al. 2020; Rodriguez et al. 2021; Yang et al. 2021

Continued

Table 1. *Continued*

Cell type	Effects of immunosenescence/effects with age	References
Innate immune cells		
Monocyte	Alterations of monocyte NF-κB p65/RelA signaling in a cohort of older medical patients, age-matched controls, and healthy young adults Novel type-1 IFN signaling-dependent monocyte subset (MO-IFN) that up-regulated IFNAR1 expression identified in the aged lung Higher inflammatory markers Reduced pNF-κB induction in response to lipopolysaccharide (LPS) and tumor necrosis factor α (TNF-α)	Tavenier et al. 2020; D'Souza et al. 2021
Granulocytes/ neutrophils	Reduced phagocytic activity due to decreased surface expression of FCγ receptor CD16 Opsonic activities to antibodies against pneumococci impaired Significant reduction in the intracellular reactive oxygen species (ROS) production after stimulation with *Staphylococcus aureus* Acute ROS production decreases but higher basal ROS levels leading to inflammaging Neutrophil bactericidal activity impaired with age Reduced neutrophil phagocytosis and chemotaxis with age NETosis decline Delay in pathogen clearance and wound healing contributing to local inflammation Very few eosinophils and basophils and some contradiction	Wenisch et al. 2000; Ogawa et al. 2008; Simell et al. 2011; Brubaker et al. 2013; Hazeldine et al. 2014; Sauce et al. 2017; Teissier et al. 2022
Natural killer cells	NK cells in cord blood displayed specific features associated with immaturity, including poor expression of KIR and LIR-1/ILT-2 and high expression of both NKG2A and IFN-γ NK cells from older subjects, on the other hand, preserved their major phenotypic and functional characteristics, but with their mature features accentuated The expression of CD57, a marker of highly differentiated NK cells, is increased in the elderly Profound decline of $CD56^{high}$ subset, rise of $CD56^{dim}$ population Conflicting reports on killer immunoglobulin-like receptor	Wendt et al. 2006; Le Garff-Tavernier et al. 2010
Dendritic cells	Diminished functions, impaired migration, and phagocytosis Increased production of TNF-α and IL-6 Reduced IL-10 upon stimulation Reduced phagocytosis leads to decreased antigen presentation, hence less B- and T-cell priming	Agrawal et al. 2009; Kornete and Piccirillo 2012; Teissier et al. 2022

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lular responses to antigen receptor stimulation may reduce the extent of clonal expansion (by cell division) of antigen-specific cells required for effective immunity or alter qualitatively the patterns of gene expression in activated lymphocytes. The latter mechanism has been recently proposed to contribute to inflammaging via increased expression of inflammatory cytokines by cells in older individuals (Bharath et al. 2020).

Third, the impact of age-associated immune dysregulation on the health span of the elderly must consider interactions between immunity and other physiological changes that occur with age. Studies that investigated relationships between immune characteristics and physiological parameters, such as frailty and multimorbidity, have found limited correlation with classic inflammaging markers (e.g., C-reactive protein, TNF-α, and IL-6) (Marcos-Pérez et al. 2018; Alberro et al. 2021). Instead, more recent investigations have moved toward multiomics approaches to identify biomarker panels that summarize changes in immune function with aging and, independent of chronological age, predict health outcomes. Alpert and colleagues (2019) used multiomic technologies on immune cells of 135 healthy adult individuals of different ages sampled longitudinally over a 9-yr period to generate an immune aging (IMM-AGE) score, which produced a more accurate estimate of one's immune status than chronological age. The same group more recently conducted a comprehensive analysis of 50 circulating immune proteins to develop an inflammatory clock of aging (iAge) that predicts multimorbidity. In this study, the authors quantified serum cytokine, chemokine, and growth factor levels in over a thousand donors between ages 8 and 96 yr. Using a neural network–based deep learning model, the investigators were able to reliably predict age-associated deterioration of immune function (Furman et al. 2017; Sayed et al. 2021). Moreover, iAge, which tracks age-associated frailty and multimorbidity in humans, identified the interferon-induced chemokine CXCL9 as a prominent inflammatory component contributing to cardiovascular aging.

It is important to point out that immune dysfunction and immunosenescence are widely considered as two components of the same age-related phenomenon (i.e., inflammaging) and that some talk about immunosenescence and inflammaging as the same dimension. Because inflammaging was originally defined by high circulating levels of proinflammatory cytokines, in this discussion we will define inflammaging as chronic immune activation, whereas we reserve the term immunosenescence to the cadre of mechanisms that reduce the immune response to acute stressors. From this perspective, clear-cut evidence of a connection between immunosenescence and inflammaging is lacking. It is possible that inflammaging promotes immunosenescence or, in other words, that immune dysregulation and inflammaging are mutually reinforcing forces that drive many aging phenotypes. The best evidence that defective immune cells can lead to an aging-like proinflammatory state comes from the studies of Yousefzadeh et al. (2021). These authors engineered a hematopoietic-specific deletion in mice of the *Ercc1* gene, which encodes a protein involved in DNA repair. Mutant animals exhibited many symptoms of age-associated immune dysfunction, including increased proportions of senescent immune cells, increased levels of SASP markers, and compromised cellular and humoral function, thus resembling normal aged mice. Importantly, prominent aging phenotypes were also evident in tissues where *Ercc1* was intact, such as the liver and kidney, and cytokine levels were elevated in the serum. These observations strongly support the notion that selective and persistent activation of inflammatory responses in immune cells (i.e., immune dysfunction) is sufficient to drive inflammaging and systemic aging features in mice. An important implication of these studies is that reducing immunosenescence, and thereby inflammaging, may have beneficial effects in the elderly beyond immune-specific outcomes, such as improved vaccine efficacy and protection against infectious disease.

The converse issue is equally important, that is, does inflammaging induce immune dysregulation? This is more difficult to address because of the complexity in disentangling inflammaging from immunosenescence. One mechanism by which inflammaging can affect immunity is by changing the milieu in which immune responses

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take place, the most obvious effects being conferred by cytokines and chemokines that are hallmarks of inflammaging. For example, $CD4^+$ T-cell responses in an IL-6-rich environment skew effector phenotypes toward proinflammatory IL-17-producing cells (Ghoreschi et al. 2010). This mechanism may underlie increased IL-17 production by $CD4^+$ T cells from older humans. Similarly, IL-17 and TNF-α have been shown to lower the threshold for $CD4^+$ T cell activation (Banerjee et al. 2005; Ben-Sasson et al. 2009, 2011) that may predispose the emergence of self-reactive cells and increased autoimmunity during aging. Such cells are constrained in a noninflammatory youthful environment by mechanisms of immune tolerance. The resulting picture is one whereby multiple features of inflammaging and immune senescence establish positive feedback effects that increase steadily with age.

INFLAMMAGING AND THE INTEGRATED STRESS RESPONSE

Several lines of evidence suggest that inflammaging is directly connected to the biological mechanisms of aging and results from the accumulation of molecular damage that is not fully offset by resilience strategies. Such damage accumulation could therefore be considered a proxy measure of accelerated aging (Fig. 1). López-Otin et al. (2013) and Kennedy et al. (2014) have identified biological mechanisms of aging that can be traced in multiple organisms, including humans. These so-called "hallmarks" encompass biological processes such as proteostasis (i.e., protein homeostasis), adaptation to stress, nutrient sensing, genome maintenance, mitochondrial function, cellular senescence, metabolism, and inflammation. There is substantial evidence of a bidirectional relationship between inflammation and these mechanisms, meaning that the underlying processes can be adversely affected by inflammation, whereas defects in these processes can trigger an inflammatory response, potentially creating a vicious cycle that can contribute to accelerated aging. From an evolutionary perspective, we can hypothesize that preservation of effective proteostasis, which encompasses the maintenance of both the level and functionality of the proteome, is essential to survival. In fact, virtually any type of biochemical pathway or stress response requires the integrity of proteins. Although we cover next the intimate relationship between proteostatic mechanisms, particularly the ISR, and inflammaging, details regarding the connection between the other mechanisms of aging and inflammation has been extensively reviewed elsewhere (Bektas et al. 2018; Ferrucci and Fabbri 2018; Franceschi et al. 2018; Furman et al. 2019).

The regulation of proteostasis involves evolutionarily conserved mechanisms that are interconnected and include the unfolded protein response (UPR) that senses and responds to misfolded protein accumulation in the endoplasmic reticulum (ER), the heat shock response (HSR) that regulates protein folding and degradation capacity, and the ISR that reprograms transcription and translation in response to stress (see Fig. 3). Broadly speaking, the ISR enables cells to pause protein synthesis to allow for sufficient time to deal with the accumulation of misfolded proteins, all while preserving the translation of proteins that play critical roles in promoting homeostasis, including cytokines and other proinflammatory mediators. Known stressors that trigger the ISR and its associated signaling stress-kinases (indicated here in parentheses) include the accumulation of misfolded proteins in the ER (PERK), amino acid deprivation (GCN2), iron deficiency and mitochondrial stress (HRI), or viral infection (PKR), although this list may very well grow as our knowledge of the complex mechanisms expands (Derisbourg et al. 2021a). Depending on the intensity and duration of the stress, ISR signaling enables the cell to either favor a return to homeostasis or apoptotic cell death. An important mediator of the stress-specific cellular response is ATF4, which becomes up-regulated following activation of the stress kinases and consequent phosphorylation of eukaryotic initiation factor 2α (eIF2α). ATF4 is a transcription factor that regulates the expression of genes specifically involved in survival responses, inducing the up-regulation of autophagy, the DNA-damage response, and inhibition of mTORC1 (Ameri and Harris 2008). However, if the stress is too

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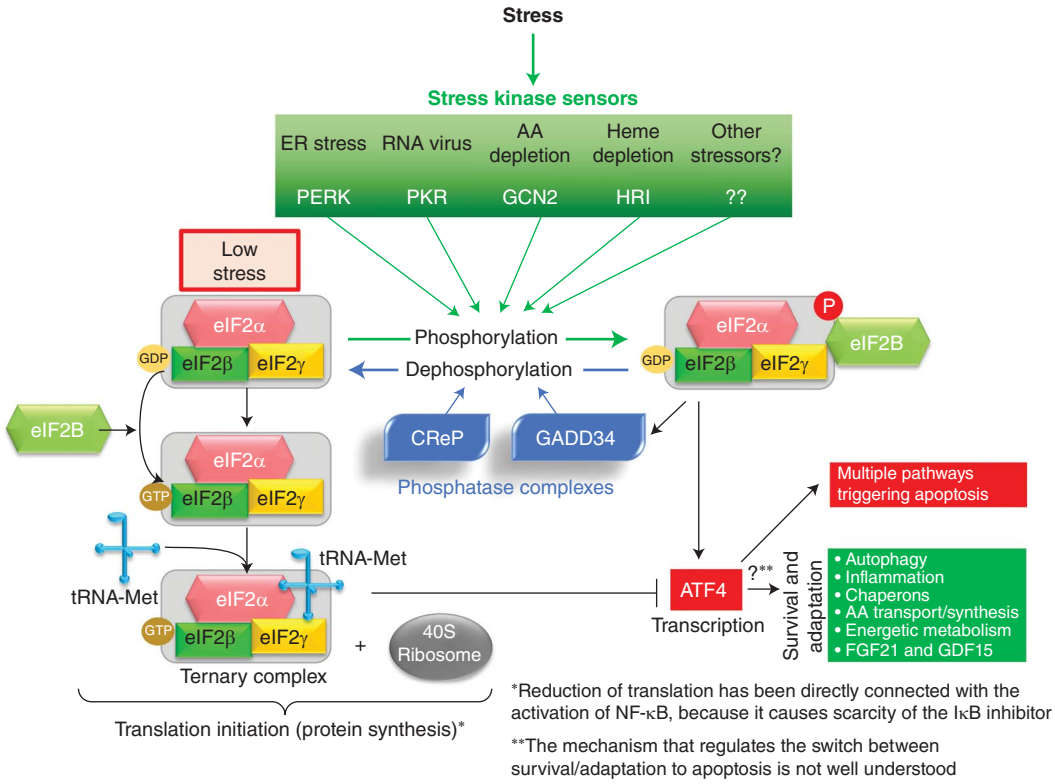

Figure 3. The integrated stress response. Translation initiation is controlled by the eIF2–GTP–Met-tRNAi ternary complex that interacts with the 40S ribosome to recognize the AUG start codon in mRNA (Derisbourg et al. 2021a). In metazoans, different types of stress are sensed, as are four different kinases—heme-regulated inhibitor (*HRI*), protein kinase R (*PKR*), general control nonderepressible 2 (*GCN2*), PKR-like ER kinase (*PERK*)—and possibly other kinases that are yet to be identified. Once activated, these kinases phosphorylate eIF2, which is no longer able to form the eIF2–GTP–Met-tRNAi ternary complex (Costa-Mattioli and Walter 2020), therefore slowing down or blocking translation. However, lowered ternary complex availability activates the transcription factor 4 (ATF4) that stimulates the transcription and translation of a subset of mRNAs that act as effectors of the ISR and enhance resilience responses. In the case of stresses that are too intense or prolonged in time, it can trigger apoptosis through different mechanisms. Of note, phosphorylate eIF2 also enhances the activity of the GADD34 phosphatase complex acting as a braking system that controls excessive ISR activation (Knowles et al. 2021).

intense or prolonged, exceeding the tolerance threshold of the cell, there is a shift toward apoptosis. The regulatory mechanisms that eventually shift the response toward cell death are not understood, but presumably involve a reaction to excessive damage accumulation. The intricate control of the ISR network through sophisticated transcriptional regulation is, in many ways, reminiscent of a subroutine in software programming and shows how a cell can mechanistically deal with stress and/or a crisis triggered by aging and inflammaging.

The link between ISR and inflammaging is supported by observations that dysregulation of the ISR is observed in many inflammaging-related disorders, including cancer, neurodegenerative disease, and metabolic syndrome (Ameri and Harris 2008). There is also emerging evidence that the ISR is up-regulated with aging and is involved in age-related diseases such as diabetes and cancer. Mechanistically, it is currently believed that the ISR activates the NF-κB transcriptional regulator (see further information in the next section) by slowing down the

translation of its short-lived protein inhibitor IκB (Tam et al. 2012). This model is consistent with the observation that ISR activation leads to secretion of inflammatory cytokines, such as IL-1β and IL-6, factors that are directly related to NF-κB activity. Thus, inhibition of the ISR is a candidate mechanism for reducing inflammation. ISR inhibition has in fact been shown to extend survival in nematodes (Derisbourg et al. 2021b) and enhance cognitive function in aged mice (Krukowski et al. 2020), suggesting pharmacological modulation of the ISR may be a future therapeutic strategy for age-related chronic diseases characterized by inflammaging (Derisbourg et al. 2021a).

AGE-RELATED DYSBIOSIS AND INFLAMMAGING

Beyond the so-far-discussed intrinsic and extrinsic triggers of inflammaging, the gut microbiome and dysbiosis are newly emerging sources for age-associated chronic inflammation. There is evidence that changes in the gut microbiome and repeated chronic infections that become more prevalent with aging may contribute to systemic inflammation and activate the components of the ISR, especially in the most severe circumstances. For example, recent data suggest that *Shigella flexneri*, which primarily infects the gastrointestinal tract and, more relevant to aging, *Porphyromonas gingivalis*, the "keystone pathogen" of chronic oral inflammatory gum periodontitis, activate the ISR (Knowles et al. 2021). In a recent review, Ghosh et al. (2022) describe evidence indicating that the microbiome affects the host's metabolic, immune, and neurological functions in a reciprocal manner, as well as modifies the risk of diseases in general and age-related diseases in particular, many of which are linked to inflammation and inflammaging.

The diversity of the human gut microbiome is vast, with almost 2000 bacterial species (Almeida et al. 2019). Observational studies suggest that the degree of "diversity" is the most important characteristic of a "healthy microbiome," as problems occur when one bacterial species becomes dominant. Comparative analysis of microbiome profiles shows that some taxa of bacterial species are more prevalent in centenarians across various nationalities and geographies and reveals that a lower number of symbionts, such as the *Faecalibacterium* species, are associated with health in younger individuals. Moreover, there is a higher number of gut microbiota genes associated with xenobiotic degradation in long-lived older individuals (Rampelli et al. 2020). Other age-related changes in the microbiome include the loss of dominant commensal taxa (such as the health-associated genus Bifidobacterium) and an increase in other commensals, such as pathobionts *Streptococcus* and *Enterobacteriaceae*, which are associated with an age-related decline in health (Jeffery et al. 2016; Ghosh et al. 2020a). Studies examining cohorts of individuals, such as those enrolled in Ireland-based ELDERMET, have found similar changes that are characterized by loss of commensals and a gain of pathobionts, such as *Enterobacteriaceae* family members and disease-associated *Clostridium* species (Ghosh et al. 2022). Moreover, in examining 25 studies that investigated gut microbiome alterations in older individuals, Ghosh et al. (2022) identified a third group of commensal microbial markers (i.e., *Akkermansia*, *Barnesiellaceae*, *Butyricimonas*, *Butyrivibrio*, *Christensenellaceae*, *Odoribacter*, and *Oscillospira*), which increase with age but decrease in various age-related conditions. As such, these species appear to represent candidate biomarkers of healthy aging or physiological decline. For example, a decrease in *Akkermansia* has been associated with cognitive decline (Manderino et al. 2017), multiple age-related diseases/comorbidities (Singh et al. 2019), mortality among centenarians (Luan et al. 2020), and progeria (Bárcena et al. 2019). *Akkermansia* promotes the growth of butyrate producers (by producing acetate), which in turn decreases the loss of the colonic bilayer and hence reduce inflammation (Ghosh et al. 2022). *Akkermansia* also reduces the activation of innate B1a cells (preventing insulin resistance) (Bodogai et al. 2018), prevents cellular senescence (Shin et al. 2021), ameliorates progeroid symptoms (Bárcena et al. 2019), and reduces the risk of cardiometabolic disease in humans who are overweight or obese (Depommier et al. 2019), all factors known to increase inflammation. Furthermore, with regard to inflammation, a decrease in microbiome produc-

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ers (such as *Blautia*, *Coprococcus*, *Dorea*, *Eubacterium*, *Faecalibacterium*, and *Roseburia*) of core short-chain fatty acids, which are known anti-inflammatory metabolites (Couto et al. 2020), has been associated with frailty (Ghosh et al. 2020a) and Alzheimer's disease (Haran et al. 2019). Of note, many of the unhealthy age-associated pathobionts mentioned result in metabolites that are connected to inflammation and oxidative stress, including trimethylamine (Lin et al. 2020), paracresol (Ghosh et al. 2022), and LPS (Awoyemi et al. 2018).

In addition to the beneficial effects of some microbial species against inflammation, evidence supports the premise that the microbiome can be an important contributor to inflammaging. Thevaranjan et al. (2017) performed a set of experiments in mice to identify connections between the microbiome profile and age-associated inflammatory changes. They found that mice maintained under germ-free conditions did not show an age-related increase in proinflammatory cytokine levels. However, co-housing germ-free mice with non-sterilely raised old mice but not young mice, increased proinflammatory cytokine levels. In TNF-α-deficient animals, age-associated microbiota changes were not observed, and the mutant mice were protected from age-associated inflammation. Finally, the investigators showed that age-associated microbiota changes in normal mice could be reversed by anti-TNF-α therapy by reducing TNF-α levels. Together, these findings suggest that inflammation is caused by both alterations in the microbiota and downstream consequences of the microbiota changes (Thevaranjan et al. 2017).

Last, lifestyle interventions such as the Mediterranean diet (Ghosh et al. 2020b), a diet rich in blueberries (Ntemiri et al. 2020), and many other diets including those that incorporate various prebiotic and microbial supplements, have been found to reduce inflammatory biomarkers or increase anti-inflammatory biomarkers. Such evidence indicates that modulation of the microbiome through dietary strategies may be one way to reduce inflammation and hence stave off physiological decline associated with aging (Ghosh et al. 2022). The connections between the microbiome and inflammation described above have motivated clinical trials to manipulate the microbiome in older individuals to reduce inflammation. Examples include prebiotic administration to affect specific microbiota that influence inflammation, such as short-chain fatty acid producers (Chung et al. 2020), and direct microbial supplementation that targets gut inflammation in age-related conditions such as Alzheimer's disease (Leblhuber et al. 2018). In the future, microbiome manipulation focusing on inflammation may also include fecal microbiota transplantation (FMT), which to date has been primarily limited to clinical trials treating chronic *Clostridioides difficile* infection (Agrawal et al. 2016; Friedman-Korn et al. 2018). However, promising experiments in mice have demonstrated that FMT from young into old animals reversed age-associated inflammation in the central nervous system and retina (Parker et al. 2022) and also improved, in the old mice, peripheral and brain immunity and cognitive behavior impairments (Boehme et al. 2021).

IS REDUCING INFLAMMATION USEFUL?

Overwhelming observational evidence indicates that inflammation is a risk factor for chronic diseases, multimorbidity, disability, frailty, and mortality, prudently favoring inflammation suppression as a first choice of intervention to combat aging. Surprisingly, whether blocking inflammation prevents a decline or improves physical function in older individuals has not been definitively established, with a few exceptions that we review later in this section (Ferrucci and Fabbri 2018). From the data presented earlier in this work, it is reasonable to hypothesize that if inflammation is effectively targeted through interventions that selectively offset the deleterious effects of an inflammatory environment while retaining its critical role in the defense, repair, and regeneration of damaged macromolecules and cells, it would result in the expansion of health span and preservation of functional status in old age. Many different pharmacological and nonpharmacological strategies are currently available to reduce inflammation besides steroids. These include, salicylates (such as aspirin), propionic acid derivatives (such as Naproxen),

acetic acid derivatives (such as Indomethacin), enolic acid (Oxicam) derivative (such as Piroxicam), anthranilic acid derivatives (such as Mefenamic), and selective COX-2 inhibitors (such as Celecoxib). Other drug classes have claimed to effectively reduce inflammation, including Losartan and Omega 3 fatty acids (in the form of fish oil). More recently, several monoclonal antibodies have been released that selectively block inflammatory mediators (cytokines) and chemokines and/or their receptors. Finally, new molecules that selectively block the NLRP3 inflammasome have been produced but will not be addressed here because of the lack of solid supporting data in animal models or humans.

In a prospective cohort comprised of 14,315 men (mean age 71 yr) who participated in the Physicians' Health Study I, a randomized controlled trial of aspirin (1982–1988) was conducted, with extended posttrial follow-up. Individuals who were regularly taking aspirin (at least 60 d/yr on average) were more likely than those that were not to self-report preserved mobility (Orkaby et al. 2022). In the ASPREE (aspirin in reducing events in the elderly) trial of 100 mg of aspirin daily versus placebo, 19,114 healthy adults aged 70+ yr (65+ yr if U.S. minority) in Australia and the United States were recruited. Over a median of 4.7 yr, incident disability in activities of daily living was similar in those receiving aspirin (776/9525) relative to placebo (787/9589). However, persistent disability in activities of daily living tended to be lower (nonsignificantly) in the aspirin group (Woods et al. 2021). The promising results of these studies is tempered by other studies that failed to demonstrate any effects of chronic aspirin administration on physical or cognitive functions and by a recent report from the ASPREE trial showing that the risk of a serious fall was significantly greater in the aspirin group (Barker et al. 2022). The ENERGIZE pilot randomized controlled trial failed to demonstrate any positive effect of Losartan and fish oil on plasma IL-6 and mobility in older persons (Pahor et al. 2020).

The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial remains the strongest evidence that reducing inflammation prevents a "hard" medical outcome, such as incident cardiovascular events (Ridker et al. 2017a). The CANTOS found that blocking IL-1 with the monoclonal antibody canakinumab significantly reduced cardiovascular events in individuals with established atherosclerotic disease who had already survived a myocardial infarction and had residual inflammatory risk. Interestingly, the protection was higher among those, who after receipt of the first dose, exhibited a decline in IL-6 and C-reactive protein. When reanalyzing the CANTOS database, canakinumab was also found to reduce the rate or incidence of lung cancer (Ridker et al. 2017b), anemia (Vallurupalli et al. 2020), hip or knee replacement (Schieker et al. 2020), and hospitalizations for heart failure (Everett et al. 2019), as well as to positively impact insulin resistance (Everett et al. 2018). These data strongly suggest that blockage of inflammation positively affects multiple chronic disease–associated health outcomes. By extension, we can hypothesize that this same approach would have beneficial effects on multiple health outcomes.

TNF-α triggers NF-κB, which, as discussed earlier, operates as a gate to many proinflammatory cytokines and inflammatory signals. There is therefore strong rationale to hypothesize that blocking TNF-α, especially in frail older persons who characteristically have an inflammatory component, will improve health outcomes and muscle function mobility in particular. In mice, pharmacological TNF-α blockade, with weekly subcutaneous injection of etanercept from 16 to 28 mo of age, prevented atrophy and loss of type II fibers and led to significant improvements in muscle function and life span (Sciorati et al. 2020). Other compounds that selectively block major inflammatory mediators, such as tocilizumab, sarilumab, and siltuximab, which interfere with IL-6 signaling; anakinra and rilonacept, which block IL-1 signaling; and infliximab and certolizumab pegol, which disrupt TNF-α signaling, to name a few, have also been tested extensively in overt inflammatory disease, such as rheumatoid arthritis or giant cell arteritis, with positive results thus far. Unfortunately, to date, none of these candidate therapeutics have been tested for their ability to prevent age-associated multimorbidity or risk of physical and cognitive disability.

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It is important to recognize that "treating" inflammation is intrinsically complex, especially in "healthy" individuals. This is a particular concern if inflammation is blocked at a central hub of one of the different defensive mechanisms, a strategy employed by many of the agents used nowadays that were designed to fight overt inflammatory conditions. Because of such complexity, scientists have looked at nonpharmacological interventions to reduce inflammation and prevent related adverse health outcomes. There is some, albeit not overwhelming, evidence that physical activity and exercise can reduce inflammation (de Lemos Muller et al. 2019). In a randomized controlled trial in older persons, exercise reduced inflammation in adipose tissue as measured by the expression of proinflammatory cytokines, especially when paired with mega-3 supplementation (Čížková et al. 2020). A number of observational studies and intervention trials have also shown that adherence to the Mediterranean diet prevents chronic disease development (Salas-Salvadó et al. 2018). Indeed, dietary regimens based on the Mediterranean diet improve proinflammatory status and prevent mobility loss, cognitive decline, and frailty in older persons, the most severe and most dreaded consequences of aging (Milaneschi et al. 2011; Tanaka et al. 2018; Wang et al. 2018; Capurso et al. 2019; Tsigalou et al. 2020).

Looking to the future, more research on the specific causes and mechanisms that trigger inflammaging, as well as the defining features of inflammaging, will certainly provide clues about the most effective targets. Hopefully, such insights will direct us to new therapeutic mechanisms that are less prone to unwanted side-effects. For example, enhancing mitophagy via administration of Urolithin A or eliminating senescent cells through new senolytic drugs are emerging, promising approaches currently being tested in human trials.

REFERENCES

Agrawal A, Tay J, Ton S, Agrawal S, Gupta S. 2009. Increased reactivity of dendritic cells from aged subjects to self-antigen, the human DNA. *J Immunol* **182:** 1138–1145. doi:10.4049/jimmunol.182.2.1138

Agrawal M, Aroniadis OC, Brandt LJ, Kelly C, Freeman S, Surawicz C, Broussard E, Stollman N, Giovanelli A, Smith B, et al. 2016. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated *Clostridium difficile* infection in 146 elderly individuals. *J Clin Gastroenterol* **50:** 403–407. doi:10.1097/MCG.0000000000000410

Alberro A, Iribarren-Lopez A, Sáenz-Cuesta M, Matheu A, Vergara I, Otaegui D. 2021. Inflammaging markers characteristic of advanced age show similar levels with frailty and dependency. *Sci Rep* **11:** 4358. doi:10.1038/s41598-021-83991-7

Almeida A, Mitchell AL, Boland M, Forster SC, Gloor GB, Tarkowska A, Lawley TD, Finn RD. 2019. A new genomic blueprint of the human gut microbiota. *Nature* **568:** 499–504. doi:10.1038/s41586-019-0965-1

Alpert A, Pickman Y, Leipold M, Rosenberg-Hasson Y, Ji X, Gaujoux R, Rabani H, Starosvetsky E, Kveler K, Schaffert S, et al. 2019. A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. *Nat Med* **25:** 487–495. doi:10.1038/s41591-019-0381-y

Alzeer J. 2022. Halalopathy: role of entropy in the aging process. *Am J Biomed Sci Res* **16:** 147–154. doi:10.34297/AJBSR.2022.16.002205

Ameri K, Harris AL. 2008. Activating transcription factor 4. *Int J Biochem Cell Biol* **40:** 14–21. doi:10.1016/j.biocel.2007.01.020

Awoyemi A, Trøseid M, Arnesen H, Solheim S, Seljeflot I. 2018. Markers of metabolic endotoxemia as related to metabolic syndrome in an elderly male population at high cardiovascular risk: a cross-sectional study. *Diabetol Metab Syndr* **10:** 59. doi:10.1186/s13098-018-0360-3

Banerjee D, Liou HC, Sen R. 2005. c-Rel-dependent priming of naive T cells by inflammatory cytokines. *Immunity* **23:** 445–458. doi:10.1016/j.immuni.2005.09.012

Bárcena C, Valdés-Mas R, Mayoral P, Garabaya C, Durand S, Rodríguez F, Fernández-García MT, Salazar N, Nogacka AM, Garatachea N, et al. 2019. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. *Nat Med* **25:** 1234–1242. doi:10.1038/s41591-019-0504-5

Barker AL, Morello R, Thao LTP, Seeman E, Ward SA, Sanders KM, Cumming RG, Pasco JA, Ebeling PR, Woods RL, et al. 2022. Daily low-dose aspirin and risk of serious falls and fractures in healthy older people: a substudy of the ASPREE randomized clinical trial. *JAMA Intern Med* **182:** 1289–1297. doi:10.1001/jamainternmed.2022.5028

Bektas A, Schurman SH, Sen R, Ferrucci L. 2018. Aging, inflammation and the environment. *Exp Gerontol* **105:** 10–18. doi:10.1016/j.exger.2017.12.015

Bektas A, Schurman SH, Franceschi C, Ferrucci L. 2020. A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? *Immun Ageing* **17:** 23. doi:10.1186/s12979-020-00196-8

Ben-Sasson SZ, Hu-Li J, Quiel J, Cauchetaux S, Ratner M, Shapira I, Dinarello CA, Paul WE. 2009. IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. *Proc Natl Acad Sci* **106:** 7119–7124. doi:10.1073/pnas.0902745106

Ben-Sasson SZ, Caucheteux S, Crank M, Hu-Li J, Paul WE. 2011. IL-1 acts on T cells to enhance the magnitude of in vivo immune responses. *Cytokine* **56:** 122–125. doi:10.1016/j.cyto.2011.07.006

Bharath LP, Agrawal M, McCambridge G, Nicholas DA, Hasturk H, Liu J, Jiang K, Liu R, Guo Z, Deeney J, et al. 2020. Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. *Cell Metab* **32:** 44–55.e6. doi:10.1016/j.cmet.2020.04.015

Bodogai M, O'Connell J, Kim K, Kim Y, Moritoh K, Chen C, Gusev F, Vaughan K, Shulzhenko N, Mattison JA, et al. 2018. Commensal bacteria contribute to insulin resistance in aging by activating innate B1a cells. *Sci Transl Med* **10:** eaat4271. doi:10.1126/scitranslmed.aat4271

Boehme M, Guzzetta KE, Bastiaanssen TFS, van de Wouw M, Moloney GM, Gual-Grau A, Spichak S, Olavarría-Ramírez L, Fitzgerald P, Morillas E, et al. 2021. Microbiota from young mice counteracts selective age-associated behavioral deficits. *Nat Aging* **1:** 666–676. doi:10.1038/s43587-021-00093-9

Boucher N, Dufeu-Duchesne T, Vicaut E, Farge D, Effros RB, Schächter F. 1998. CD28 expression in T cell aging and human longevity. *Exp Gerontol* **33:** 267–282. doi:10.1016/S0531-5565(97)00132-0

Britanova OV, Putintseva EV, Shugay M, Merzlyak EM, Turchaninova MA, Staroverov DB, Bolotin DA, Lukyanov S, Bogdanova EA, Mamedov IZ, et al. 2014. Age-related decrease in TCR repertoire diversity measured with deep and normalized sequence profiling. *J Immunol* **192:** 2689–2698. doi:10.4049/jimmunol.1302064

Brubaker AL, Rendon JL, Ramirez L, Choudhry MA, Kovacs EJ. 2013. Reduced neutrophil chemotaxis and infiltration contributes to delayed resolution of cutaneous wound infection with advanced age. *J Immunol* **190:** 1746–1757. doi:10.4049/jimmunol.1201213

Brueggeman JM, Zhao J, Schank M, Yao ZQ, Moorman JP. 2022. Trained immunity: an overview and the impact on COVID-19. *Front Immunol* **13:** 837524. doi:10.3389/fimmu.2022.837524

Cano-Gamez E, Soskic B, Roumeliotis TI, So E, Smyth DJ, Baldrighi M, Willé D, Nakic N, Esparza-Gordillo J, Larminie CGC, et al. 2020. Single-cell transcriptomics identifies an effectorness gradient shaping the response of $CD4^+$ T cells to cytokines. *Nat Commun* **11:** 1801. doi:10.1038/s41467-020-15543-y

Capurso C, Bellanti F, Lo Buglio A, Vendemiale G. 2019. The Mediterranean diet slows down the progression of aging and helps to prevent the onset of frailty: a narrative review. *Nutrients* **12:** 35. doi:10.3390/nu12010035

Cartwright TN, Worrell JC, Marchetti L, Dowling CM, Knox A, Kiely P, Mann J, Mann DA, Wilson CL. 2018. HDAC1 interacts with the p50 NF-κB subunit via its nuclear localization sequence to constrain inflammatory gene expression. *Biochim Biophys Acta Gene Regul Mech* **1861:** 962–970. doi:10.1016/j.bbagrm.2018.09.001

Chang LY, Li Y, Kaplan DE. 2017. Hepatitis C viraemia reversibly maintains subset of antigen-specific $T\text{-}bet^+$ tissue-like memory B cells. *J Viral Hepat* **24:** 389–396. doi:10.1111/jvh.12659

Chemin K, Gerstner C, Malmström V. 2019. Effector functions of $CD4^+$ T cells at the site of local autoimmune inflammation—lessons from rheumatoid arthritis. *Front Immunol* **10:** 353. doi:10.3389/fimmu.2019.00353

Chung WSF, Walker AW, Bosscher D, Garcia-Campayo V, Wagner J, Parkhill J, Duncan SH, Flint HJ. 2020. Relative abundance of the Prevotella genus within the human gut microbiota of elderly volunteers determines the inter-individual responses to dietary supplementation with wheat bran arabinoxylan-oligosaccharides. *BMC Microbiol* **20:** 283. doi:10.1186/s12866-020-01968-4

Čížková T, Štěpán M, Daďová K, Ondrůjová B, Sontáková L, Krauzová E, Matouš M, Koc M, Gojda J, Kračmerová J, et al. 2020. Exercise training reduces inflammation of adipose tissue in the elderly: cross-sectional and randomized interventional trial. *J Clin Endocrinol Metab* **105:** dgaa630.

Cleveland H, Jacobs G. 1999. Human choice: the genetic code for social development. *Futures* **31:** 959–970. doi:10.1016/S0016-3287(99)00055-5

Coleman MJ, Zimmerly KM, Yang XO. 2021. Accumulation of $CD28^{null}$ senescent T-cells is associated with poorer outcomes in Covid19 patients. *Biomolecules* **11:** 1425. doi:10.3390/biom11101425

Conway J, Duggal NA. 2021. Ageing of the gut microbiome: potential influences on immune senescence and inflammaging. *Ageing Res Rev* **68:** 101323. doi:10.1016/j.arr.2021.101323

Correia-Melo C, Birch J, Fielder E, Rahmatika D, Taylor J, Chapman J, Lagnado A, Carroll BM, Miwa S, Richardson G. 2019. Rapamycin improves healthspan but not inflammaging in $nfκb1^{-/-}$ mice. *Aging Cell* **18:** e12882. doi:10.1111/acel.12882

Cortegano I, Rodríguez M, Martín I, Prado MC, Ruíz C, Hortigüela R, Alía M, Vilar M, Mira H, Cano E, et al. 2017. Altered marginal zone and innate-like B cells in aged senescence-accelerated SAMP8 mice with defective IgG1 responses. *Cell Death Dis* **8:** e3000. doi:10.1038/cddis.2017.351

Costa-Mattioli M, Walter P. 2020. The integrated stress response: from mechanism to disease. *Science* **368:** eaat5314. doi:10.1126/science.aat5314

Couto MR, Gonçalves P, Magro F, Martel F. 2020. Microbiota-derived butyrate regulates intestinal inflammation: focus on inflammatory bowel disease. *Pharmacol Res* **159:** 104947. doi:10.1016/j.phrs.2020.104947

Davizon-Castillo P, McMahon B, Aguila S, Bark D, Ashworth K, Allawzi A, Campbell RA, Montenont E, Nemkov T, D'Alessandro A, et al. 2019. TNF-α-driven inflammation and mitochondrial dysfunction define the platelet hyperreactivity of aging. *Blood* **134:** 727–740. doi:10.1182/blood.2019000200

de Lemos Muller CH, Roberto de Matos J, Grigolo GB, Schroeder HT, Rodrigues-Krause J, Krauseet M. 2019. Exercise training for the elderly: inflammaging and the central role for HSP70. *J Sci Sport Exerc* **1:** 97–115. doi:10.1007/s42978-019-0015-6

Demaret J, Corroyer-Simovic B, Alidjinou EK, Goffard A, Trauet J, Miczek S, Vuotto F, Dendooven A, Huvent-Grelle D, Podvin J, et al. 2021. Impaired functional T-cell response to SARS-CoV-2 after two doses of BNT162b2 mRNA vaccine in older people. *Front Immunol* **12:** 778679. doi:10.3389/fimmu.2021.778679

Cold Spring Harbor Perspectives in Medicine
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Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, Falony G, Raes J, Maiter D, Delzenne NM, et al. 2019. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat Med* **25:** 1096–1103. doi:10.1038/s41591-019-0495-2

Derisbourg MJ, Hartman MD, Denzel MS. 2021a. Perspective: modulating the integrated stress response to slow aging and ameliorate age-related pathology. *Nat Aging* **1:** 760–768. doi:10.1038/s43587-021-00112-9

Derisbourg MJ, Wester LE, Baddi R, Denzel MS. 2021b. Mutagenesis screen uncovers lifespan extension through integrated stress response inhibition without reduced mRNA translation. *Nat Commun* **12:** 1678. doi:10.1038/s41467-021-21743-x

D'Souza SS, Zhang Y, Bailey JT, Fung ITH, Kuentzel ML, Chittur SV, Yang Q. 2021. Type I interferon signaling controls the accumulation and transcriptomes of monocytes in the aged lung. *Aging Cell* **20:** e13470.

Ehrhardt GR, Hijikata A, Kitamura H, Ohara O, Wang JY, Cooper MD. 2008. Discriminating gene expression profiles of memory B cell subpopulations. *J Exp Med* **205:** 1807–1817. doi:10.1084/jem.20072682

Elyahu Y, Hekselman I, Eizenberg-Magar I, Berner O, Strominger I, Schiller M, Mittal K, Nemirovsky A, Eremenko E, Vital A, et al. 2019. Aging promotes reorganization of the CD4 T cell landscape toward extreme regulatory and effector phenotypes. *Sci Adv* **5:** eaaw8330. doi:10.1126/sciadv.aaw8330

Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, Glynn RJ, Libby P, Ridker PM. 2018. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* **71:** 2392–2401. doi:10.1016/j.jacc.2018.03.002

Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, Libby P, Glynn RJ, Ridker PM. 2019. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation* **139:** 1289–1299. doi:10.1161/CIRCULATIONAHA.118.038010

Ferrucci L, Fabbri E. 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* **15:** 505–522. doi:10.1038/s41569-018-0064-2

Fielder E, Tweedy C, Wilson C, Oakley F, LeBeau FEN, Passos JF, Mann DA, von Zglinicki T, Jurk D. 2020. Anti-inflammatory treatment rescues memory deficits during aging in *nfkb1*$^{-/-}$ mice. *Aging Cell* **19:** e13188. doi:10.1111/acel.13188

Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann NY Acad Sci* **908:** 244–254. doi:10.1111/j.1749-6632.2000.tb06651.x

Franceschi C, Salvioli S, Garagnani P, de Eguileor M, Monti D, Capri M. 2017. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. *Front Immunol* **8:** 982. doi:10.3389/fimmu.2017.00982

Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14:** 576–590. doi:10.1038/s41574-018-0059-4

Frasca D, Romero M, Garcia D, Diaz A, Blomberg BB. 2021. Hyper-metabolic B cells in the spleens of old mice make antibodies with autoimmune specificities. *Immun Ageing* **18:** 9. doi:10.1186/s12979-021-00222-3

Friedman-Korn T, Livovsky DM, Maharshak N, Aviv Cohen N, Paz K, Bar-Gil Shitrit A, Goldin E, Koslowsky B. 2018. Fecal transplantation for treatment of *Clostridium difficile* infection in elderly and debilitated patients. *Dig Dis Sci* **63:** 198–203. doi:10.1007/s10620-017-4833-2

Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, Witkowski JM, Franceschi C. 2018. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? *Front Immunol* **8:** 1960. doi:10.3389/fimmu.2017.01960

Fulop T, Larbi A, Pawelec G, Khalil A, Cohen AA, Hirokawa K, Witkowski JM, Franceschi C. 2023. Immunology of aging: the birth of inflammaging. *Clin Rev Allergy Immunol* **64:** 109–122. doi:10.1007/s12016-021-08899-6

Furman D, Chang J, Lartigue L, Bolen CR, Haddad F, Gaudilliere B, Ganio EA, Fragiadakis GK, Spitzer MH, Douchet I, et al. 2017. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. *Nat Med* **23:** 174–184. doi:10.1038/nm.4267

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, et al. 2019. Chronic inflammation in the etiology of disease across the life span. *Nat Med* **25:** 1822–1832. doi:10.1038/s41591-019-0675-0

García-García VA, Alameda JP, Page A, Casanova ML. 2021. Role of NF-κB in ageing and age-related diseases: lessons from genetically modified mouse models. *Cells* **10:** 1906. doi:10.3390/cells10081906

Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, et al. 2010. Generation of pathogenic T_H17 cells in the absence of TGF-β signalling. *Nature* **467:** 967–971. doi:10.1038/nature09447

Ghosh TS, Das M, Jeffery IB, O'Toole PW. 2020a. Adjusting for age improves identification of gut microbiome alterations in multiple diseases. *eLife* **9:** e50240. doi:10.7554/eLife.50240

Ghosh TS, Rampelli S, Jeffery IB, Santoro A, Neto M, Capri M, Giampieri E, Jennings A, Candela M, Turroni S, et al. 2020b. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut* **69:** 1218–1228. doi:10.1136/gutjnl-2019-319654

Ghosh TS, Shanahan F, O'Toole PW. 2022. The gut microbiome as a modulator of healthy ageing. *Nat Rev Gastroenterol Hepatol* **19:** 565–584. doi:10.1038/s41575-022-00605-x

Gibson KL, Wu YC, Barnett Y, Duggan O, Vaughan R, Kondeatis E, Nilsson BO, Wikby A, Kipling D, Dunn-Walters DK. 2009. B-cell diversity decreases in old age and is correlated with poor health status. *Aging Cell* **8:** 18–25. doi:10.1111/j.1474-9726.2008.00443.x

Goronzy JJ, Weyand CM. 2012. Immune aging and autoimmunity. *Cell Mol Life Sci* **69:** 1615–1623. doi:10.1007/s00018-012-0970-0

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Goronzy JJ, Weyand CM. 2013. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol* **14:** 428–436. doi:10.1038/ni.2588

Grants JM, Wegrzyn J, Hui T, O'Neill K, Shadbolt M, Knapp DJHF, Parker J, Deng Y, Gopal A, Docking TR, et al. 2020. Altered microRNA expression links IL6 and TNF-induced inflammaging with myeloid malignancy in humans and mice. *Blood* **135:** 2235–2251. doi:10.1182/blood.2019003105

Hao Y, O'Neill P, Naradikian MS, Scholz JL, Cancro MP. 2011. A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice. *Blood* **118:** 1294–1304. doi:10.1182/blood-2011-01-330530

Haran JP, Bhattarai SK, Foley SE, Dutta P, Ward DV, Bucci V, McCormick BA. 2019. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. *MBio* **10:** e00632-19. doi:10.1128/mBio.00632-19

Hashimoto K, Kouno T, Ikawa T, Hayatsu N, Miyajima Y, Yabukami H, Terooatea T, Sasaki T, Suzuki T, Valentine M, et al. 2019. Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians. *Proc Natl Acad Sci* **116:** 24242–24251. doi:10.1073/pnas.1907883116

Hazeldine J, Harris P, Chapple IL, Grant M, Greenwood H, Livesey A, Sapey E, Lord JM. 2014. Impaired neutrophil extracellular trap formation: a novel defect in the innate immune system of aged individuals. *Aging Cell* **13:** 690–698. doi:10.1111/acel.12222

Hu Y, Chen Y, Chen Z, Zhang X, Guo C, Yu Z, Xu P, Sun L, Zhou X, Gong Y, et al. 2022. Dysregulated peripheral invariant natural killer T cells in plaque psoriasis patients. *Front Cell Dev Biol* **9:** 799560. doi:10.3389/fcell.2021.799560

Jeffery IB, Lynch DB, O'Toole PW. 2016. Composition and temporal stability of the gut microbiota in older persons. *ISME J* **10:** 170–182. doi:10.1038/ismej.2015.88

Joseph M, Wu Y, Dannebaum R, Rubelt F, Zlatareva I, Lorenc A, Du ZG, Davies D, Kyle-Cezar F, Das A, et al. 2022. Global patterns of antigen receptor repertoire disruption across adaptive immune compartments in COVID-19. *Proc Natl Acad Sci* **119:** e2201541119. doi:10.1073/pnas.2201541119

Jurk D, Wilson C, Passos JF, Oakley F, Correia-Melo C, Greaves L, Saretzki G, Fox C, Lawless C, Anderson R, et al. 2014. Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nat Commun* **5:** 4172. doi:10.1038/ncomms5172

Kaushik S, Tasset I, Arias E, Pampliega O, Wong E, Martinez-Vicente M, Cuervo AM. 2021. Autophagy and the hallmarks of aging. *Ageing Res Rev* **72:** 101468. doi:10.1016/j.arr.2021.101468

Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto RI, Pessin JE, et al. 2014. Geroscience: linking aging to chronic disease. *Cell* **159:** 709–713. doi:10.1016/j.cell.2014.10.039

Knowles A, Campbell S, Cross N, Stafford P. 2021. Bacterial manipulation of the integrated stress response: a new perspective on infection. *Front Microbiol* **12:** 645161. doi:10.3389/fmicb.2021.645161

Knox JJ, Buggert M, Kardava L, Seaton KE, Eller MA, Canaday DH, Robb ML, Ostrowski MA, Deeks SG, Slifka MK, et al. 2017. T-bet^{+} B cells are induced by human viral infections and dominate the HIV gp140 response. *JCI Insight* **2:** e92943. doi:10.1172/jci.insight.92943

Kornete M, Piccirillo CA. 2012. Functional crosstalk between dendritic cells and Foxp3^{+} regulatory T cells in the maintenance of immune tolerance. *Front Immunol* **3:** 165. doi:10.3389/fimmu.2012.00165

Krukowski K, Nolan A, Frias ES, Boone M, Ureta G, Grue K, Paladini MS, Elizarraras E, Delgado L, Bernales S, et al. 2020. Small molecule cognitive enhancer reverses age-related memory decline in mice. *eLife* **9:** e62048. doi:10.7554/eLife.62048

Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. 2018. Probiotic supplementation in patients with Alzheimer's dementia—an explorative intervention study. *Curr Alzheimer Res* **15:** 1106–1113. doi:10.2174/1389200219666180813144834

Lee GH, Lee WW. 2016. Unusual CD4^{+}CD28^{-} T cells and their pathogenic role in chronic inflammatory disorders. *Immune Netw* **16:** 322–329. doi:10.4110/in.2016.16.6.322

Lee KA, Flores RR, Jang IH, Saathoff A, Robbins PD. 2022. Immune senescence, immunosenescence and aging. *Front Aging* **3:** 900028. doi:10.3389/fragi.2022.900028

Le Garff-Tavernier M, Béziat V, Decocq J, Siguret V, Gandjbakhch F, Pautas E, Debré P, Merle-Beral H, Vieillard V. 2010. Human NK cells display major phenotypic and functional changes over the life span. *Aging Cell* **9:** 527–535. doi:10.1111/j.1474-9726.2010.00584.x

Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, Doolman R, Asraf K, Mendelson E, Ziv A, et al. 2021. Waning immune humoral response to BNT162b2 COVID-19 vaccine over 6 months. *N Engl J Med* **385:** e84. doi:10.1056/NEJMoa2114583

Lin H, Liu T, Li X, Gao X, Wu T, Li P. 2020. The role of gut microbiota metabolite trimethylamine N-oxide in functional impairment of bone marrow mesenchymal stem cells in osteoporosis disease. *Ann Transl Med* **8:** 1009. doi:10.21037/atm-20-5307

Listì F, Candore G, Modica MA, Russo M, Di Lorenzo G, Esposito-Pellitteri M, Colonna-Romano G, Aquino A, Bulati M, Lio D, et al. 2006. A study of serum immunoglobulin levels in elderly persons that provides new insights into B cell immunosenescence. *Ann N Y Acad Sci* **1089:** 487–495. doi:10.1196/annals.1386.013

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. 2013. The hallmarks of aging. *Cell* **153:** 1194–1217. doi:10.1016/j.cell.2013.05.039

Luan Z, Sun G, Huang Y, Yang Y, Yang R, Li C, Wang T, Tan D, Qi S, Jun C, et al. 2020. Metagenomics study reveals changes in gut microbiota in centenarians: a cohort study of Hainan centenarians. *Front Microbiol* **11:** 1474. doi:10.3389/fmicb.2020.01474

Manderino L, Carroll I, Azcarate-Peril MA, Rochette A, Heinberg L, Peat C, Steffen K, Mitchell J, Gunstad J. 2017. Preliminary evidence for an association between the composition of the gut microbiome and cognitive function in neurologically healthy older adults. *J Int Neuropsychol Soc* **23:** 700–705. doi:10.1017/S1355617717000492

Marcos-Pérez D, Sánchez-Flores M, Maseda A, Lorenzo-López L, Millán-Calenti JC, Gostner JM, Fuchs D, Pásaro E, Laffon B, Valdiglesias V. 2018. Frailty in older adults is

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associated with plasma concentrations of inflammatory mediators but not with lymphocyte subpopulations. *Front Immunol* **9:** 1056. doi:10.3389/fimmu.2018.01056

Milaneschi Y, Bandinelli S, Corsi AM, Lauretani F, Paolisso G, Dominguez LJ, Semba RD, Tanaka T, Abbatecola AM, Talegawkar SA, et al. 2011. Mediterranean diet and mobility decline in older persons. *Exp Gerontol* **46:** 303–308. doi:10.1016/j.exger.2010.11.030

Mills KHG. 2023. IL-17 and IL-17-producing cells in protection versus pathology. *Nat Rev Immunol* **23:** 38–54. doi:10.1038/s41577-022-00746-9

Mogilenko DA, Shchukina I, Artyomov MN. 2022. Immune ageing at single-cell resolution. *Nat Rev Immunol* **22:** 484–498. doi:10.1038/s41577-021-00646-4

Naradikian MS, Myles A, Beiting DP, Roberts KJ, Dawson L, Herati RS, Bengsch B, Linderman SL, Stelekati E, Spolski R, et al. 2016. Cutting edge: IL-4, IL-21, and IFN-γ interact to govern T-bet and CD11c expression in TLR-activated B cells. *J Immunol* **197:** 1023–1028. doi:10.4049/jimmunol.1600522

Netea MG, Quintin J, van der Meer JW. 2011. Trained immunity: a memory for innate host defense. *Cell Host Microbe* **9:** 355–361. doi:10.1016/j.chom.2011.04.006

Nikolich-Žugich J. 2018. The twilight of immunity: emerging concepts in aging of the immune system. *Nat Immunol* **19:** 10–19. doi:10.1038/s41590-017-0006-x

Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. 2020. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *Geroscience* **42:** 505–514. doi:10.1007/s11357-020-00186-0

Ntemiri A, Ghosh TS, Gheller ME, Tran TTT, Blum JE, Pellanda P, Vlckova K, Neto MC, Howell A, Thalacker-Mercer A, et al. 2020. Whole blueberry and isolated polyphenol-rich fractions modulate specific gut microbes in an in vitro colon model and in a pilot study in human consumers. *Nutrients* **12:** 2800. doi:10.3390/nu12092800

Nussbaum L, Chen YL, Ogg GS. 2021. Role of regulatory T cells in psoriasis pathogenesis and treatment. *Br J Dermatol* **184:** 14–24. doi:10.1111/bjd.19380

Ogawa K, Suzuki K, Okutsu M, Yamazaki K, Shinkai S. 2008. The association of elevated reactive oxygen species levels from neutrophils with low-grade inflammation in the elderly. *Immun Ageing* **5:** 13. doi:10.1186/1742-4933-5-13

Orkaby AR, Dufour AB, Yang L, Sesso HD, Gaziano JM, Djousse L, Driver JA, Travison TG. 2022. Long-term aspirin use and self-reported walking speed in older men: the physicians' health study. *J Frailty Aging* **11:** 12–17.

Pahor M, Guralnik JM, Anton SD, Ambrosius WT, Blair SN, Church TS, Espeland MA, Fielding RA, Gill TM, Glynn NW, et al. 2020. Impact and lessons from the lifestyle interventions and independence for elders (LIFE) clinical trials of physical activity to prevent mobility disability. *J Am Geriatr Soc* **68:** 872–881. doi:10.1111/jgs.16365

Pang WW, Schrier SL, Weissman IL. 2017. Age-associated changes in human hematopoietic stem cells. *Semin Hematol* **54:** 39–42. doi:10.1053/j.seminhematol.2016.10.004

Parker A, Romano S, Ansorge R, Aboelnour A, Le Gall G, Savva GM, Pontifex MG, Telatin A, Baker D, Jones E, et al. 2022. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain. *Microbiome* **10:** 68. doi:10.1186/s40168-022-01243-w

Pereira BI, De Maeyer RPH, Covre LP, Nehar-Belaid D, Lanna A, Ward S, Marches R, Chambers ES, Gomes DCO, Riddell NE, et al. 2020. Sestrins induce natural killer function in senescent-like $CD8^+$ T cells. *Nat Immunol* **21:** 684–694. doi:10.1038/s41590-020-0643-3

Povoleri GAM, Lalnunhlimi S, Steel KJA, Agrawal S, O'Byrne AM, Ridley M, Kordasti S, Frederiksen KS, Roberts CA, Taams LS. 2020. Anti-TNF treatment negatively regulates human $CD4^+$ T-cell activation and maturation in vitro, but does not confer an anergic or suppressive phenotype. *Eur J Immunol* **50:** 445–458. doi:10.1002/eji.201948190

Pritz T, Lair J, Ban M, Keller M, Weinberger B, Krismer M, Grubeck-Loebenstein B. 2015. Plasma cell numbers decrease in bone marrow of old patients. *Eur J Immunol* **45:** 738–746. doi:10.1002/eji.201444878

Puchta A, Naidoo A, Verschoor CP, Loukov D, Thevaranjan N, Mandur TS, Nguyen PS, Jordana M, Loeb M, Xing Z, et al. 2016. TNF drives monocyte dysfunction with age and results in impaired anti-pneumococcal immunity. *PLoS Pathog* **12:** e1005368. doi:10.1371/journal.ppat.1005368

Rampelli S, Soverini M, D'Amico F, Barone M, Tavella T, Monti D, Capri M, Astolfi A, Brigidi P, Biagi E, et al. 2020. Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. *mSystems* **5:** e00124-20. doi:10.1128/mSystems.00124-20

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. 2017a. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* **377:** 1119–1131. doi:10.1056/NEJMoa1707914

Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, CANTOS Trial Group. 2017b. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* **390:** 1833–1842.

Rodriguez IJ, Lalinde Ruiz N, Llano León M, Martínez Enríquez L, Montilla Velásquez MDP, Ortiz Aguirre JP, Rodríguez Bohórquez OM, Velandia Vargas EA, Hernández ED, Parra López CA. 2021. Immunosenescence study of T cells: a systematic review. *Front Immunol* **11:** 604591. doi:10.3389/fimmu.2020.604591

Rubtsov AV, Rubtsova K, Fischer A, Meehan RT, Gillis JZ, Kappler JW, Marrack P. 2011. Toll-like receptor 7 (TLR7)–driven accumulation of a novel $CD11c^+$ B-cell population is important for the development of autoimmunity. *Blood* **118:** 1305–1315. doi:10.1182/blood-2011-01-331462

Rubtsova K, Rubtsov AV, Cancro MP, Marrack P. 2015. Age-associated B cells: a T-bet-dependent effector with roles in protective and pathogenic immunity. *J Immunol* **195:** 1933–1937. doi:10.4049/jimmunol.1501209

Sabini E, O'Mahony A, Caturegli P. 2023. MyMD-1 improves health span and prolongs lifespan in old mice: a noninferiority study to rapamycin. *J Gerontol A Biol Sci Med Sci* **78:** 227–235. doi:10.1093/gerona/glac142

Sakata-Kaneko S, Wakatsuki Y, Matsunaga Y, Usui T, Kita T. 2000. Altered Th1/Th2 commitment in human $CD4^+$ T cells with ageing. *Clin Exp Immunol* **120:** 267–273. doi:10.1046/j.1365-2249.2000.01224.x

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Salas-Salvadó J, Becerra-Tomás N, García-Gavilán JF, Bulló M, Barrubés L. 2018. Mediterranean diet and cardiovascular disease prevention: what do we know? *Prog Cardiovasc Dis* **61:** 62–67. doi:10.1016/j.pcad.2018.04.006

Santoro A, Bientinesi E, Monti D. 2021. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? *Ageing Res Rev* **71:** 101422. doi:10.1016/j.arr.2021.101422

Sauce D, Dong Y, Campillo-Gimenez L, Casulli S, Bayard C, Autran B, Boddaert J, Appay V, Elbim C. 2017. Reduced oxidative burst by primed neutrophils in the elderly individuals is associated with increased levels of the $CD16^{bright}/CD62L^{dim}$ immunosuppressive subset. *J Gerontol A Biol Sci Med Sci* **72:** 163–172. doi:10.1093/gerona/glw062

Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, Grawe AP, Gao T, Tibshirani R, Hastie T, Alpert A, Cui L, et al. 2021. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nat Aging* **1:** 598–615. doi:10.1038/s43587-021-00082-y

Schieker M, Conaghan PG, Mindeholm L, Praestgaard J, Solomon DH, Scotti C, Gram H, Thuren T, Roubenoff R, Ridker PM. 2020. Effects of interleukin-1β inhibition on incident hip and knee replacement: exploratory analyses from a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* **173:** 509–515. doi:10.7326/M20-0527

Sciorati C, Gamberale R, Monno A, Citterio L, Lanzani C, De Lorenzo R, Ramirez GA, Esposito A, Manunta P, Manfredi AA, et al. 2020. Pharmacological blockade of TNFα prevents sarcopenia and prolongs survival in aging mice. *Aging (Albany NY)* **12:** 23497–23508. doi:10.18632/aging.202200

Selvarani R, Mohammed S, Richardson A. 2021. Effect of rapamycin on aging and age-related diseases—past and future. *Geroscience* **43:** 1135–1158. doi:10.1007/s11357-020-00274-1

Sen R, Smale ST. 2010. Selectivity of the NF-κB response. *Cold Spring Harb Perspect Biol* **2:** a000257.

Sharma R. 2021. Perspectives on the dynamic implications of cellular senescence and immunosenescence on macrophage aging biology. *Biogerontology* **22:** 571–587. doi:10.1007/s10522-021-09936-9

Shin J, Noh JR, Choe D, Lee N, Song Y, Cho S, Kang EJ, Go MJ, Ha SK, Chang DH, et al. 2021. Ageing and rejuvenation models reveal changes in key microbial communities associated with healthy ageing. *Microbiome* **9:** 240. doi:10.1186/s40168-021-01189-5

Shive C, Pandiyan P. 2022. Inflammation, immune senescence, and dysregulated immune regulation in the elderly. *Front Aging* **3:** 840827. doi:10.3389/fragi.2022.840827

Simell B, Vuorela A, Ekström N, Palmu A, Reunanen A, Meri S, Käyhty H, Väkeväinen M. 2011. Aging reduces the functionality of anti-pneumococcal antibodies and the killing of streptococcus pneumoniae by neutrophil phagocytosis. *Vaccine* **29:** 1929–1934. doi:10.1016/j.vaccine.2010.12.121

Singh H, Torralba MG, Moncera KJ, DiLello L, Petrini J, Nelson KE, Pieper R. 2019. Gastro-intestinal and oral microbiome signatures associated with healthy aging. *Geroscience* **41:** 907–921. doi:10.1007/s11357-019-00098-8

Squarzoni S, Schena E, Sabatelli P, Mattioli E, Capanni C, Cenni V, D'Apice MR, Andrenacci D, Sarli G, Pellegrino V, et al. 2021. Interleukin-6 neutralization ameliorates symptoms in prematurely aged mice. *Aging Cell* **20:** e13285. doi:10.1111/acel.13285

Solá P, Mereu E, Bonjoch J, Casado M, Reina O, Blanco E, Esteller M, DiCroce L, Heyn H, Solanas G, et al. 2023. Targeting lymphoid-derived IL-17 signaling to delay skin aging. *Nat Aging* **3:** 688–704. doi:10.1038/s43587-023-00431-z

Songkiatisak P, Rahman SMT, Aqdas M, Sung MH. 2022. NF-κB, a culprit of both inflamm-ageing and declining immunity? *Immun Ageing* **19:** 20. doi:10.1186/s12979-022-00277-w

Tabibian-Keissar H, Hazanov L, Schiby G, Rosenthal N, Rakovsky A, Michaeli M, Shahaf GL, Pickman Y, Rosenblatt K, Melamed D, et al. 2016. Aging affects B-cell antigen receptor repertoire diversity in primary and secondary lymphoid tissues. *Eur J Immunol* **46:** 480–492. doi:10.1002/eji.201545586

Tam AB, Mercado EL, Hoffmann A, Niwa M. 2012. ER stress activates NF-κB by integrating functions of basal IKK activity, IRE1 and PERK. *PLoS ONE* **7:** e45078. doi:10.1371/journal.pone.0045078

Tanaka T, Talegawkar SA, Jin Y, Colpo M, Ferrucci L, Bandinelli S. 2018. Adherence to a Mediterranean diet protects from cognitive decline in the Invecchiare in Chianti study of aging. *Nutrients* **10:** 2007. doi:10.3390/nu10122007

Taniguchi K, Karin M. 2018. NF-κB, inflammation, immunity and cancer: coming of age. *Nat Rev Immunol* **18:** 309–324. doi:10.1038/nri.2017.142

Tavenier J, Rasmussen LJH, Houlind MB, Andersen AL, Panum I, Andersen O, Petersen J, Langkilde A, Nehlin JO. 2020. Alterations of monocyte NF-κB p65/RelA signaling in a cohort of older medical patients, age-matched controls, and healthy young adults. *Immun Ageing* **17:** 25. doi:10.1186/s12979-020-00197-7

Teissier T, Boulanger E, Cox LS. 2022. Interconnections between inflammageing and immunosenescence during ageing. *Cells* **11:** 359. doi:10.3390/cells11030359

Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, Loukov D, Schenck LP, Jury J, Foley KP, et al. 2017. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host Microbe* **21:** 455–466.e4. doi:10.1016/j.chom.2017.03.002

Tilstra JS, Robinson AR, Wang J, Gregg SQ, Clauson CL, Reay DP, Nasto LA, St Croix CM, Usas A, Vo N, et al. 2012. NF-κB inhibition delays DNA damage-induced senescence and aging in mice. *J Clin Invest* **122:** 2601–2612. doi:10.1172/JCI45785

Tsigalou C, Konstantinidis T, Paraschaki A, Stavropoulou E, Voidarou C, Bezirtzoglou E. 2020. Mediterranean diet as a tool to combat inflammation and chronic diseases. An overview. *Biomedicines* **8:** 201.

Vallurupalli M, MacFadyen JG, Glynn RJ, Thuren T, Libby P, Berliner N, Ridker PM. 2020. Effects of interleukin-1β inhibition on incident anemia: exploratory analyses

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from a randomized trial. *Ann Intern Med* **172:** 523–532. doi:10.7326/M19-2945

Verma N, Dimitrova M, Carter DM, Crevar CJ, Ross TM, Golding H, Khurana S. 2012. Influenza virus H1N1pdm09 infections in the young and old: evidence of greater antibody diversity and affinity for the hemagglutinin globular head domain (HA1 domain) in the elderly than in young adults and children. *J Virol* **86:** 5515–5522. doi:10.1128/JVI.07085-11

Walford RL. 1969. Immunologische aspekte des alterns [Immunologic aspects of aging]. *Klin Wochenschr* **47:** 599–605. doi:10.1007/BF01876949

Walker KA, Basisty N, Wilson DM 3rd, Ferrucci L. 2022. Connecting aging biology and inflammation in the omics era. *J Clin Invest* **132:** e158448. doi:10.1172/JCI158448

Wang S, Wang J, Kumar V, Karnell JL, Naiman B, Gross PS, Rahman S, Zerrouki K, Hanna R, Morehouse C, et al. 2018. IL-21 drives expansion and plasma cell differentiation of autoreactive CD11c^{hi}T-bet^{+} B cells in SLE. *Nat Commun* **9:** 1758. doi:10.1038/s41467-018-03750-7

Wang Y, Hao Q, Su L, Liu Y, Liu S, Dong B. 2018. Adherence to the Mediterranean diet and the risk of frailty in old people: a systematic review and meta-analysis. *J Nutr Health Aging* **22:** 613–618. doi:10.1007/s12603-018-1020-x

Wendt K, Wilk E, Buyny S, Buer J, Schmidt RE, Jacobs R. 2006. Gene and protein characteristics reflect functional diversity of CD56^{dim} and CD56^{bright} NK cells. *J Leukoc Biol* **80:** 1529–1541. doi:10.1189/jlb.0306191

Weng N, Akbar AN, Goronzy J. 2009. CD28^{-} T cells: their role in the age-associated decline of immune function. *Trends Immunol* **30:** 306–312. doi:10.1016/j.it.2009.03.013

Wenisch C, Patruta S, Daxböck F, Krause R, Hörl W. 2000. Effect of age on human neutrophil function. *J Leukoc Biol* **67:** 40–45. doi:10.1002/jlb.67.1.40

Woods RL, Espinoza S, Thao LTP, Ernst ME, Ryan J, Wolfe R, Shah RC, Ward SA, Storey E, Nelson MR, et al. 2021. Effect of aspirin on activities of daily living disability in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* **76:** 2007–2014. doi:10.1093/gerona/glaa316

Yang X, Wang X, Lei L, Sun L, Jiao A, Zhu K, Xie T, Liu H, Zhang X, Su Y, et al. 2021. Age-related gene alteration in naive and memory T cells using precise age-tracking model. *Front Cell Dev Biol* **8:** 624380. doi:10.3389/fcell.2020.624380

Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, Cui Y, Angelini L, Lee KA, McGowan SJ, et al. 2021. An aged immune system drives senescence and ageing of solid organs. *Nature* **594:** 100–105. doi:10.1038/s41586-021-03547-7

Zhang L, Zhao J, Mu X, McGowan SJ, Angelini L, O'Kelly RD, Yousefzadeh MJ, Sakamoto A, Aversa Z, LeBrasseur NK, et al. 2021. Novel small molecule inhibition of IKK/NF-κB activation reduces markers of senescence and improves healthspan in mouse models of aging. *Aging Cell* **20:** e13486.

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