Journal Pre-proof

Inflamm-aging as a diverse and context-dependent process: from species and population differences to individual trajectories

Maximilien Franck, Camille Daunizeau, Jacob E. Aronoff, Kamaryn Tanner, Benjamin C. Trumble, Claudio Franceschi, Johannes Hertel, Tamás Fülöp, Maël Lemoine, Michael Gurven, Alan A. Cohen

PII: S1568-1637(25)00226-0

DOI: https://doi.org/10.1016/j.arr.2025.102880

Reference: ARR102880

To appear in: *Ageing Research Reviews*

Received date: 18 June 2025
Revised date: 11 August 2025
Accepted date: 23 August 2025

Please cite this article as: Maximilien Franck, Camille Daunizeau, Jacob E. Aronoff, Kamaryn Tanner, Benjamin C. Trumble, Claudio Franceschi, Johannes Hertel, Tamás Fülöp, Maël Lemoine, Michael Gurven and Alan A. Cohen, Inflamm-aging as a diverse and context-dependent process: from species and population differences to individual trajectories, *Ageing Research Reviews,* (2025) doi:https://doi.org/10.1016/j.arr.2025.102880

Inflamm-aging as a diverse and context-dependent process: from species and population differences to individual trajectories

Maximilien Franck[1*], Camille Daunizeau[2], Jacob E. Aronoff[3], Kamaryn Tanner[4], Benjamin C. Trumble[3], Claudio Franceschi[5], Johannes Hertel[6,7], Tamás Fülöp[1], Maël Lemoine[8], Michael Gurven[9], and Alan A. Cohen[4*]

[1] Research Center on Aging, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, QC, Canada

[2] Population Health and Optimal Health Practices Branch, CHU de Québec Research Center, Québec, QC, Canada

[3] Center for Evolution and Medicine, School of Human Evolution and Social Change, Institute of Human Origins, Arizona State University, Tempe, AZ, USA

[4] Department of Environmental Health Sciences, Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, NY, USA

[5] Institute of Biogerontology, Lobachevsky State University, Nizhny Novgorod, Russia

[6] Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany

[7] German Center for Cardiovascular Diseases, partner site, Greifswald, Germany

[8] ImmunoConcept (UMR5164), CNRS, Department of Biological and Health Sciences, University of Bordeaux, Bordeaux, France

[9] Department of Anthropology, University of California Santa Barbara, Santa Barbara, CA, USA

***Corresponding Authors**

Maximilien Franck and Alan A. Cohen

maximilien.franck5@gmail.com

aac2277@cumc.columbia.edu

Keywords

Inflamm-aging; Inflammation; Homeostasis; Immunosenescence; Macroph-aging; Cytokines; Multivariate inflammatory measurements; Bow-tie architecture; Chronic diseases; Evolutionary immunology; Mismatched environments; Systems biology; Hormesis; Non-industrialized populations

Abstract

Inflamm-aging is widely considered a hallmark of aging, yet emerging evidence challenges its universality. Here, we re-examine inflamm-aging through an eco-evolutionary lens, underlining its context dependence across biological scales. Combining mechanistic, evolutionary, comparative, anthropological, genetic, and environmental evidence, we show how fundamental inflammatory mechanisms are integrated and regulated in diverse biological contexts, representing a suite of flexible stress responses. Drawing on studies from non-industrialized populations, which suggest that inflamm-aging reflects mismatches between evolved human biology and industrialized exposomes, we explore how population-specific evolutionary histories and environmental exposures shape differential predispositions and trajectories of inflamm-aging. We propose that, to the extent that inflammation represents this broad suite of stress responses, increases in at least some dimensions of inflammation with age should be nearly universal, as other physiological processes break down and internal stresses mount. However, the particular set of internal stressors that is triggered in a given species, environmental context, or individual is likely more specific, implying that there is unlikely to be any universal signature of inflamm-aging. The question of whether inflamm-aging is universal thus hinges on whether it is defined broadly as any increase in activation of any inflammatory systems, or more narrowly as a particular suite, such as those activated in industrialized populations with high levels of sedentary behavior and cardiometabolic diseases. Inflamm-aging is ultimately a norm of reaction – an aging-related inflammatory profile whose phenotypic expression varies with genotype and environment – and research should therefore focus on understanding how ecological, evolutionary, and environmental factors modulate inflammation and its age-related trajectory.

I. Introduction

a) Definition and importance of inflamm-aging

Aging involves changes in various aspects of human biology, including immune-related changes known as immunosenescence [1,2]. As aging progresses, the immune system undergoes complex remodeling, characterized by both functional alterations and adaptive changes, resulting in altered immune responses and increased susceptibility to infections and chronic non-communicable diseases (CNCDs). Importantly, a progressive reshaping of the expression patterns of inflammatory mediators produced by immune cells establishes a non-resolving, chronic, low-grade, systemic, sterile (without overt infection), inflammatory state referred to as 'inflamm-aging' [3]. Concurrently, senescent cells that accumulate across tissues contribute to this phenomenon through a steady trickle of pro-inflammatory mediators, especially as immunosenescence increasingly impairs their clearance by immune cells [4–9]. Inflamm-aging has been implicated in the loss of cognitive and physical function and in the pathogenesis of many age-related CNCDs [10,11]. In very old individuals, frailty has been strongly associated with elevated inflammatory mediators (CRP, IL-6, TNF-α), while no significant associations were observed with cellular aging (telomere length, oxidative stress, or DNA damage/repair), underscoring the importance of systemic inflammation (inflamm-aging) in late-life physiological decline [12]. Inflamm-aging is thought to result from lifelong stress, notably the cumulative lifetime exposure to antigenic load, driven by both clinical and subclinical infections, as well as noninfectious antigen exposure [3,13]. As accumulating evidence suggests a cause-effect relationship between inflamm-aging and age-related tissue deterioration, Claudio Franceschi, who coined inflamm-aging, underlined the importance of tissue-resident macrophages in the production of inflammatory mediators, due to increasing stimulation by damage-associated molecular patterns (DAMPs) (oxidized, misfolded, glycated, or ubiquitinylated proteins, extracellular ATP, mitochondrial DNA, ceramides, cardiolipin, formyl peptides, etc.), a phenomenon he called 'macroph-aging' [3,14]. Age-related tissue deterioration is significantly influenced by extracellular matrix (ECM) remodeling, marked by changes in stiffness (through collagen cross-linking and glycation), composition (e.g. collagen, elastin, proteoglycans), and signaling [15,16]. Critically, by releasing proteases that degrade ECM into fragments, senescent cells both promote tissue deterioration and fuel macroph-aging [17–19].

b) Measurement of inflamm-aging

There is no consensus measurand for inflamm-aging – that is, no agreed-upon specific biomarker or standardized metric that definitively captures this process (Figure 1). In most human epidemiological studies, inflamm-aging has been characterized by elevated blood levels of pro-inflammatory mediators, such as C-reactive protein (CRP), interleukin (IL)-6, IL-1β, IL-8, IL-15, tumor necrosis factor (TNF)-α, C-X-C motif chemokine ligand (CXCL) 9, and colony-stimulating factor 1, as well as other inflammation-associated markers like platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) family members [20–31]. However, there is no definitive list, and the markers used vary widely across studies. Certain studies target proteins involved in intracellular signaling pathways. For instance, the iAge metric, a multivariate inflammatory clock predicting multimorbidity, is based on circulating cytokine levels; its relevance, however, has been validated through phosphorylation levels of signal transducer and activator of transcription (STAT) proteins (STAT1, STAT3, and STAT5) in peripheral

blood mononuclear cells stimulated with interferon (IFN)-α, IL-6, IL-10, and IL-2 [27]. Other studies have examined: the phosphorylation of the p65 subunit of nuclear factor-κB (NF-κB) in total monocytes and their subsets, either at baseline or following exposure to lipopolysaccharide (LPS) or TNF-α [32]; basal phosphorylation of both the p65 subunit of NF-κB and STAT proteins (STAT1, STAT3, and STAT5) in total peripheral blood mononuclear cells and in monocyte and lymphocyte subsets, as well as in vitro toll-like receptor (TLR)-4-stimulated monocytic production of IL-6 and TNF-α in response to LPS [33]. Similarly, in mice, inflamm-aging has been measured through the phosphorylation of mechanistic target of rapamycin (mTOR) and of the p65 subunit of NF-κB in colonic cells and peritoneal macrophages [34]; in *Drosophila*, through the cleavage and nuclear translocation of the NF-κB-like transcription factor Relish in the fat body [35] and in the brain [36]; in great tits, through leukotriene B4 levels [37]; and in mice, rats, rhesus monkeys, and humans, in skeletal muscles, through the ratio of phospho-active NF-κB to total NF-κB, cytokine transcripts (TNF-α, IL-1β, IL-6, and IL-10), and levels of cyclooxygenase-2 (an enzyme involved in the conversion of arachidonic acid to prostaglandin H2) [38].

c) Inflamm-aging as a universal hallmark of aging?

Because inflamm-aging has been documented in diverse species—including rodents [34], dogs [39,40], monkeys [38], birds [37], fishes [41,42], and even flies [35,36]—it is widely accepted in the scientific community as part of the aging process, common to mammals and possibly all bilaterians (e.g., *Drosophila*). As a result, it was incorporated into the "hallmarks of aging" framework [43], which is central in geroscience. Inflamm-aging is viewed as a "hub" for aging, tightly interconnected with other hallmarks and regarded as both a cause and an effect of age-related cellular changes [44]. In this framework, accumulating cellular damage from primary hallmarks (e.g., genomic instability, loss of proteostasis, disabled macroautophagy) and the initially adaptive, but ultimately detrimental, responses of antagonistic hallmarks (e.g., cellular senescence, deregulated nutrient sensing) collectively drive the emergence of integrative hallmarks, including inflamm-aging [2]. By definition, a hallmark of aging must manifest during physiological aging, worsen aging when experimentally intensified, and slow aging when experimentally mitigated, thereby increasing lifespan [2]. Thus, inflamm-aging is viewed as a universal, inexorable process inherent to aging, one that could be slowed by an optimal lifestyle or accelerated by a poor lifestyle. However, recent studies suggest that inflamm-aging may be absent in certain Indigenous, non-industrialized populations (NIPs) [45,46], calling into question the notion that inflamm-aging is truly universal, and forcing a re-examination of its fundamental nature and boundaries.

This essay synthesizes evidence from immunology, evolutionary biology, cellular and systems biology, and anthropology to delineate the nature and scope of inflamm-aging. The argumentative line is as follows: We first define inflammation and explore its evolutionary origins by tracing ancestral cellular stress responses and the diversification of inflammatory signaling pathways (section II). Clarifying these evolutionary roots helps us to understand why inflammatory responses are inherently context-dependent, complicating the search for universal measurands (section III). We then explore species-specific differences in inflammatory signaling components, homeostatic regulation, and life-history strategies (section IV), questioning the universality of inflamm-aging and discussing the challenge posed by the 'public' nature of inflamm-aging and the 'private' nature of perturbations (section V). Next, we shift our focus to within-species variability by examining how the human exposome shapes inflamm-aging

trajectories, highlighting recent comparative studies between industrialized and non-industrialized populations and their implications for interpreting inflamm-aging (section VI). We follow with a focused look at macrophages, showing how environmental pressures modulate macrophage polarization and "macroph-aging." (section VII). Finally, we propose that inflamm-aging is best conceptualized as a norm of reaction shaped by evolutionary mismatch, and highlight the difficulty of defining consistent measurands across diverse species and contexts (section VIII).

II. Evolutionary origins of inflammation

a) Conceptual framework: definitions and scope of inflammation

The immune system comprises a complex network of cells and molecules, dispersed throughout the body, designed to recognize non-self-elements and elicit protective responses. Inflammation, an evolutionarily conserved mechanism, is at the core of this defense. It is traditionally defined as the organism's defense reaction to infection or tissue injury; however, inflammation can also manifest in the absence of these triggers, as observed in instances such as obesity (meta-inflammation [47]), CNCDs, and aging (inflamm-aging), thus highlighting that factors other than infections and injuries can elicit inflammation. Ruslan Medzhitov conceptualized substantial and continued perturbations of homeostasis in mammals, with a major implication of macrophages, to be a root cause of CNCDs that invariably are accompanied by inflammation [48,49]. Biological systems actively maintain certain variables near set-point values in the face of environmental or internal perturbations through homeostatic circuits at the levels of the cell, tissue, and organism [49]. His perspective suggests that inflammation arises when perturbations cause deviations from homeostasis that exceed the capacity of homeostatic mechanisms [48,50,51]. Inflammation-inducing perturbations and their detection mechanisms by the organism are diverse, but substantial homeostatic deviation remains their common denominator (Figure 1). Typically, the detection through pattern recognition receptors (PRRs) of both pathogen-associated molecular patterns (PAMPs), anticipating a potential infection, or DAMPs, monitoring the consequences of tissue damage (which can be due to an infection or an injury) can induce an inflammatory response [52]. But beyond loss of structural integrity (resulting from injuries or infections), which represent extreme perturbations, loss of tissue-specific functionalities such as the disruption of mucociliary clearance in the respiratory tract by airborne particulates (e.g., pollutants, pollen, chitin) [53] or loss of regulation of physiological processes induced, for instance, by cold exposure [54], starvation [55], dehydration [56], or intense physical activity [57], can also induce different modalities of inflammation. The inflammatory response is thus a tissue/system-wide process aimed at restoring structural and functional homeostasis that integrates stress cues, immune, metabolic, and neuroendocrine signals, and orchestrates immune effector engagement, tissue remodeling, metabolic adjustments, and behavioral responses [51].

Systemic homeostasis relies on endocrine and autonomic sensors, such as sensory neurons and endocrine cells, to regulate variables like temperature, blood glucose and pH through hormonal and neural feedback, while tissue level homeostasis primarily depends on macrophages, which act as local sensors by monitoring ECM integrity (e.g., density, stiffness, cell composition, oxygen levels, osmolality) and effectors by removing apoptotic and senescent cells, and by orchestrating ECM remodeling through context-specific transcriptional programs [48–50].

Macrophages are present in nearly all tissues in the organism (e.g., Kupffer cells, microglia, alveolar macrophages, Langerhans cells, Hofbauer cells, histiocytes) and undergo gene expression alterations in response to various perturbations, adapting their production of inflammatory mediators (e.g., cytokines, chemokines, eicosanoids, growth factors) [58]. They bridge homeostatic and inflammatory processes through shared mechanisms: even under optimal conditions, there are always byproducts (e.g., metabolic, structural debris/ DAMPs) that must be managed. The clearance of these byproducts is part of the homeostatic role of macrophages, but their overload can trigger inflammation. For instance, apoptotic bodies are continuously generated as part of normal tissue homeostasis and are removed by macrophages through efferocytosis, which prevents secondary necrosis and promotes the release of anti-inflammatory cytokines; however, when clearance is impaired (either due to excessive apoptotic burden or defects in macrophage function) the accumulation of apoptotic debris triggers the release of pro-inflammatory cytokines [59]. Thus, senescent cells actively inhibit macrophage efferocytosis by upregulating the 'do not eat me' signal CD47, which prevents macrophages from clearing both senescent and neighboring apoptotic corpses, thereby compromising tissue level homeostasis [6]. This way, many 'inflammatory' mediators routinely participate in normal physiological processes without triggering any overt inflammation [60]; for instance, IL-22 promotes intestinal epithelial proliferation, Paneth cell differentiation, and antimicrobial peptide secretion, thereby contributing to gut homeostasis under physiological conditions [61].

Therefore, Medzhitov proposed that inflammation manifests along a spectrum: at one end is the acute canonical inflammatory response, characterized by the cardinal signs of inflammation in the context of infection or injury. Further along the spectrum, cellular effectors and molecular mediators of inflammation are also engaged in lower-grade responses to factors such as temperature fluctuations, pregnancy, lactation, major dietary shifts, or even emotional disturbances. At the other end, they are engaged in normal homeostatic processes in the absence of any perturbations [51,52]. But how can the same mechanisms be engaged in responding to such diverse perturbations? How did the inflammatory response become so integrated? When we assess inflamm-aging across species, we risk overlooking the main point by focusing solely on pathways and signaling molecules: inflammation arises when homeostatic capacities are exceeded. Even if some central biomarkers are evolutionarily well conserved, pathways, signaling molecules, and even homeostatic mechanisms have diverged across species over the course of evolution, showing that inflammation is not a fixed molecular program, but a flexible, integrative response shaped by evolutionary history and context.

From there, we will first explore how the pathways diversified from unicellular organisms to vertebrates and how the escalating tissue and systemic level homeostatic requirements of multicellular organisms shaped an increasingly integrated, multi-system inflammatory response.

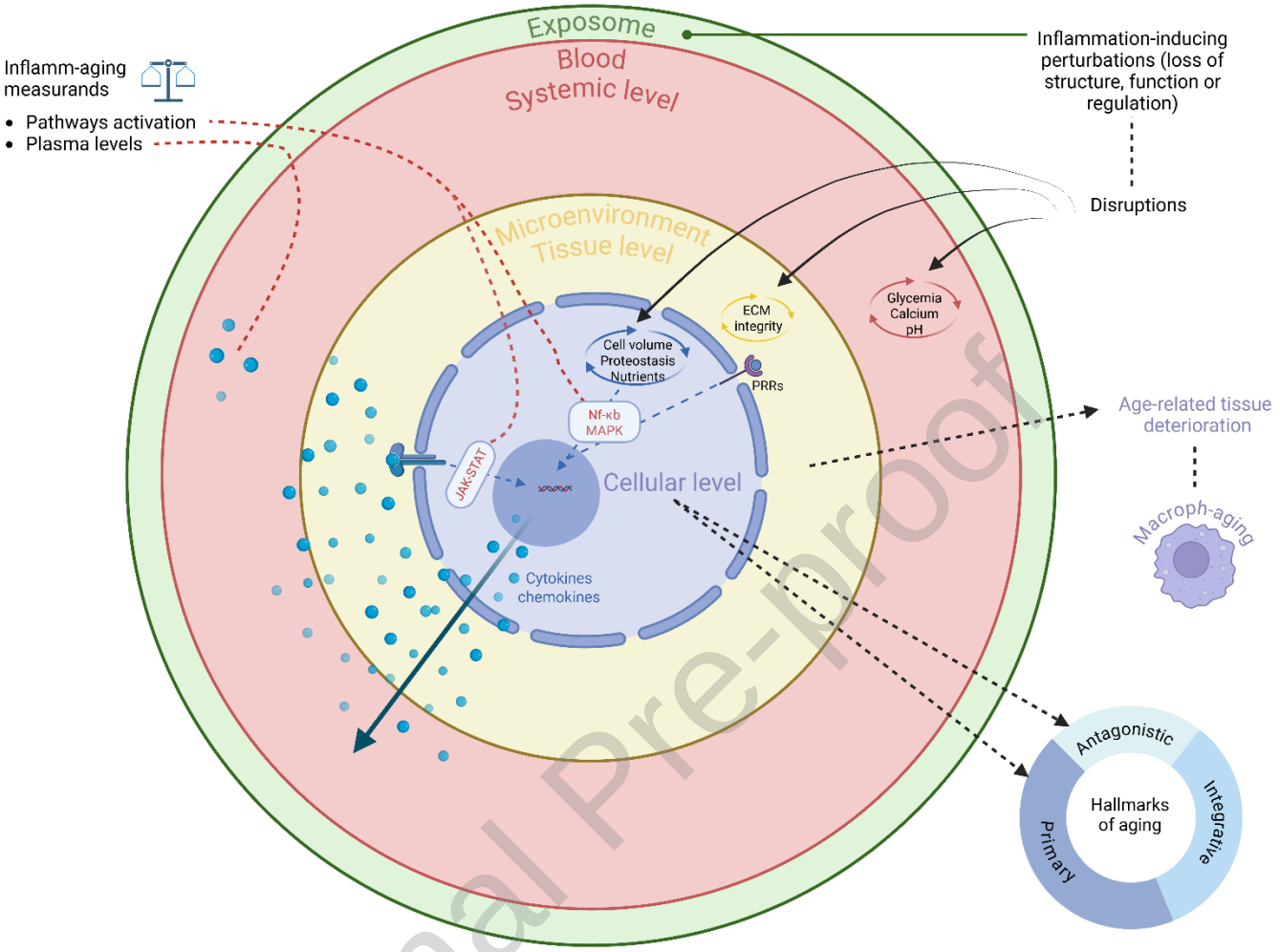


Figure 1. Conceptual diagram illustrating inflamm-aging/inflammation as a multi-scale process integrating cellular, tissue, and systemic levels. Inflammation-inducing perturbations shape the aging/inflamm-aging trajectory throughout life. Most hallmarks of aging manifest at the cellular level, and while homeostasis is primarily studied at the cellular and systemic levels, disruptions can occur at all three levels (cellular, tissue, organismal), with perturbations at one level often propagating to the others. Perturbations initially activate intracellular inflammatory pathways, primarily NF-κB, leading stressed or damaged cells to release cytokines such as IL-6, which subsequently propagate inflammation by activating secondary signaling cascades, notably the JAK-STAT pathway. The tissue level, in particular, plays a crucial role in amplifying and sustaining these inflammatory signals, contributing to age-related tissue deterioration and macroph-aging. Inflamm-aging is primarily assessed by measuring plasma levels of inflammatory mediators (e.g., IL-6, CRP) and the activation of intracellular pathways (NF-κB subunits and STAT proteins) (created with https://BioRender.com).

b) Evolution of homeostatic challenges and inflammation

The evolution of the inflammatory response was shaped by selective pressures to maintain homeostasis across increasing levels of biological organization. Our unicellular ancestors first evolved cellular stress response mechanisms to counter environmental fluctuations such as osmotic, thermal, or oxidative stress when homeostatic capacity was exceeded. With the advent of multicellularity, intracellular components

of inflammatory signaling pathways we know today, notably NF-κB and Janus kinase (JAK)-STAT, were co-opted and integrated into systems coordinating not only homeostatic maintenance at the cellular level but also at the tissue level (e.g., tissue integrity, coordinated cell responses). Evolutionarily, the fully assembled and ligand-responsive cytokine receptor-JAK-STAT signaling pathway likely emerged in *Bilateria* [62,63]; for instance, *Drosophila* already possesses a complete, functional pathway comprising three cytokine-like proteins, one receptor, one JAK kinase, and one STAT transcription factor [64]. See Supplementary Note 1 for details on the evolutionary emergence of cellular stress response mechanisms and inflammatory signaling pathways. Overall, the distinction between stress responses and inflammation lies primarily in scale: stress responses are localized, cell-autonomous mechanisms aimed at restoring cellular homeostasis, whereas inflammation represents a multicellular response that begins at the tissue level and can escalate to a systemic response when localized efforts are insufficient or the perturbation spreads beyond the initial site [49,65].

PRRs and xenobiotic-sensing receptors evolved to directly detect pathogens and noxious xenobiotics, respectively, signaling the presence of insults that can disrupt homeostasis; however, insults are highly diverse and unpredictable (e.g., toxins, poisons, allergens) [49]. Consequently, from an evolutionary perspective, the detection of homeostatic disruptions, such as perturbations in transcription, translation, or mitochondrial respiration, likely predates PRR-mediated inflammation, as seen in early-diverging metazoans like *Caenorhabditis elegans*, which lack PRRs but sense pathogen-induced disruptions of these core cellular functions and activate immune and detoxification responses [66]. Similarly, in mouse macrophages, *Legionella pneumophila* effectors inhibit host translation, triggering mitogen-activated protein kinase pathways (MAPK) activation independently of known PRRs [67]. Thus, vertebrate macrophages, in addition to PRR-triggered inflammation, sense cellular and tissue stress conditions, such as hyperosmolality [68], hypoxia [69], or microgravity [70], and convert them into inflammatory responses.

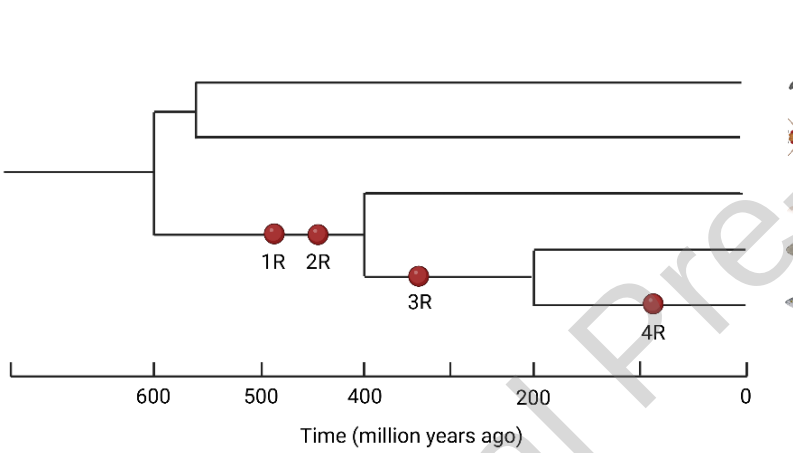
Most hallmarks of aging (primary and antagonistic) either directly represent disruptions of homeostatic control at the cellular level (e.g., loss of proteostasis, mitochondrial dysfunction), or contribute to such disruptions over time (e.g., genomic instability, deregulated nutrient sensing). But, although metacellular aging is not reducible to the aging of individual cells and has a lot to do with the cost of maintaining tissue integrity in multicellular organisms [71], tissue and system level homeostasis disruptions are not directly represented in the hallmarks of aging framework (e.g., senescence contributes to homeostatic disruption at the tissue level, inflamm-aging is the consequence of homeostasis disruptions at all levels) (Figure 1).

c) Evolutionary expansion and functional diversification of cytokine signaling pathways

In vertebrates, studies of orthology and paralogy relationships among genes encoding PRRs [72,73], cytokines [74], their receptor complexes [75], suppressor of cytokine signaling (SOCS), and components of the NF-κB [76] and JAK-STAT pathways [77] reveal an evolutionary history of gene duplications (whole-genome and tandem), starting from the smaller set of ancestral genes presented above. Globally, nearly all vertebrates share two early rounds of whole-genome duplication, while specific groups, such as teleost fishes and salmonids, underwent additional lineage-specific duplications[78,79] alongside tandem and segmental

duplications that further expanded various gene families across many groups and species, including primates [80] (Figure 2). Following these duplications, the relaxation of selective pressures, coupled with episodes of positive and diversifying selection, permitted the accumulation of mutations in the duplicated genes, driving sequence and functional divergence that expanded the repertoires of PRRs, cytokines, signaling proteins (e.g., JAKs, STATs and SOCS), and receptors [81–83].

Cytokine repertoires vary markedly across species, and although most of our current understanding of cytokine signaling derives from studies in mice and humans (such as those cited in section III), eco-immunology underscores the importance of investigating cytokine signaling in diverse species (primarily vertebrates) to reveal taxonomic differences in immune regulation, and evolutionary adaptations [84]. See Supplementary Note 2 for detailed examples illustrating how inflammatory signaling has diversified across species.



NF-κB subunits	STAT genes	SOCS genes	IL-1 superfamily
0	1	0	0
2	1	3	0
5	7	8	11
3	8	5	3
3	14	27	3

Figure 2. Evolutionary expansion of inflammatory signaling components following whole-genome duplications. The phylogenetic tree depicts the evolutionary relationships among *Caenorhabditis elegans*, *Drosophila melanogaster*, *Homo sapiens*, *Danio rerio*, and *Salmo salar*, with whole-genome duplication events (1R–4R) indicated by red circles. The table provides examples of key inflammatory signaling components/genes, including NF-κB subunits [85], STAT genes [77], SOCS genes [79,86], and members of the IL-1 superfamily [87], illustrating their expansion in vertebrates. These gene families are shown as representative cases; additional members of the IL superfamily and other immune-related genes could have been included. The accumulation of these genes following whole-genome duplications suggests increased complexity and diversification of inflammatory regulation across evolutionary time (created with https://BioRender.com).

III. Context and functional-specificity in inflammatory responses

a) Cytokine pleiotropy and redundancy

Over the course of this evolutionary history, pruning through pseudogenization and purifying selection reduced redundancy in certain components, particularly in intermediary signaling proteins, resulting in a "bow-tie" structure with many cytokines and receptors converging onto a smaller, conserved set of JAKs and STATs [88] (Figure 2). This structure repeatedly emerges in complex biological systems, as it mediates

effective trade-offs among robustness, efficiency, and evolvability [89]. It can integrate complex and chaotic inputs into functional, coordinated responses thus balancing versatility and control [90]. Hence, in the case of inflammatory signaling, multiple signals, cues, and microenvironmental parameters (particularly those actively monitored and homeostatically maintained by cells) converge through this structure, enabling cells to efficiently produce context-dependent responses.

Overall, these evolutionary processes—duplication, mutation-driven divergence, and pruning—underpin the key characteristics of cytokine-JAK-STAT signaling: the bow-tie architecture of the pathway, as well as the functional pleiotropy and redundancy of cytokines, which together confer plasticity to the inflammatory response. For example, while IFN-γ is a potent activator of STAT1, it only weakly induces STAT3 in cells with functional STAT1 [91]. By contrast, IL-6 primarily signals through STAT3, but at higher concentrations or with prolonged exposure, it can also activate STAT1 [91]. Although both IL-6 and IL-10 activate STAT3, they engage distinct JAK combinations, leading to different outcomes: IL-6 signals through JAK1 and JAK2, triggering transient STAT3 activation that supports pro-inflammatory processes such as acute-phase protein production and Th17 differentiation, whereas IL-10 signals via JAK1 and TYK2, resulting in sustained STAT3 activation that reduces pro-inflammatory cytokines production and promotes regulatory T cell development. This is a clear illustration of how bow-tie signaling creates an efficient, versatile mechanism to generate precise regulatory signals with a limited number of interacting components (Figure 3).

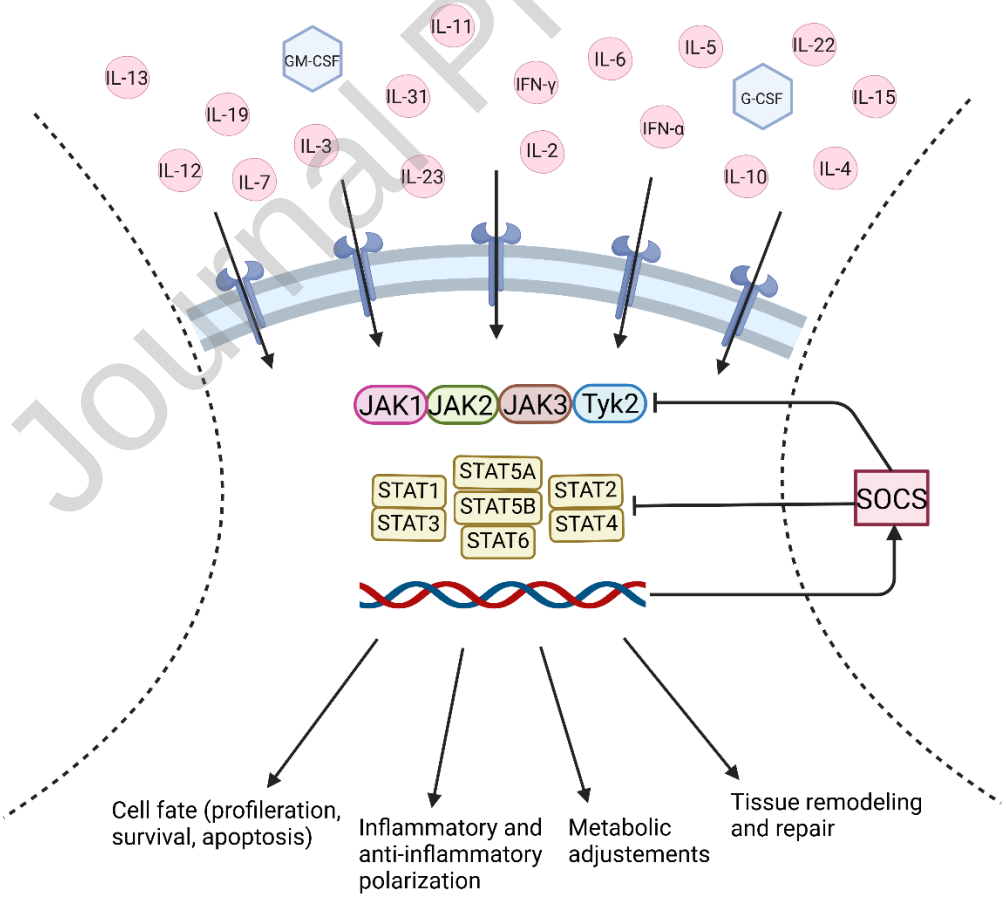


Figure 3. Bow-tie architecture of cytokine–JAK–STAT signaling. A diverse set of cytokines and growth factors converge on a limited core of JAK-STAT proteins, forming a bow-tie structure. Each cytokine engages a specific combination of JAKs and STATs. Despite sharing the same signaling hub, cells can enact a wide range of context-dependent outcomes, including proliferation, survival, apoptosis, metabolic shifts, tissue remodeling, acute-phase responses, and pro- or anti-inflammatory polarization. Negative feedback by SOCS and crosstalk with other pathways (e.g., NF-κB, MAPK) further refine these responses, ensuring precise and adaptable control of inflammatory and homeostatic processes (created with https://BioRender.com).

b) Cooperation of signaling components

Importantly, the outcome of cytokine-JAK-STAT signaling depends heavily on the context, implying that a single cytokine can trigger divergent outcomes in different cellular milieus. Beyond receptor-ligand affinities, the pathway's versatility is shaped by its crosstalk with other pathways (e.g., NF-κB, mTOR, MAPK, Notch), the involvement of other cytokines, and intracellular modulators like SOCS, which create negative feedback by blocking the phosphorylation of certain JAKs or STATs [92], collectively shaping the cellular response.

These other mediators, receptor complexes, signaling pathways, and regulatory proteins are part of the cellular/tissular context that will determine a cytokine's action. Thus, in the absence of SOCS3, which normally inhibits IL-6 signaling by preventing sustained STAT3 activation through the glycoprotein (gp) 130 receptor, IL-6 induces prolonged STAT3 activation, thereby shifting its effects to mimic IL-10 [93,94]. The IL-6-STAT3-driven production of acute-phase proteins in hepatocytes is modulated by IL-1 through NF-κB signaling [95]. Certain acute-phase proteins' gene promoters (e.g., CRP, serum amyloid A) possess binding sites for both STAT3 and NF-κB, leading to their synergistic upregulation during inflammatory conditions when IL-6 and IL-1 levels are elevated[96]. In the same vein, upstream cytokine production signaling pathways cooperate by integrating multiple stimuli. For instance, NF-κB and MAPK pathways are activated at distinct ligand concentrations in macrophages: NF-κB activation occurs at lower concentrations of TLR4 ligands, promoting homeostatic functions and macrophage priming, whereas MAPK activation requires higher ligand concentrations and drives the production of pro-inflammatory cytokines such as TNF-α, IL-6, macrophage inflammatory protein 1-α, monocyte chemotactic protein 1 (MCP-1), and CXCL1 [97]. This is consistent with the notion of a spectrum of inflammatory responses.

c) Microenvironmental modulation of cytokine activity

Moreover, numerous examples illustrate how environmental factors modulate cytokine activity through these pathways and regulatory proteins. For instance, alcohol consumption downregulates STAT1 and STAT3 signaling induced by IL-6, IFN-α, and IFN-γ in monocytes, mainly through the upregulation of SOCS3 and SOCS1 gene expression [98]. Similarly, when exposed to malarial antigens, whole blood specimens from helminth-infected individuals exhibit higher IL-10 production compared to those from non-infected individuals, due to increased SOCS3 gene expression [99]. The cytomegalovirus immediate-early 1 protein binds to STAT3, preventing its phosphorylation by JAK1, thereby repressing STAT3-dependent gene expression while simultaneously activating STAT1-dependent responses, shifting the balance from a pro-survival IL-6-type response to a more antiviral, IFN-γ-like response [100]. In macrophages, changes in ECM stiffness lead to cytoskeletal remodeling (mechanosensing), which modulates IL-4–induced gene expression via changes in STAT6 phosphorylation [101]. Likewise, acidic pH

in the tissue microenvironment modulates macrophage inflammatory responses by disrupting transcriptional hubs that regulate gene expression, selectively repressing cytokines like IL-6, IL-12b, and serum amyloid A3, while amplifying IFN-β and IL-23a, thus acting as a negative feedback mechanism to calibrate inflammation [102]. Importantly, the tissue microenvironment changes with age [103,104]. Thus, in old mice, while bone marrow-derived monocytes and macrophages maintained phagocytic function, tissue-resident peritoneal macrophages were impaired [105]. This extrinsic, microenvironment-driven defect was associated with increased B and T cell presence and elevated B cell-derived IL-10 levels—both at baseline and following LPS stimulation—suggesting that these factors contribute to the impairment. Accordingly, when macrophages from young mice were injected into the peritoneum of old mice, they exhibited reduced phagocytosis [105].

d) Functional specificity

On the whole, despite shared signaling pathways, cytokines achieve functional specificity through mechanisms such as cytokine-specific receptor combinations, differential JAK and STAT levels across cells, receptor-ligand interaction kinetics, regulatory proteins, and engagement of multiple pathways [106]. This specificity is evident in the case of IL-6, where its source determines its half-life and biological action. Muscle-derived IL-6 has a plasma half-life of approximately five minutes post-exercise, whereas IL-6 from acute inflammation can persist for up to 15 hours, and IL-6 remains chronically elevated in cancer patients [107]. Adipocyte-derived IL-6 promotes macrophage infiltration in adipose tissue and reduces insulin sensitivity, while exercise-induced IL-6 from skeletal muscles (dependent on lactate produced during exercise) suppresses macrophage infiltration in adipose tissue and enhances insulin sensitivity [108]. This example illustrates the extent to which a single signaling molecule can take on diverse roles across tissues and contexts, even within an individual. While evolutionarily and functionally efficient, this structure complicates our ability to understand the system and assign clear conceptual roles to individual signaling molecules. This makes it particularly hard to define proper biomarkers/measurands.

e) Measuring inflammation

Acute inflammation, typically triggered by infections, is a high-amplitude, short-lived process, well characterized by elevated levels of canonical biomarkers (IL-1β, IL-6, TNF-α, and CRP) [109]. A successful acute inflammatory recovery, regardless of the type of perturbation, follows consistent, universal dynamics characterized by the return of blood cell populations to homeostatic setpoints [110]. By contrast, chronic inflammation is a low-amplitude, prolonged, and diffuse process that may result from the persistence of the initial trigger or, more commonly, from dysregulated signaling pathways influenced by a complex interplay of factors rather than a single identifiable cause [44]. An important unanswered question is whether the predictable dynamics and precise return to setpoints that characterize acute inflammatory resolution [110] might also be partially relevant for chronic inflammatory conditions, or if chronic inflammation exclusively operates through fundamentally different biological principles.

Chronic inflammation involves a broader array of mediators, making it less amenable to standardization [109]. As an example, while CRP is an acute-phase reactant that rises in response to infection or vaccination—making it a well-established marker of acute inflammation—its levels in chronic conditions

like cardiovascular diseases can vary significantly depending on factors such as disease stage, comorbidities, and individual patient characteristics [111,112]. In the US 35% of adults have elevated CRP levels; this rises to 42% among those with diagnosed cardiometabolic conditions, and even 15% of those without cardiometabolic conditions display elevated CRP levels [113], showing that CRP alone is a poor predictor of cardiovascular disease, contrary to previous beliefs [114]. Yet, in aging adults, a cytokine-response score incorporating STAT phosphorylation (STAT1, STAT3, and STAT5) in several peripheral immune cell subsets following stimulation with IL-6, IFN-α, IFN-γ, and IL-21 more accurately predicts cardiovascular disease and chronic inflammation than CRP [115].

This cytokine-response score [115] prefigured methodologically and conceptually the iAge metric [27], first in its aim to build a multivariate metric (across levels of biological organization—cellular and systemic), and second by showcasing the relations between chronic inflammation, aging, and age-related diseases. By suggesting that inflammaging is not merely a correlate of aging but a driver of functional decline, notably at the cellular level, and that targeting inflammaging may slow down aging, these studies helped build the case for integrating inflammaging into the hallmarks of aging framework [43,44].

Overall, due to the multifaceted and multidimensional nature of inflammatory signaling, there are, to date, no canonical biomarkers, nor any clear theoretical or measurement framework, to categorize and assess inflammatory responses that do not fall at the extreme end of the spectrum corresponding to acute inflammation. Individual biomarkers appear to be better measurands within specific contexts, and multivariate measurands that integrate several levels of biological organization thus more effectively capture the inflammatory response as it lies at the intersection of multiple dimensions. These observations are drawn from human studies; however, when considering other species, the complexity of interpretation increases substantially, owing to their evolutionary divergence.

IV. Species-specific adaptations in inflammatory responses

a) Increasing regulation shaped inflammation

Overall, inflammatory signaling is mediated by a dynamic network of interacting molecules that orchestrates responses by integrating signals additively, synergistically (with combinations yielding effects greater than the sum of their individual actions), or antagonistically (tempering the overall response) through interactions that occur either simultaneously or sequentially, with temporal dynamics modulated by the varying half-lives of the components. However, features of inflammatory signaling such as cytokine pleiotropy and redundancy, bow-tie, and multi-level feedback loops did not arise in isolation – they were co-shaped by the need to integrate inflammatory responses with other physiological controls. As organismal complexity increased, inflammatory signaling networks co-evolved with the increasingly integrated regulatory systems that maintain homeostasis across cells, tissues, and the whole organism. The transition to bilaterians marked a major change for how homeostasis is maintained, for how organisms respond to perturbations, and for how damage accumulates, compromises homeostatic maintenance over time, and drives aging [71,116,117].

In early bilaterians, the shift to fast, genetically hardwired development reduced the role of metabolic signaling previously used to suppress aberrant cell behavior, completely changing how tissue-level

homeostasis is maintained; notably, senescence evolved as a by-product of the new need to control somatic cell variation in the absence of environmentally responsive signals [116]. This shift toward genetically hardwired, spatially patterned development also led to the emergence of a centralized nervous system in early bilaterians, which established the basis for more complex homeostatic regulation [117]. As bilaterians diversified, the emergence of internal circulatory systems [118] and specialized endocrine structures [119] enabled more distributed sensing and systemic regulation of physiological variables. This opened the path for the evolution of complex homeostatic strategies in vertebrates, including multi-organ feedback loops and hypothalamic-pituitary axes that homeostatically maintain certain physiological variables.

b) Species-specific adaptations: homeostatic regulation

We saw that inflammation arises whenever a system encounters a perturbation (i.e., a loss of structure, function, or regulation) that exceeds homeostatic buffering capacity (subsection II.a). Although losses of structure rely mainly on PRRs, losses of function or regulation depend on which parameters fall under homeostatic control, making inflammation-inducing perturbations highly species-dependent.

For any given physiological variable (e.g., temperature, oxygen levels, pH, osmolality, or metabolites like glucose or calcium), strategies of environmental adaptation can be categorized into regulation (homeostatic) and conformity (non-homeostatic) [120,121]. For example, endotherms (mammals and birds) are thermoregulators that maintain their body temperature within a narrow range through homeostatic circuits, involving metabolic heat production and physiological adjustments, whereas ectotherms rely on external heat sources, resulting in body temperatures that conform to the environment [122]. These strategies can be variable-/metabolite-, species-, organ-, and context-specific, with different strategies often coexisting within a single species or system. For instance, certain fishes, such as tuna, exhibit regional endothermy, maintaining elevated temperatures in specific body regions, including their slow-twitch muscles and brain [123]. Euryhaline fish homeostatically regulate osmotic balance when transitioning between freshwater and seawater, yet conform to external temperatures, whereas marine mammals thermoregulate but rely on dietary water intake and reniculate kidneys for less tightly controlled osmoregulation [124]. Nonetheless, for many variables, homeostasis at the systemic/organismal level is confined to endotherms: apparently, homeostatic regulation of body temperature also requires homeostatic regulation of metabolic processes to stabilize physico-chemical parameters and adapt to fluctuating energy demands [125]. Consequently, the regulation of key physiological variables such as temperature, oxygen, osmolality, ion concentrations, glycemia, and cell volume emerged interdependently through the coevolution of various systems, allowing organisms to regulate multiple aspects of their internal environment homeostatically at the systemic level in response to external fluctuations (e.g., the renal system for osmoregulation and nitrogen excretion, the endocrine system for hormonal integration of homeostasis, the circulatory and respiratory systems for thermoregulation and energy supply, and the nervous system for coordinating adaptive responses) [125].

Within mammals, although core homeostatic variables are universal, species-specific thresholds and ranges reflect fine-tuned adaptations to distinct ecological niches [120,124,126]. Even among human populations, subtle differences suggest variation in certain regulatory mechanisms [127–130]. This species-specificity in homeostasis holds profound implications for understanding the nature and thresholds of

inflammation-inducing perturbations across species, the resulting inflammatory responses and their consequences, and whether certain signaling mechanisms involved are conserved or divergent across taxa (Figure 4).

Conformers rely on environmental stability for physiological function, as their internal variables largely mirror external conditions, leaving them vulnerable to sudden or extreme environmental changes. By contrast, regulators can thrive in a wide range of ecological niches and better withstand mismatched environments, exposing them to 'diseases of homeostasis' (e.g., metabolic disorders), in which environmental changes and/or shifting physiological priorities disrupt certain homeostatic circuits, leading to maladaptive physiological states and chronic inflammation. This can either be a primary driver of dysregulation or a downstream consequence that perpetuates pathological states [48]. Thus, unlike mammals, which maintain tight glycemic control, teleost fishes and other ectothermic vertebrates exhibit remarkable tolerance to substantial glycemic fluctuations, with species such as *Oncorhynchus mykiss* and *Petromyzon marinus* sustaining prolonged periods of severe hypo- or hyperglycemia without adverse physiological consequences [126].

Importantly, although not homeostatically regulated in the strict Cannonian sense (subsection II.a), many variables are nonetheless regulated, within broader or shifting ranges (e.g., iron levels, circadian rhythms), with regulatory mechanisms and tolerances that vary substantially across species; these variables can be disrupted or regulated by inflammation or contribute to it when dysregulated.

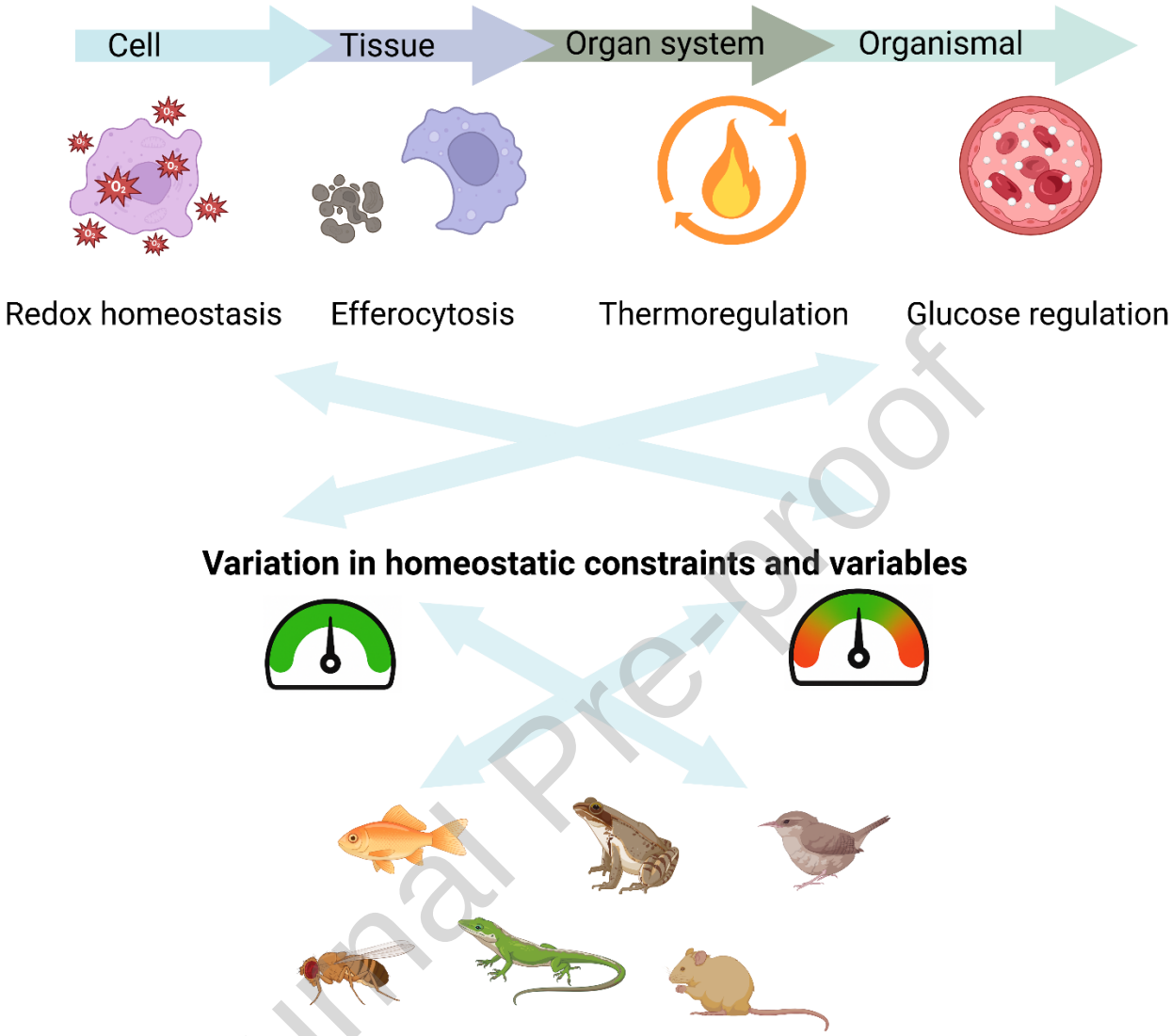


Figure 4. Species variations in homeostatic regulation across levels of biological organization. The variables, ranges, and mechanisms by which homeostasis is maintained differ across species, and this variation occurs at the organismal, tissue, and cellular levels. For example, glycemia is more tightly regulated in mammals than in other vertebrates. Regulatory processes percolate across scales: thermoregulation, for instance, is shaped by interspecific differences in mitochondrial metabolism and macrophage responses to cold varies across species. Even tissue level processes such as efferocytosis vary across species, both in how they are integrated into broader physiological systems and in the degree to which their dynamics are constrained or flexible (created with https://BioRender.com).

Although these interspecies differences have been primarily studied at the systemic level, they exist at all levels of biological organization, as processes percolate across scales: cellular and tissue level processes are integrated into broader physiological systems. An obvious example is mitochondria, where endotherms sustain higher proton leak rates and metabolic heat production to maintain elevated aerobic metabolism, whereas ectotherms exhibit lower mitochondrial activity and greater metabolic flexibility, optimizing energy efficiency rather than sustaining constant ATP synthesis [122]. Mitochondria regulate energy and redox homeostasis at the cellular level, and their activity, number, and distribution are tightly

controlled to sustain tissue level homeostasis, with an involvement of macrophages in certain tissues [131,132]. In fact, immune cells and notably macrophages, which are major sensors and effectors of tissue level homeostasis, exhibit phenotypic and functional variation across species. For instance, peritoneal macrophages from fishes and amphibians, both ectothermic vertebrates, exhibit species-specific functional responses to temperature fluctuations, with variations in adherence, enzymatic activity, and endocytic efficiency [133].

Efferocytosis is influenced by hormonal and metabolic [134] contexts such as insulin sensitivity [135], and is therefore likely to vary markedly across species in accordance with their respective physiological contexts. More specifically, fish and mammalian macrophages both display pro- and anti-inflammatory responses when exposed to pathogenic particles and apoptotic bodies, respectively, though to varying degrees, suggesting that the distinct polarization of macrophages in response to inflammatory or homeostatic stimuli was already established in early vertebrates, but that the extent and regulation of these responses have continued to evolve [136]. Additionally, the contact-dependent anti-inflammatory response to apoptotic bodies occurs in neutrophils only in mammals, indicating that their regulatory role in resolving inflammation is a more recent evolutionary adaptation [136]. Tissue level homeostasis is indeed maintained by precise control of tissue renewal through a dynamic equilibrium between cellular differentiation and proliferation, which varies across species. Notably, cancer risk varies according to species size and lifespan (Peto's paradox [137]); thus, the relative prevalence and roles of apoptosis and senescence are shaped by life-history strategies [138], reflecting interspecies differences in how these processes influence tissue level homeostasis and inflammatory responses throughout the lifespan.

c) Species-specific adaptations: life-history strategies

We saw that the evolution from ectothermy to endothermy was driven by the development of increasingly sophisticated feedback control circuits, which became progressively integrated within nervous, endocrine, immune and metabolic systems. Here, we extend this idea to life-history strategies, examining how they further shape the configuration and cost of inflammatory responses. Greater interconnectedness between systems led to the possibility of more trade-offs between functions, and from an evolutionary perspective, between life-history traits. In vertebrates, hormones and cytokines influence metabolism indirectly through interactions with the three major hypothalamic-pituitary axes: the hypothalamic-pituitary-adrenal axis, the growth hormone–insulin-like growth factor axis, and the hypothalamic-pituitary-gonadal axis. These axes regulate hypothalamic setpoints (e.g., temperature, appetite, circadian rhythms), growth, tissue repair, and metabolism, as well as gonadotropins and reproductive hormones [139]. Their regulatory roles align closely with life-history traits: maintenance and survival mechanisms during environmental or physiological stress, growth and somatic development, and reproductive investment [139].

Indeed, the inflammatory response has a high energetic cost, induces collateral tissue damage, and operates at the expense of other physiological functions. Thus, cytokine activation generally drives the reallocation of resources toward defense mechanisms at the expense of growth and reproduction. For example, pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, released by macrophages during bacterial infection, collectively inhibit reproductive hormone synthesis [140] and insulin signaling [141–143], promote osteoclastogenesis to release minerals [144,145], and induce changes in homeostatic setpoints for

appetite, temperature, and sleep [146]. This resource reallocation strategy is generally thought to become maladaptive in the setting of chronic inflammation [10,147,148]. However, the level of cytokine responsiveness that balances the benefits of inflammation against its costs (e.g., immunopathology, resource expenditure, tissue damage, reduced reproduction) varies with life-history traits. Inflammatory strategies have thus been hypothesized to reflect species' life-history strategies, with larger, longer-lived species tending to favor more regulated inflammatory responses to mitigate risks of immunopathology and maximize somatic maintenance, while smaller, shorter-lived species often exhibit more rapid and less tightly controlled inflammatory responses, consistent with prioritizing immediate reproductive investment over long-term somatic maintenance [149]. For example, elephants have multiple copies of the tumor suppressor gene *TP53*, thereby enhancing apoptotic responses to DNA damage and contributing to cancer resistance despite their large body size and long lifespan [138,150]. Notably, *TP53* and NF-κB are engaged in an antagonistic crosstalk: *TP53* activation inhibits NF-κB-mediated inflammatory signaling, while activation of NF-κB inhibits *TP53* [151,152] (which helps explain the association between inflamm-aging and cancer [153]). This reciprocal inhibition illustrates how somatic maintenance (including tissue level homeostasis) and inflammatory responses are differently balanced across species.

On another note, bats (unusually long-lived for their size) have evolved mechanisms that minimize excessive inflammation and tissue damage while maintaining antiviral defenses, including constitutively high basal expression of IFN-stimulated gene coupled with rapid induction and downregulation upon infection, suppression of inflammasome activation, and restricted IL-1β processing [149,154,155]. A further example is that, among terrestrial mammals, larger species tend to have higher neutrophil concentrations than expected based on body mass, a pattern that may reflect differences in life-history strategy [149,156]. Importantly, across mammalian species, neutrophils vary not only in blood density but also in half-life, secreted molecules (including cytokines), receptor profiles, and activity [157,158]. These differences may extend to the efferocytosis of apoptotic bodies by neutrophils and of apoptotic neutrophils by macrophages, with significant implications for tissue level homeostasis and inflammatory regulation. Remarkably, JAK-STATs recruited downstream of endocrine hormones (primarily JAK2 and, to a lesser extent, JAK1, along with STAT3 and STAT5a/5b) show a markedly higher primary sequence conservation, indicating that they have been subject to stronger negative selection compared with those that convey inflammatory signals (primarily JAK3 and TYK2, along with STAT1, STAT2, STAT4, and STAT6), reflecting constant adaptations to changing pathogen pressures, consistent with the Red Queen theory [159]. This suggests that many evolutionary adjustments, whether along the homeostatic regulation/strategies of environmental adaptation axis, or on the life-history strategy axis, may have happened through modifications in cytokine-JAK-STAT signaling.

V. Reevaluating the universality of inflamm-aging

a) Diversity of inflammation, but universality of inflamm-aging?

Throughout evolution, inflammation-inducing perturbations exerted selection pressures not only on organismal inflammatory strategies but also on strategies of environmental adaptation/homeostatic regulation and life-history strategies; all interconnected through various mechanisms, including shared

inflammatory signaling components, among which cytokines likely evolved as key "adjustment variables" due to their evolutionary plasticity. Their central position in inflammatory and homeostatic signaling networks means that small changes in their expression, receptor affinity, or tissue distribution can propagate through downstream gene networks, modulating systemic responses, and enabling organisms to fine-tune physiological strategies across different ecological and life-history contexts (Figure 5).

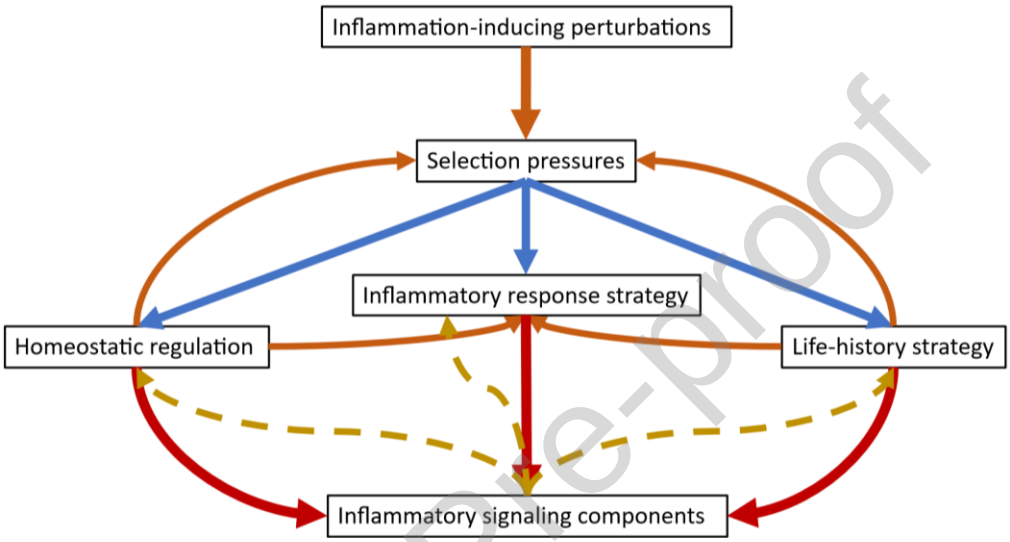


Figure 5. Inflammation-inducing perturbations as major selection pressures (blue arrows). The extent to which these perturbations exert selection pressures on homeostatic regulation, and life-history strategies varies across species. These strategies, in turn, determine the nature and limits of the selection pressures acting upon them (orange arrows). Part of the adaptation of these strategies occurs through changes in inflammatory signaling components (red arrows). In this way, evolutionary events such as genome duplications provide species with opportunities to adapt not only their inflammatory response strategy but also their homeostatic regulation and life-history strategies (dashed yellow arrows), consistent with the notion of the spectrum of inflammatory responses.

To illustrate this, an analysis of evolutionary divergence between mouse and human orthologs revealed rapid changes in genes linked to immunity, olfaction, and reproduction; notably, around half of the top 50 most divergent genes are immune-related, including cytokines and their receptor complexes, underscoring cytokines as some of the most rapidly evolving genes within mammals [160]. This way, although acute inflammatory stresses (trauma, burns, and endotoxemia) result in highly consistent gene expression patterns across these stressors in humans, the corresponding responses in murine models—assessed by comparing orthologous genes—exhibit minimal correlation with both human data and with each other [161]. This observation echoes the context-dependency of inflammatory signaling (section III) and highlights the idea that the species determines a big part of this context.

But if inflammation is so species-specific, what are the implications for inflamm-aging?

As explored above, there is an extraordinary diversity in strategies of environmental adaptation/homeostatic regulation and life-history strategies, and thus in lifespan [162], and though core components are evolutionarily conserved, there is substantial variation among certain inflammatory signaling components, even within mammals. How, then, can we reconcile the seemingly near-universality

of inflamm-aging in bilaterians with the highly species-specific, context-dependent nature of inflammation? If we take mammals, for instance, is it possible that whatever combination of inflammation-inducing perturbations they meet throughout their lifetime, whatever trade-offs their organism makes, they will develop inflamm-aging, but just sooner or later depending on their aging rate?

b) Inflamm-aging, public or private?

Partridge and Gems introduced a framework to distinguish aging mechanisms as either 'public' or 'private' [163]. 'Public' mechanisms refer to aging processes that are broadly conserved across species, such as oxidative damage or mitochondrial dysfunction, and thus represent fundamental biological principles common to diverse-taxa, whereas 'private' mechanisms are specific to certain lineages or ecological contexts, shaped by unique evolutionary histories and environmental exposures [163].

In essence, aging refers to the progressive accumulation of molecular and cellular damage over time, impairing homeostatic circuits and organismal function and increasing vulnerability to disease and death. It is largely characteristic of metazoans, particularly bilaterians (e.g., mammals, birds, and insects), driven by the progressive accumulation of damage from mechanisms such as DNA damage, loss of proteostasis, and mitochondrial dysfunction, which evolved as layers of interconnected processes in metazoans [71]. Cellular hallmarks drive damage that activates inflammatory pathways, which in turn amplify other hallmarks, creating a self-reinforcing feedback loop [44].

As detailed in subsection IV.a, bilaterians underwent major changes in tissue-level homeostatic regulation, inflammation, and damage control, due to their increased organismal complexity and emergence of tightly coordinated tissue functions. In line with this, while most cellular hallmarks of aging were already present in early metazoans, bilaterians uniquely evolved additional hallmarks, including cellular senescence and inflamm-aging [71].

Concordant with the *Danaid theory of aging* [164] an upregulation of the inflammatory response with age, driven by cellular hallmarks of aging, seems inevitable in bilaterians, due to their complex immune systems and need for intercellular regulation. Thus, in bilaterians, whatever its rate, aging leads to an accumulation of molecular and cellular damage, which inevitably will end up disrupting homeostasis in some tissue or system, driving inflammation and resulting in a vicious cycle that exacerbates damage (Figure 6). However, species differ in how much damage they accumulate, what types of damage they accumulate, which homeostatic circuits are compromised and in what order, what kind of vicious cycle this sets in motion, and how rapidly it increases the risk of disease and death. Put simply, because aging inevitably increases internal stress levels in one way or another, it likely drives an upregulation of pro-inflammatory pathways as a universal hallmark of aging across species, but the form, magnitude and health impact of this inflammatory upregulation differ significantly.

Thus, inflamm-aging has been observed in numerous species, and seems inevitable in bilaterians, which would seem to make it a 'public' mechanism and fully validate its inclusion in the hallmarks of aging framework. This issue directly relates to measurement, because claiming to study the same phenomenon requires a common, or at least comparable, measurand that should thus necessarily be linked to a 'public' mechanism, but although certain core inflammatory components are evolutionarily conserved, the

'private' biological context pertaining to each species/lineage might have changed radically, making the comparison of some measurands across species irrelevant.

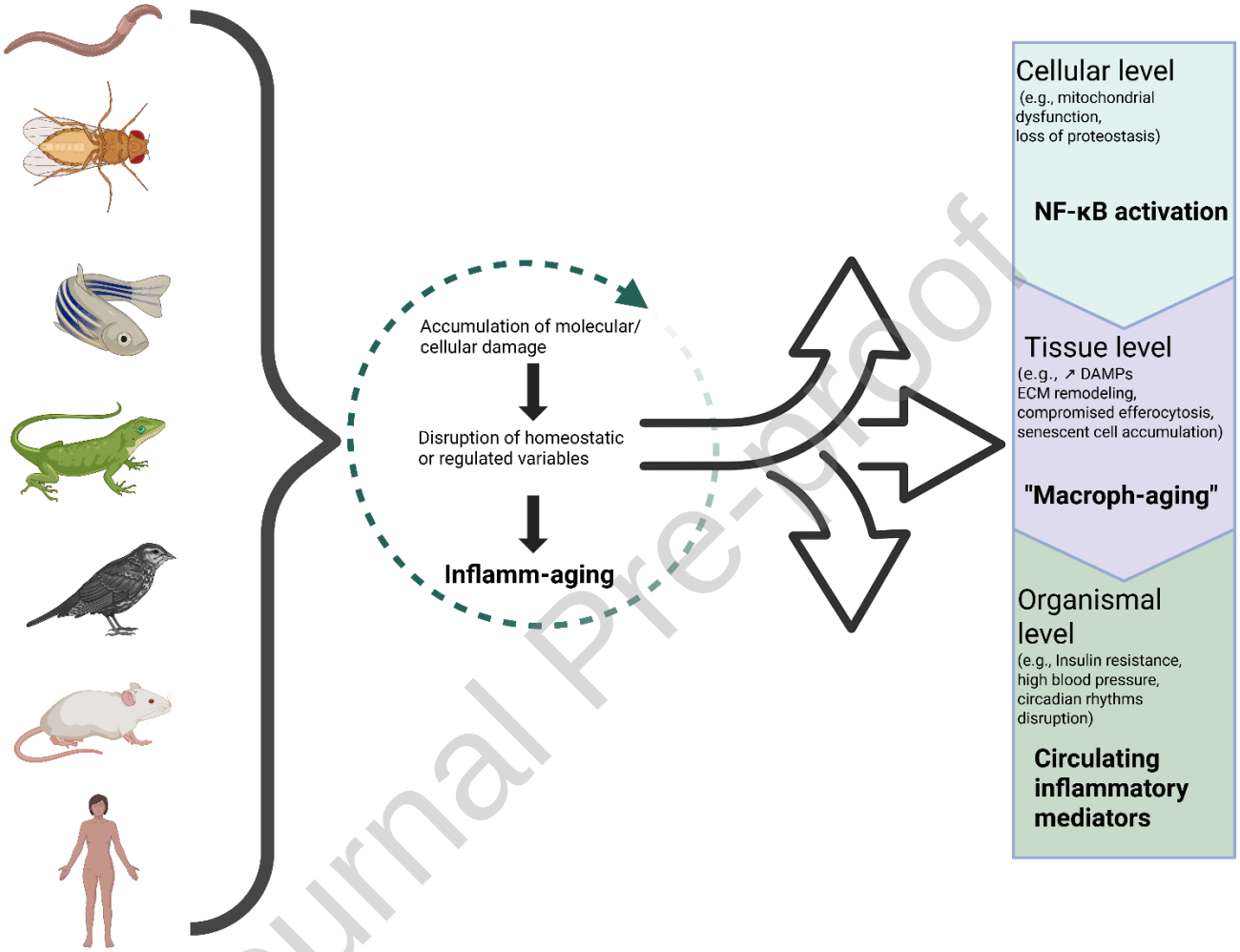


Figure 6. Inflamm-aging as a near-universal yet diverse aspect of aging across species. In invertebrates such as *Drosophila* and *C. elegans*, age-related activation of intracellular inflammatory pathways (e.g., via NF-κB orthologues) has been observed. However, in the absence of a closed circulatory system and of organismal level homeostatic regulation, inflamm-aging in these species differs fundamentally from that observed in vertebrates. In ectothermic vertebrates, including reptiles, and fish, inflamm-aging occurs, but its systemic consequences (and the associated feedback loop) likely differ from those seen in endothermic species (created with https://BioRender.com).

Thus, although universal among bilaterians, the dominance of specific pathways (and even tissue-susceptibility) that drive inflamm-aging may vary widely across species, at the system, tissue, and cellular levels. Pathways involved will vary depending on species-specific differences in the inflammatory signaling repertoire (subsection II.d), but also depending on which variables are homeostatically maintained, within what ranges (subsection IV.b), and which functions/life-history traits can be compromised and under what context (subsection IV.c). At the cellular level, mechanisms of anti-aging that efficiently counteract the progressive accumulation of molecular and cellular damage are not

uniformly present across species. For example, elephants have multiple copies of TP53, enhancing DNA damage sensing and apoptosis [138]; naked mole rats maintain proteostasis through high proteasome activity, elevated basal autophagy, and a tightly regulated unfolded protein response [165]; bowhead whale exhibits upregulated DNA repair genes and adaptations in heat shock proteins [166]. This makes the relative importance of each cellular hallmark of aging unique to each species, and thereby internal inflammation-inducing perturbations 'private'. In other words, what is meant by "homeostatic disruption"—whether at the organismal or tissue level—is somewhat 'private'. The mechanisms underlying inflamm-aging may thus represent an interplay of conserved biological pathways and lineage-specific adaptations, challenging its classification as purely 'public' or 'private'.

A study investigated several hallmarks of aging, including inflamm-aging, in muscle tissue from mice, rats, rhesus monkeys, and humans, reporting a consistent age-related decline in mitochondrial function, a progressive increase in oxidative stress markers, and the upregulation of cytokines across all species [38]. Remarkably, mice showed reduced mTORC1 activity, whereas humans and monkeys demonstrated upregulated mTORC1 activity. Additionally, compared to other species, humans showed a delayed decline in mitochondrial transcripts and exhibited increased NF-κB phosphorylation, while monkeys showed a decline in NF-κB phosphorylation, despite the highest upregulation of TNF-α, IL-6, and IL-10. This study underscores the consistent interconnection of several hallmarks of aging across mammals, despite species-specific differences in their regulation and intensity, supporting the universality of inflamm-aging in mammals, while highlighting the necessity for species-specific models/measurands to unravel its underlying mechanisms.

The species to which an individual belongs determines a big part of the context (the first layers of context), but we saw that environmental factors can modulate inflammatory signaling at the cellular level. So, to what extent do subsequent layers matter?

Inflamm-aging seems to be universal in principle, yet variable across species due to each species' private biology. If part of the phenomenon is 'private' to each species, a single cross-species measurand may be inappropriate, but are species-specific measurands appropriate? Recent findings [45,46] suggest that inflamm-aging is contingent upon particular exposomes rather than an inevitable outcome of biological aging itself, challenging the assumption of public inflamm-aging markers within the human species. We will now shift focus to how further layers of context shape individual trajectories, notably aging phenotypes and inflammatory states.

VI. The importance of the exposome: evidence from diverse human populations

a) The exposome and immunobiography

Unlike physics or chemistry, which study universals (for example, electrons have no individuality/historicity), biology centers on individuals who are, by definition, the fruit of a trajectory of individuation, which inevitably results in interindividual variability, whatever the biological property being studied [167,168]. Consequently, aging is not a pre-determined, uniform decline. Each individual is shaped by a unique combination of heritable (i.e., germline inheritance) and non-heritable influences,

including de novo mutations, stochastic epigenetic changes, and environmental exposures, leading to an increase in interindividual variability with aging on various levels [169–172]. In the immune system, non-heritable influences, particularly cumulative environmental exposures, play a dominant role in driving this variability, especially as individuals age [173]. The diverse stimuli (both harmful and beneficial) encountered across an individual's lifespan progressively shape its immune structure and function, a phenomenon coined "immunobiography" by Claudio Franceschi [171].

Thus, repeated environmental exposures, collectively referred to as the "exposome" – such as contact with pathogenic and symbiotic microorganisms [174], vaccinations [175], various nutritional factors [174,176,177], psychosocial stress [178,179], pollution [180], physical activity [177], or circadian rhythm disruptions [181] – profoundly shape inflammatory basal state and responses. As an example, cytomegalovirus seropositivity was associated with significantly higher iAge scores, emphasizing the strong influence of the exposome on "inflammatory trajectories" [27].

Consequently, each individual's "inflammatory trajectory" is uniquely shaped by cumulative and interacting processes, including shifts in immune cell frequencies (notably a decline in naïve T cells and expansion of memory subsets [182]), divergence in immune cell functions and secretory activity (e.g., lymphocyte activity, macrophage polarization [183]), and infiltration of immune cells into tissues [184]. For instance, higher iAge scores were associated with amplified cytokine responsiveness in monocytes but attenuated responsiveness in B and T cells [27], indicating that individuals with divergent "inflammatory trajectories" also undergo divergent immune cell-specific functional changes.

Beyond direct immune-related changes, the accumulation of senescent cells across tissues (with wide variation in secretory profiles [8,185]), disruptions in gut epithelial barrier function driven by shifts in microbiota composition and activity [186], as well as hormonal (e.g., hypothalamic-pituitary axes downregulation and desynchronization [187,188]) and metabolic (e.g., increased visceral fat [189]) alterations, among other factors, all, to varying degrees, influence the organism's inflammatory state and responses.

These lifelong changes reflect how the different systems in the organism have adapted and/or deteriorated upon diverse environmental pressures, shaping unique inflammatory trajectories and contributing to the marked interindividual variability of inflamm-aging (illustrated in Figure 8 in subsection VIII.a below).

This perspective casts inflamm-aging as a *reaction norm*: a context-dependent inflammatory phenotype that emerges with aging, shaped by both genetic background and environmental exposures. Due to this individuation process, older adults show greater variability in inflammatory states, responses to stimuli, and aging phenotypes, including the prevalence of CNCDs [169–172]. While unrelated young individuals tend to have similar immune cell compositions, older individuals display increased variability in immune cell population frequencies [190]. Likewise, immune responses to vaccines are far more heterogeneous among older adults than among the young [175]. Remarkably, centenarians displayed greater interindividual variability in their iAge scores compared to younger controls, reinforcing the idea that inflammatory aging follows heterogeneous trajectories and that this heterogeneity increases with age and indicating that certain inflammatory phenotypes are compatible with exceptional longevity.

In the same vein, the Tsimane forager-horticulturalists of the Bolivian Amazon – a representative NIP – exhibit remarkably low rates of CNCDs typically associated with aging compared to industrialized populations [191–195], despite persistently high levels of circulating inflammatory mediators due to their high-infection environment. The Tsimane's subsistence lifestyle involves arduous daily physical activity (e.g., hunting, foraging, fishing, and farming) and a minimally processed diet rich in fibers and carbohydrates [196,197]. These lifestyle factors, together with continuous pathogen exposure, notably helminths, likely shape their distinct inflammatory and aging profile [198–200]. See Supplementary Note 3 for a detailed exposome characterization of this population. Epigenetic clocks also suggest lower methylation age among adult Tsimane compared to other populations, indicating that inflammation may not accelerate aging in this population as strongly as expected [201]. By contrast, a Brazilian study comparing high- and low-infection areas found that chronic antigenic exposure was associated with higher methylation age [202], highlighting how the Tsimane represent a notable outlier in the relationship between inflammation and aging.

Given that inflamm-aging and chronic inflammation in general are thought to drive aging and CNCDs, these observations raise questions regarding the definition and boundaries of the inflamm-aging phenomenon, and its role in aging and CNCD development in centenarians and NIPs. As the exposome clearly contributes to interindividual differences, NIPs are of particular interest due to their unique exposome.

Lately, we and other researchers have built upon these industrial/non-industrial differences to examine relationships between inflammatory patterns, age, and diseases in order to highlight potential inflamm-aging discrepancies across populations.

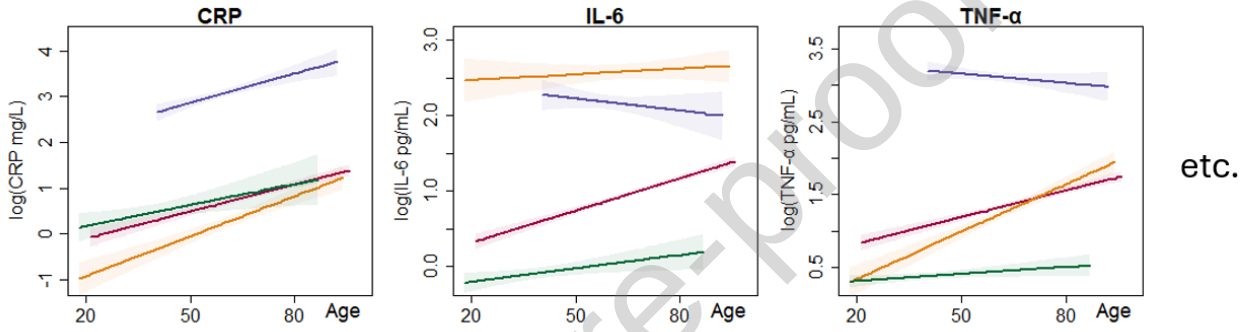
b) Lack of inflamm-aging in non-industrialized human populations?

One study compared how the associations of 15 cytokines with age differed between the Moseten and the Tsimane (THLHP), two genetically similar Indigenous populations from the Bolivian Amazon [46]. The Tsimane, who maintain a subsistence-based lifestyle and live in a high-infection environment (e.g., helminths, giardia, leishmaniasis), showed minimal age-related differences in cytokines, except for IL-2, IL-10, IL-6, and IFN-γ whereas the Moseten, culturally and linguistically similar to the Tsimane but with greater market integration, Western cultural influence, and more access to modern medicine, exhibited more pronounced age-related increases in cytokines, specifically IL-6, IL-10, IL-12, IL-15, IFN-γ, IL-1β, and TNF-α. By comparison, individuals from a Brazilian high-infection area (e.g., schistosomiasis, leishmaniasis, leprosy, dengue, cytomegalovirus) exhibited elevated basal levels of IL-12, IL-17, and IL-9, along with higher methylation age, while individuals from a nearby low-infection area showed elevated levels of IL-6, IL-1β, IL-2, IL-1RA, and IL-10. Moreover, during infection (flu-like symptoms or COVID-19), endemic-area individuals produced significantly more IL-12, IL-6, IL-1β, IL-2, IL-1RA, and IL-10 than individuals from the other group [202]. Though the experimental designs and contexts of these two studies differ, both highlight the influence of the exposome (notably chronic antigenic stimulation) on the age-related trajectory of the basal inflammatory state and response to stimuli.

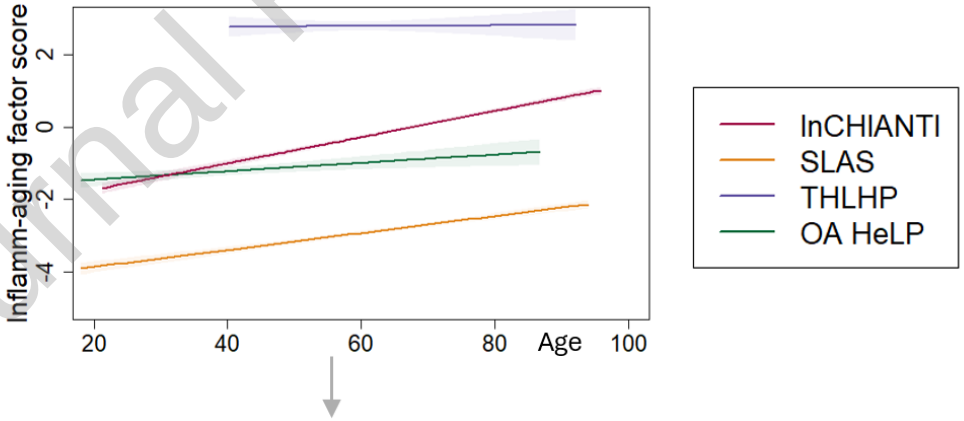
Another study [45] compared two industrialized populations, an Italian cohort (InCHIANTI) and a Singaporean one (SLAS), with two Indigenous, NIPs, a Tsimane cohort (THLHP) and an Orang Asli

cohort (OA HeLP), the aboriginal people of Peninsular Malaysia (Figure 7). Inflamm-aging was measured using an inflammatory axis derived from factor analysis and previously identified by principal component analysis of 19 cytokines in InCHIANTI [31], and characterized by joint up-regulation of soluble TNF receptor (sTNF-R) I, sTNF-RII, CRP, IL-6, TNF-α, IL-18, and IL-1RA. The main inflammatory axes within the other cohorts were also identified through factor analysis. The InCHIANTI-calibrated inflamm-aging axis increased with age and predicted multiple CNCDs in InCHIANTI and SLAS but was largely unassociated with age or health status in THLHP or OA HeLP. Crucially, the inflamm-aging axis did not appear to exist in THLHP or OA HeLP: these inflammatory mediators were not associated with each other in those populations.

A



B



C

Odds Ratio of association of inflammaging factor score with health outcomes				
	InCHIANTI	SLAS	THLHP	OA HeLP
High blood pressure	1.00	1.44***	0.96	1.07
Stroke	1.92***	1.15		
Cong. heart failure	2.01***	0.76		
Cancer	2.55**	1.24		
Kidney disease	5.75***	4.75***	0.84	
Diabetes	1.29*	1.55***		0.84

Figure 7. **(A-C)** Contrasting patterns of inflamm-aging between industrialized populations (InCHIANTI: Italy; SLAS: Singapore) and non-industrialized populations (THLHP: Tsimane; OA HeLP: Orang Asli). (A) Examples of cytokine concentrations (CRP, IL-6, TNF-α, IL-1RA) across age by population. (B) Age-related trajectories of inflamm-aging scores derived through factor analysis calibrated on InCHIANTI. (C) Associations between inflamm-aging factor scores and CNCD prevalence. Data presented in this figure are adapted from Franck et al. [45].

Additionally, while InCHIANTI and SLAS axis structures broadly align, NIPs (THLHP and OA HeLP) exhibited markedly different axis structures, with minimal association with age or CNCDs (Figure 7B, C).

These results raise a key question: does this mean the measurement of inflamm-aging used is failing in NIPs contexts, or does it mean inflamm-aging itself is defined by context? (See Box 1)

Box 1. Inflamm-aging: a measurement problem, a definition problem, or both?

Conceptually, the findings of Aronoff et al. [46] and Franck et al. [45] raise two possibilities regarding inflamm-aging's universality. Either inflamm-aging suffers from a measurement problem, in which circulating cytokines fail to reliably indicate an underlying, universal inflamm-aging process, implying the need for better "context-independent"/"universal" biomarkers; or it suffers from a definition problem, and should not be considered universal in its manifestations, but rather apprehended through metrics that explicitly incorporate ecological and population-specific factors. In the end, inflamm-aging may be considered universally present in principle (at a conceptual level), but in practice it manifests in highly variable, context-dependent ways. We propose reframing inflamm-aging as a norm of reaction – meaning that its actual form and consequences vary across environmental and biological contexts. Thus, there is no single manifestation for inflamm-aging, although some contexts lead to recurrent trajectories (mismatched or not) at the population level. Moreover, truly "context-independent" markers do not exist in biology, even if some that show high specificity and robustness across contexts seem to approach it in practice.

These results suggest significant exposome impacts on inflammatory variation, leading to differences in how inflammation drives disease susceptibility across populations. Because factor analysis is inherently dependent on the specific structure of correlations present within a given dataset, it reveals cohort-specific dimensions of inflammatory responses, underlying common health phenotypes and shaped by local exposome factors. These are the main dimensions identified in each cohort, by which individuals cope with 'deviations' from homeostasis provoked by their exposome (and genetic susceptibility to a lesser extent). Hence, inflamm-aging scores were calculated relative to a reference population (InCHIANTI), which provided the statistical norm for "inflamm-aging" (see subsection VIII.b). Applying this factor to a different industrialized cohort (SLAS) yields a similar association with both age and CNCDs, supporting the hypothesis that it captures an inflammatory state provoked by the industrialized exposome. The association between certain lifestyle-related variables (smoking, body mass index, eosinophilia, and leukocytosis) and the different axes were examined. InCHIANTI and SLAS showed positive associations of BMI and smoking with inflamm-aging scores, while only BMI was associated in OA HeLP and neither in THLHP; leukocytosis (but not eosinophilia) was generally associated with inflamm-aging in OA HeLP and THLHP—findings consistent with expectations.

Overall, inflamm-aging assessments in NIPs, conducted using cytokine panel measurements typically applied in industrialized settings, reveal minimal or no association between these measurands and age or CNCDs. Such findings suggest that inflamm-aging, as traditionally conceptualized or measured

epidemiologically, might not be a fundamental process of aging, but rather a consequence of aging in a mismatched industrialized environment, implying that inflamm-aging might be more context-dependent than previously thought. Therefore, the significant differences observed between the non-industrialized and industrialized cohorts should be considered in light of their unique exposomes. A recent study comparing Yakutians, who live in one of the coldest inhabited regions on Earth, with Central Russians from a milder climate, similarly revealed distinct age-related trends in inflammatory markers, with some increasing more with age in Yakutians (e.g., PDGFB, CD40 ligand, VEGFA, PDGFA, CXCL10), also supporting the idea that inflamm-aging is shaped by population-specific factors, including climate, lifestyle, and genetic background [30]. These variable patterns related to degree of industrialization and other aspects of the exposome contrast with the substantial evidence outlined in the introduction that inflammatory processes are related to aging across a broad diversity of animal life. Ultimately, inflamm-aging does not have a single trajectory, but a range of possible trajectories (likely variable within each species) driven by the exposome – consistent with the idea of a reaction norm and the right measurement method for inflamm-aging in these NIPs remains to be found.

VII. Macroph-aging and hormesis-driven macrophage activation patterns

a) Environmental pressures and macrophage plasticity

The unique exposomes of NIPs clearly lead to distinct immunological and physiological profiles. The Aronoff [46] and Franck studies [45] did not isolate specific environmental drivers, though they proposed that helminth infections, endemic in both NIPs, could contribute to mitigating inflamm-aging and lowering the risk of associated diseases by promoting anti-inflammatory M2-like polarization of macrophages. Macrophages exhibit functional plasticity, adapting to their microenvironmental conditions and stimuli by developing tissue-specific phenotypes through a process known as polarization. Their production of inflammatory mediators changes alongside aging tissues, making macroph-aging a central driver of inflamm-aging. Better understanding of the effects of environmental pressures on monocyte-macrophage lineage cells could help explain the discrepancies in inflamm-aging observed in NIPs. Helminths, which were prevalent in hominins and ancient human populations [203], exerted constant selective pressures, potentially explaining why the human immune system is mismatched to sanitized modern environments, consistent with the hygiene and "old friends" hypotheses. More broadly, the immune system is adapted to certain types of perturbations, and their absence may disrupt specific equilibria, though we still do not fully understand which perturbations are "evolutionarily expected" and in what contexts. Illustratively, regular physical activity increases the proportion of M2-like macrophages within muscle tissue [204] and downregulates MCP-1 receptor expression on circulating monocytes, which may limit their recruitment to inflamed tissues [205]. Intermittent fasting promotes M1-polarization of macrophages in adipose tissue, and M2 within muscle tissue [206]. Exposure to cold [207], toxicants [208,209], circadian rhythm disruption [210], infections and virtually all perturbations, will alter macrophage polarity/activity.

b) Microenvironmental influences on monocyte–macrophage lineage differentiation

The differentiation of macrophages is regulated by transcription factors and signaling interactions that partly converge upon STAT1, which drives pro-inflammatory M1-like polarization, and STAT3/STAT6,

which drive anti-inflammatory M2-like polarization. In laboratory settings, M1-like macrophage polarization is typically induced by LPS and IFN-γ, and M2-like by IL-4 and IL-13; however, in vivo, macrophage activation exists along a continuum [211] influenced by microenvironmental cues and signals (e.g., other PAMPs, DAMPs, cytokines, chemokines, growth factors, glucocorticoids, dietary factors, lactate, hypoxia, ECM stiffness) [101,102,105,212]. Therefore, the M1/M2 framework does not fully capture macrophage heterogeneity in physiological or pathological contexts [211,213–216]. As an example, inhibitor of NF-κB subunit β, an upstream regulator of NF-κB, inhibits STAT1-driven M1 macrophage polarization in specific contexts, such as infections with Group B *Streptococcus* or *Cryptococcus neoformans* [217]. Similarly, in macrophages stimulated with LPS and IFN-γ, bicarbonate exposure increases STAT1 phosphorylation by elevating both extracellular and intracellular pH, thereby enhancing polarization toward an M1-like inflammatory phenotype [218].

Macrophages originate either from embryonic or fetal precursors (e.g., microglia, Kupffer cells, Langerhans cells, alveolar macrophages) [219] or from bone marrow–derived circulating monocytes that migrate into tissues [220]. Critically, microenvironmental influences can have long-lasting or irreversible changes on hematopoietic precursors of monocytes, which are echoed in monocytes and their derived macrophages [220]. Subsequent microenvironmental factors further shape monocytes and macrophages, leading to interindividual variability in monocyte and macrophage subset proportions and functional phenotypes, even in healthy individuals.

c) Hormesis-driven macrophage activation and trained immunity

Macrophage functionality is modulated in a dose-dependent manner, with effects observable both in immediate responses and through longer-term changes. Low-dose exposure to certain microbial stimuli can prime macrophages for an enhanced pro-inflammatory response upon re-exposure (a phenomenon known as trained immunity), while high-dose exposures may induce tolerance, reducing pro-inflammatory signaling, both mediated by differential epigenetic reprogramming [221]. Moreover, macrophage activation/polarization frequently follows a biphasic dose-response pattern characteristic of hormesis, where different doses of a stimulus—be it microbial, chemical, or physical—elicit opposing effects, often shifting macrophages between M1-like and M2-like states [222].

For instance, low doses of ionizing radiation have been shown to promote M2-polarization, whereas higher doses favor M1-polarization [223–225]. At low levels, mitochondrial reactive oxygen species in macrophages trigger mitohormesis, notably activating hypoxia-inducible factor 1-α and nuclear factor erythroid 2-related factor 2 (key transcriptional regulators involved in the response to hypoxia and protection against oxidative stress, respectively) [226], while at high levels, they drive the production of pro-inflammatory cytokines like IL-1β and IL-18 through the activation of the NOD-like receptor family pyrin domain containing 3 inflammasome [227]. Similarly, hormetic dose-responses have been observed for LPS: low-dose LPS induces tolerance in human monocytes (M2-like features), while high-dose LPS leads to a pro-inflammatory response (M1-like state) [228]; in Kupffer cells, low-dose LPS can drive M2-polarization [229]; in microglia, acute LPS stimulation is associated with an M1-like phenotype, while persistent TLR4 signaling can promote microglial polarization toward M2-like phenotype [230]. One of the mechanisms that underlies this signaling dichotomy is the presence of distinct activation thresholds for NF-κB and MAPK pathways, where NF-κB responds to lower ligand concentrations to enable macrophage priming, while MAPK activation occurs in a switch-like manner at higher concentrations, enforcing a threshold for pro-

inflammatory cytokine production and effectively segregating low-level microbial sensing from high-level pathogenic responses to prevent unnecessary inflammation [97].
This illustrates that the application of the concept of hormesis [231] to macrophage activation directly stems from the context-dependency of inflammatory signaling that enables the same stimulus to produce different effects based on its concentration and the cellular context.

d) Macroph-aging and inflamm-aging

In its initial conception, inflamm-aging was predominantly centered on the innate immune system and macrophages, with a focus on the role of inflammatory responses as a key feature of immunosenescence [1]. Over time, the theory has evolved into a more comprehensive framework, first by encompassing contributions from various systems and tissues, including adipose tissue and skeletal muscle, acknowledged as significant cytokine producers, but also the gut microbiota [232]; and second by integrating its interplay with hallmarks of aging [44]. In this broader framework, macrophages remain central due to their significant inflammatory mediator production capacity [233], their ubiquitous presence across tissues, their role as sensors of homeostatic deviations [68] (notably the increasing 'self-garbage' with age [14]) and in senescent cell clearance [5,9], their functional plasticity enabling reversible adaptation to changing microenvironments, and their tendency toward impaired polarization with age [234,235].

As mentioned earlier, iAge scores were positively correlated with enhanced STAT1, STAT3, and STAT5 phosphorylation in monocytes upon cytokine stimulation [27]. In older U.S. adults, advancing age was associated with elevated basal phosphorylation of STAT1, STAT3, and STAT5 across both monocytes and lymphocytes, while no significant relationship was observed between age and NF-κB signaling in LPS-stimulated monocytes [33]. A Danish study demonstrated that monocytes from older adults have a reduced ability to induce NF-κB signaling in response to LPS and TNF-α compared to young adults, with an even greater reduction in those recently admitted to the emergency department, who also showed higher basal NF-κB phosphorylation levels than age-matched controls [32].
Considering the role of lifestyle in inflammation and the central role of monocyte-macrophage lineage cells in inflamm-aging, it seems clear that major changes in environmental pressures impact monocyte-macrophage activation and polarization. It also emerges that the activation thresholds of intracellular signaling pathways in monocyte-macrophage lineage cells (as shown above with STATs and NF-κB) are altered, consistent with the context-dependent outcomes of the activation of these pathways. Overall, the industrialized exposome may drive monocyte-macrophage lineage cells along trajectories that promote macroph-aging/inflamm-aging so that macroph-aging as commonly conceptualized may just as well result from an evolutionary mismatch. The metabolic disorders and gut dysbiosis driven by Westernized dietary patterns appear to play a major role [47,232,236]. The unique environment of NIPs may give more opportunities to macrophages to polarize into M2-like states and exhibit hormetic responses, tending to steer them away from such trajectories and explaining the lower association of a high inflammatory status with chronic diseases, as observed among Tsimane. As stated above, the M1/M2 framework is a simplified model that does not fully represent the heterogeneous and complex behavior of macrophages in various contexts, including physiological and pathological conditions. For example, M1-like macrophages play a significant role in atherosclerosis (which appears to be largely absent among Tsimane [191]), but also remove senescent cells in certain contexts [5,9]. One possibility, then, is that the Tsimane accumulate fewer senescent cells due

to more effective macrophage-mediated clearance, implying that their elevated levels of inflammatory mediators originate from alternative sources and potentially explaining why their high inflamm-aging scores in Franck et al. [45] were not associated with age or CNCDs.

VIII. Norms of reaction shaped by evolutionary mismatch

a) Environmental transitions and evolutionary mismatches

Nutrition and exposure to pathogenic and symbiotic microorganisms, which are among the strongest selective pressures, have varied throughout evolutionary history across populations in conjunction with subsistence modes [236–238]. Here, we consider how major shifts in human niches/ subsistence modes may have created evolutionary mismatches directly influencing inflamm-aging form and magnitude. During the transition from hunting and gathering to farming (Neolithic transition), populations modified their subsistence niche, impacting a series of selective pressures, including energy supply, dietary diversity, and exposure to microorganisms [236,238]. This major transition and its associated shifts in selective pressures varied geographically and temporally, leading to diverse adaptations across populations.

Remarkably, a population genomics study examining sub-Saharan African, European, American, and East Asian populations found that most positively selected coding variations in innate immunity genes arose in the last 6,000–13,000 years, coinciding with the Neolithic transition period [239]. This is particularly interesting when considering Franck's findings [45], given that Europeans split from East Asians ~41,000 years ago [240], Native Americans from East Asians ~36,000 years ago [241], and Malaysian ethnic groups, including Orang Asli and Malay, from East Asians around 12,000–6,000 years ago [242]. More precisely, in post-Neolithic Europe, most genetic adaptations occurred after the Bronze Age, around 4,500 years ago; several genetic variants underwent pathogen-driven selection, enhancing resistance to infections but simultaneously increasing the risk of inflammatory disorders, supporting a significant role for antagonistic pleiotropy in the emergence of CNCDs [237]. Polygenic scores for eosinophil proportions among granulocytes significantly decreased over this period, whereas those for lymphocytes, monocytes, and neutrophil counts increased [237]. These findings could be put into perspective with the reduced monocyte and heightened eosinophil counts of the Tsimane compared to Caucasian populations, driven primarily by parasitic infections, though a genetic predisposition in the Tsimane cannot be ruled out. Likewise, the increase of polygenic scores for the proportion of monocytes in Europeans following Neolithic transition, might contribute to a higher propensity to macroph-aging/inflamm-aging compared to NIPs. Another study analyzing polygenic risk scores for cytokine production and immune-mediated diseases across European genomes spanning the Upper Paleolithic to the post-Neolithic identified the Neolithic transition as a turning point in the evolution of cytokine response profiles and susceptibility to immune-mediated diseases [243].

The major "exposome shift" caused by the Neolithic transition presumably led to a mismatch between genetics and the environmental selective pressures, particularly microbial exposures (pathogenic and symbiotic) and nutritional resources. The first generations likely experienced increased inflammation, potentially both acute and chronic, with significant variations in the magnitude/implementation of inflammatory states depending on populations and their respective exposome, which led to adaptations on

different timescales, including genomic adaptation on the evolutionary timescale. The industrial revolution reshuffled the deck again, leading to a major mismatch directly related to the prevalence of chronic inflammation in industrialized populations.

Inflamm-aging as commonly conceived/measured epidemiologically may thereby just be a manifestation of this mismatch, explaining why the Tsimane do not seem to experience it when both industrialized cohorts do and even the Moseten, who are genetically similar, do (Figure 8). This is potentially not confined to humans, as some findings indicate that domestic, laboratory and captive animals are subjected to similar chronic inflammatory states (echoing subsection IV.b). Laboratory rodents and monkeys for instance have a lifestyle more akin to industrialized humans, with low exercise, a relatively sterile environment, artificial lights, and chow diets formulated and manufactured from milled or extruded ingredients, often at ad libitum levels. Likewise, companion dogs have lifestyles that mirror their owners' and are often treated to prevent parasitic worms. Cross-species analyses revealing parallel increases in obesity rates among diverse animal populations inhabiting human-influenced environments further support the existence of shared environmental determinants underlying these chronic inflammatory states [244].

Inflamm-aging as commonly conceived/measured and meta-inflammation appear to share largely the same underlying molecular mechanisms, with gut dysbiosis playing a central role, as previously mentioned [232]. *Homo sapiens* has a unique evolutionary trajectory, particularly regarding dietary adaptations, even prior to the Neolithic transition. Notably, the rapid evolution of its digestive tract (shortening of the colon and lengthening of the small intestine [245]) may have left *Homo sapiens* more vulnerable than other species to gut dysbiosis and metabolic endotoxemia [236]. Interestingly, the positive selection of the more active LPS-binding protein gene variant in European populations after the Bronze Age [237] may have increased their susceptibility to metabolic endotoxemia, considering the critical role of LPS in it. This would make Westernized dietary patterns a key aspect of this mismatch and a critical driver of inflamm-aging as commonly conceived/measured.

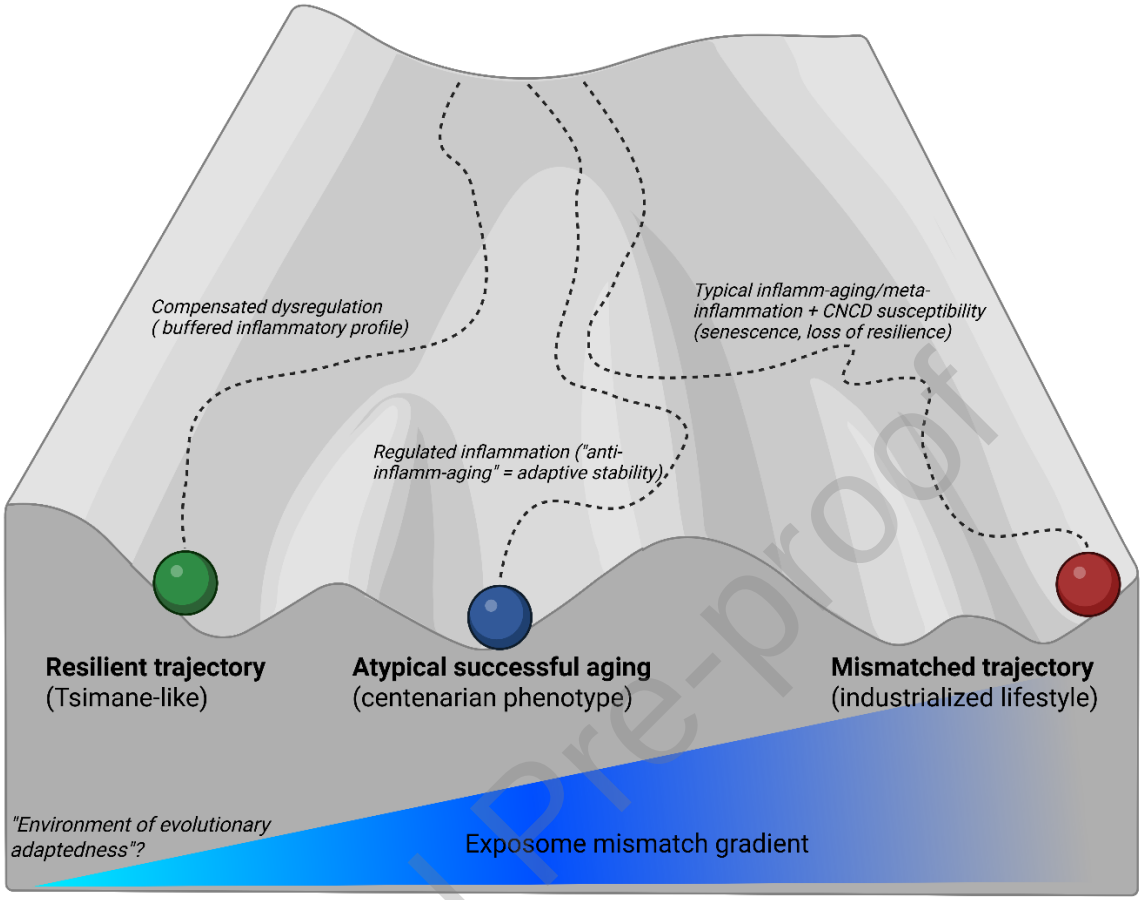


Figure 8. Inflamm-aging as a norm of reaction. Waddington-inspired landscape illustrating how different exposomes can shape divergent inflammatory aging trajectories. The horizontal axis represents a gradient of increasing mismatch between evolutionary expectations (i.e., evolved human biology) and environmental exposures. Valleys represent quasi-stable attractor states of immune-inflammatory regulation. Trajectories are shaped by the cumulative impact of exposome factors interacting with the current state of the system, determining descent into specific attractor valleys. Adapted from Franceschi et al. [171] (created with https://BioRender.com).

b) Statistical norms for inflamm-aging: species-private or contextual?

The notion of mismatch is relative to a specific population or species, its current exposome, and the extent to which that exposome differs from its "environment of evolutionary adaptedness", that is, the set of conditions under which its reaction norms were shaped by recurring selection pressures. Whichever measurand one uses to assess a phenomenon like inflamm-aging, it has to be calibrated against a sample deemed representative of a particular population or species. Each individual carries both its inherited evolutionary trajectory (via its genetic background) and its individual trajectory (shaped by its particular exposome), whether that exposome is mismatched or not. In simplified terms, in any sample of individuals, the most recurring inflammatory patterns/states will statistically reflect the outcome of the most common/decisive environmental pressures (present and past at another timescale through the gene pool of the population in question), the precision of which will depend heavily on the sample's genetic and exposomic 'homogeneity'. Populations respond to environmental pressures via multiple mechanisms on different timescales, from within-generation short-term homeostatic/inflammatory

responses/adaptations to developmental plasticity and long-term genomic adaptation on the evolutionary timescale [246]. Concretely, variation in scores along the InCHIANTI-calibrated inflamm-aging axis captures, in some way, the typical individuation trajectory of an Italian subject with the exposome typical of the Chianti region. Whether or not this trajectory is mismatched, and to what extent, is hard to tell, given the challenges in circumscribing an environment of evolutionary adaptedness (Paleolithic, Neolithic?). Nevertheless, the fact that variation in scores along the same axis, in a genetically different population, and exposed to a different industrialized context, also aligned with the inflamm-aging notion, suggests that this axis does capture a characteristic 'mismatched' trajectory.

The term inflamm-aging was coined upon assessing this characteristic 'mismatched' trajectory in industrialized human populations and model organisms living under artificial conditions. Thus, rather than being purely 'private' to the human species, the recent findings of Aronoff et al. [46] and Franck et al. [45] prompt reconsideration of this typical inflamm-aging trajectory as a contextual aging mechanism: one contingent upon particular exposomes rather than an inevitable outcome of biological aging itself. Indeed, in humans, exposome-driven 'contextual' variation may be substantial enough to obscure, overlay, or modulate the expression of conserved inflammatory features, complicating their identification and interpretation across populations/individuals. Viewing individuals as the result of an individuation trajectory (subsection VI.a) rather than a "static functional coherence" underscores the deeply contextual nature of biological processes like inflamm-aging, shaped by both evolutionary history and present contingencies. Hence, a study using explainable artificial intelligence identified individual-specific combinations of inflammatory mediators while also revealing key biomarkers at the population scale that were predictive of aging, demonstrating both interindividual variability and consistent age-associated inflammatory changes [29].

c) Toward better measurands?

Individuation and context-dependency make it difficult to define what should be measured as a representation of inflammation, because measurands should be operationally defined in a way that ensures comparability. Though some signaling components are evolutionarily conserved, such as the JAK-STAT and NF-κB pathways in metazoans, or certain cytokines and their receptor complexes across vertebrates, many components of these pathways have undergone extensive evolution. Additionally, their function and the extent of the involvement of well conserved components may have diverged, such as IL-6, which is involved in acute inflammation of all vertebrates, but has also been co-opted for functions in thermoregulation [247] and lactation [248] in mammals.

Moreover, beyond the pathways, there may be species- and even population-specific variations in how diverse immune cell types employ these signals and in the trends of their regulation with age. For example, the contact-dependent anti-inflammatory response to apoptotic bodies occurs in neutrophils in mammals but is absent in fishes (subsection IV.b), neutrophil proportions appear to have co-evolved with life-history strategies in mammals (subsection IV.d), and polygenic scores for lymphocyte, monocyte, and neutrophil counts increased in post-Neolithic European populations (subsection VIII.a). For this reason, applying multi–cell type approaches (such as Sayed et al.'s [27]) to NIPs could yield particularly valuable insights.

All these layers of context, each of them exhibiting variation across species and individuals (intracellular components, cellular/tissular microenvironment, cytokines combinatory dynamics, systemic homeostasis and life-history necessities, exposome→individuation) leave us with no good lead on how to circumscribe a perfect measurand for this seemingly nearly universal aging process. Inflamm-aging appears to function like a reaction norm, with its expression varying across population-specific ecologies and histories; thus, any metric must account for these contextual differences. Promising approaches include: (1) building individualized clocks [29]; (2) combining multiple signaling readouts (e.g., several STATs across several cell types [27]); and (3) comparing populations with distinct exposomes [30,45,46]. Recent efforts to build 'inflamm-aging clocks' using machine learning and deep learning have shown that it is feasible to quantify inflamm-aging at the individual level, accounting for each person's unique exposome and immunobiography/individuation trajectory [29].

Furthermore, although inflamm-aging research often focuses on blood markers, the role of macroph-aging suggests that measuring only blood immune cells and mediators may be insufficient, as tissue level analyses might reveal additional insights. A better understanding of how homeostasis is disrupted at the tissue level may be central to comprehending and measuring macroph-aging and inflamm-aging. While homeostasis is well characterized at the cellular and systemic levels, the tissue level remains a gap that a growing number of studies are beginning to address [52,101,102,249]. Cell populations fluctuate around tightly regulated, individual-specific setpoints that reflect underlying physiological homeostasis; recent findings underscore their potential as clinically relevant biomarkers for individualized risk stratification and early detection of age-related inflammatory dysregulation [250]. Inflammatory mediators (cytokines, acute-phase proteins, growth factors, eicosanoids) are regulators of hematopoiesis [251], influencing the production, mobilization, differentiation, and apoptosis of blood cells, thus shaping these homeostatic setpoints. As interindividual setpoint differences reflect, inter alia, chronic diseases, aging, and genetic background [250], characterizing deviations from these individual-specific setpoints in conjunction with individual-specific inflammatory trajectories (inflamm-aging) could significantly enhance precision in the early detection of age-related and chronic disease risks. A similar approach could later be extended to tissues. Overall, advancing our understanding will require better characterization of: (1) homeostatic processes and setpoints across tissues and levels of biological organization, (2) the role of inflammatory mediators in both deviations from and return to these setpoints (consistent with the view of the spectrum of inflammatory responses), (3) how these processes and setpoints are affected throughout life by each individual's unique succession of inflammation-inducing perturbations (individuation).

d) Can we prevent or treat inflamm-aging?

Our perspective places inflamm-aging as an inevitable yet diverse process across species and individuals, more specifically, as a norm of reaction. The enormous complexity of maintaining homeostasis in bilaterians makes the accumulation of damage inevitable and leads, with age, to a breakdown in homeostatic regulation that progressively drives increased inflammatory activity. In absolute terms, completely avoiding inflamm-aging appears impossible. An achievable goal is to minimize mismatched inflammatory trajectories, such as "industrialized inflamm-aging". Reducing well-known mismatch exposures (e.g., ultra-processed food consumption, physical inactivity) is advisable; nonetheless, the

distinctive inflammatory profile observed among the Tsimane highlights the limits of our understanding of how the exposome shapes inflammatory trajectories and their links to aging. It also shows the limits of focusing too narrowly on pathways and signaling molecules in complex, systemic, and multifactorial systems. Against this backdrop, and given that many of the targeted pathways and signaling molecules also have homeostatic functions, gerotherapeutics (senolytics, geroprotectors, etc.) may help, but they also may not: in practice, they may simply modify age-related inflammatory trajectories in ways that will vary across individuals and contexts, with an uncertain net benefit at present. In short, which targets, combinations, and timing will safely re-route age-related inflammatory trajectories remains uncertain and is likely context-specific. Until longitudinal, exposome-aware, clock-guided trials resolve who benefits from what, and when, a generalized pharmacological depression of inflamm-aging is not warranted [252].

IX. Perspectives and concluding remarks

Inflammation is a fundamental, evolutionarily conserved, and highly integrated response triggered when living systems encounter perturbations. As a complex system phenomenon, it is shaped by multiple layers of biological and environmental context and cannot be fully grasped by cataloging cytokines and pathways. Schematically, inflammation complexified throughout evolution, from primitive cellular stress response in pre-eukaryotes, to an integrated multicellular response in early metazoans, to the current multi-system response of vertebrates that diversified across species alongside their respective strategies of environmental adaptation, adding more and more layers of 'bureaucracy'. Despite the incredible complexity and diversity of inflammation, directly stemming from evolution, inflamm-aging appears to be a universal phenomenon. However, emerging evidence suggests that it is more context-dependent than previously assumed.

In living systems, interactions are dynamic and context-dependent, generating various effects across different timescales. In the case of inflamm-aging, hormetic and feedback mechanisms provide mechanistic explanations for the non-linear effects of certain stimuli, which may help to explain disparate findings. Thus, our synthesis suggests that inflamm-aging is a broadly conserved aging-related inflammatory process whose specific manifestations vary with species and context. Although inflamm-aging has traditionally been assessed via blood levels of specific inflammatory mediators, it clearly manifests across multiple biological levels of organization. Future research challenges include (1) identifying and addressing the myriad sources of context dependence to improve our understanding, predictive capacity, and ability to generalize findings; and (2) designing measurands that account for the dynamic, context-dependent nature of feedback and hormetic mechanisms across biological levels of organization. Such approaches could help clarify the extent to which inflamm-aging represents an intrinsic aspect of physiological aging versus an environment-driven, context-specific phenomenon.

This way, while the influence on the inflammatory state/response of specific exposome factors (diet, physical activity, sleep patterns, psychosocial stress, environmental toxicants, light exposure, and microbiota composition) is well-recognized, their relative contributions and interactions remain incompletely understood. For example, although the harmful effects of ultra-processed foods are well-documented, our understanding of optimal dietary patterns beyond caloric balance and micronutrients is

still limited [253]. Moving forward, the development of individualized or population-specific inflammatory "clocks" or signatures (grounded in comparative biology and integrative immunology) will likely be critical for elucidating the complex relationship between inflammation and aging. Comparative studies of species with diverse homeostatic strategies may help us to understand the evolutionary 'logic' underlying the spectrum of inflammatory responses, the often-blurred distinction between homeostasis and inflammation, hormetic thresholds, and between inflammation-inducing perturbations that accelerate mismatched trajectories, such as inflamm-aging as commonly conceived, versus those that align with "evolutionary expectations" of equilibrium maintenance.

Finally, our review suggests that the apparent contradictions about inflamm-aging's universality resolve when one appreciates context: inflamm-aging is 'public' in principle, yet so 'private' in its manifestation that its measurement must be tailored to each context.

Acknowledgements

We thank Thomas Kraft and the anonymous reviewers for their constructive feedback on the manuscript.

Funding

This work was financially supported by the *Impetus program*. The funders were not involved in the writing of the manuscript or the decision to publish. J.H. received funding support from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under project ID 499552394 (SFB 1597/1).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used GPT-4o to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Authors' Contributions

MF wrote the manuscript. AAC provided substantive revisions. MF, CD, and KT prepared the figures. All authors reviewed the manuscript.

Conflicts of Interest

The authors declare no competing interests.

References

1. Fülöp, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E. H., Cohen, A. A., Witkowski, J. M. & Franceschi, C. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? *Front. Immunol.* **8**, 1960 (2018).
2. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The Hallmarks of Aging. *Cell* **153**, 1194–1217 (2013).
3. Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E. & De Benedictis, G. Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Annals of the New York Academy of Sciences* **908**, 244–254 (2000).
4. Matacchione, G., Perugini, J., Di Mercurio, E., Sabbatinelli, J., Prattichizzo, F., Senzacqua, M., Storci, G., Dani, C., Lezoche, G., Guerrieri, M., Giordano, A., Bonafè, M. & Olivieri, F. Senescent macrophages in the human adipose tissue as a source of inflammaging. *GeroScience* **44**, 1941–1960 (2022).
5. Prata, L. G. P. L., Ovsyannikova, I. G., Tchkonia, T. & Kirkland, J. L. Senescent cell clearance by the immune system: Emerging therapeutic opportunities. *Seminars in Immunology* **40**, 101275 (2018).
6. Schloesser, D., Lindenthal, L., Sauer, J., Chung, K.-J., Chavakis, T., Griesser, E., Baskaran, P., Maier-Habelsberger, U., Fundel-Clemens, K., Schlotthauer, I., Watson, C. K., Swee, L. K., Igney, F., Park, J. E., Huber-Lang, M. S., Thomas, M.-J., El Kasmi, K. C. & Murray, P. J. Senescent cells suppress macrophage-mediated corpse removal via upregulation of the CD47-QPCT/L axis. *Journal of Cell Biology* **222**, e202207097 (2023).
7. Ovadya, Y., Landsberger, T., Leins, H., Vadai, E., Gal, H., Biran, A., Yosef, R., Sagiv, A., Agrawal, A., Shapira, A., Windheim, J., Tsoory, M., Schirmbeck, R., Amit, I., Geiger, H. & Krizhanovsky, V. Impaired immune surveillance accelerates accumulation of senescent cells and aging. *Nat Commun* **9**, 5435 (2018).
8. Schafer, M. J., Zhang, X., Kumar, A., Atkinson, E. J., Zhu, Y., Jachim, S., Mazula, D. L., Brown, A. K., Berning, M., Aversa, Z., Kotajarvi, B., Bruce, C. J., Greason, K. L., Suri, R. M., Tracy, R. P., Cummings, S. R., White, T. A. & LeBrasseur, N. K. The senescence-associated secretome as an indicator of age and medical risk. *JCI Insight* **5**, e133668 (2020).
9. Kale, A., Sharma, A., Stolzing, A., Desprez, P.-Y. & Campisi, J. Role of immune cells in the removal of deleterious senescent cells. *Immun Ageing* **17**, 16 (2020).
10. Lencel, P. & Magne, D. Inflammaging: The driving force in osteoporosis? *Medical Hypotheses* **76**, 317–321 (2011).
11. Franceschi, C. & Campisi, J. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **69**, S4–S9 (2014).
12. Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C. M., Isaacs, J., Kolenda, C., Parker, C., Dunn, M., Catt, M., Jagger, C., Von Zglinicki, T. & Kirkwood, T. B. L. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: Cross-sectional findings from the Newcastle 85+ Study. *Mechanisms of Ageing and Development* **133**, 456–466 (2012).

13. De Martinis, M., Franceschi, C., Monti, D. & Ginaldi, L. Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. *FEBS Letters* **579**, 2035–2039 (2005).
14. Franceschi, C., Garagnani, P., Vitale, G., Capri, M. & Salvioli, S. Inflammaging and 'Garb-aging'. *Trends in Endocrinology & Metabolism* **28**, 199–212 (2017).
15. Statzer, C., Park, J. Y. C. & Ewald, C. Y. Extracellular matrix dynamics as an emerging yet understudied hallmark of aging and longevity. *Aging and Disease* **14**, 670 (2023).
16. Lampi, M. C. & Reinhart-King, C. A. Targeting extracellular matrix stiffness to attenuate disease: From molecular mechanisms to clinical trials. *Science translational medicine* **10**, eaao0475 (2018).
17. Takaya, K., Asou, T. & Kishi, K. Aging Fibroblasts Adversely Affect Extracellular Matrix Formation via the Senescent Humoral Factor Ependymin-Related Protein 1. *Cells* **11**, 3749 (2022).
18. Scheibner, K. A., Lutz, M. A., Boodoo, S., Fenton, M. J., Powell, J. D. & Horton, M. R. Hyaluronan Fragments Act as an Endogenous Danger Signal by Engaging TLR2. *The Journal of Immunology* **177**, 1272–1281 (2006).
19. Coppé, J.-P., Desprez, P.-Y., Krtolica, A. & Campisi, J. The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression. *Annu. Rev. Pathol. Mech. Dis.* **5**, 99–118 (2010).
20. Alley, D. E., Crimmins, E., Bandeen-Roche, K., Guralnik, J. & Ferrucci, L. Three-Year Change in Inflammatory Markers in Elderly People and Mortality: The Invecchiare in Chianti Study. *J American Geriatrics Society* **55**, 1801–1807 (2007).
21. Bruunsgaard, H., Andersen-Ranberg, K., Hjelmborg, J. v.B, Pedersen, B. K. & Jeune, B. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. *The American Journal of Medicine* **115**, 278–283 (2003).
22. Harris, T. B., Ferrucci, L., Tracy, R. P., Corti, M. C., Wacholder, S., Ettinger, W. H., Heimovitz, H., Cohen, H. J. & Wallace, R. Associations of elevated Interleukin-6 and C-Reactive protein levels with mortality in the elderly**Access the "Journal Club" discussion of this paper at http:/www.elsevier.com/locate/ajmselect/. *The American Journal of Medicine* **106**, 506–512 (1999).
23. Puzianowska-Kuźnicka, M., Owczarz, M., Wieczorowska-Tobis, K., Nadrowski, P., Chudek, J., Slusarczyk, P., Skalska, A., Jonas, M., Franek, E. & Mossakowska, M. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing* **13**, 21 (2016).
24. Samson, L. D., Buisman, A., Ferreira, J. A., Picavet, H. S. J., Verschuren, W. M. M., Boots, A. M. & Engelfriet, P. Inflammatory marker trajectories associated with frailty and ageing in a 20-year longitudinal study. *Clin & Trans Imm* **11**, e1374 (2022).
25. Varadhan, R., Yao, W., Matteini, A., Beamer, B. A., Xue, Q. -l., Yang, H., Manwani, B., Reiner, A., Jenny, N., Parekh, N., Fallin, M. D., Newman, A., Bandeen-Roche, K., Tracy, R., Ferrucci, L. & Walston, J. Simple Biologically Informed Inflammatory Index of Two Serum Cytokines Predicts 10 Year All-Cause Mortality in Older Adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **69A**, 165–173 (2014).
26. Roubenoff, R., Harris, T. B., Abad, L. W., Wilson, P. W. F., Dallal, G. E. & Dinarello, C. A. Monocyte Cytokine Production in an Elderly Population: Effect of Age and Inflammation. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **53A**, M20–M26 (1998).

27. Sayed, N., Huang, Y., Nguyen, K., Krejciova-Rajaniemi, Z., Grawe, A. P., Gao, T., Tibshirani, R., Hastie, T., Alpert, A., Cui, L., Kuznetsova, T., Rosenberg-Hasson, Y., Ostan, R., Monti, D., Lehallier, B., Shen-Orr, S. S., Maecker, H. T., Dekker, C. L., Wyss-Coray, T., Franceschi, C., Jojic, V., Haddad, F., Montoya, J. G., Wu, J. C., Davis, M. M. & Furman, D. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nat Aging* **1**, 598–615 (2021).
28. Hirata, T., Arai, Y., Yuasa, S., Abe, Y., Takayama, M., Sasaki, T., Kunitomi, A., Inagaki, H., Endo, M., Morinaga, J., Yoshimura, K., Adachi, T., Oike, Y., Takebayashi, T., Okano, H. & Hirose, N. Associations of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages. *Nat Commun* **11**, 3820 (2020).
29. Kalyakulina, A., Yusipov, I., Kondakova, E., Bacalini, M. G., Franceschi, C., Vedunova, M. & Ivanchenko, M. Small immunological clocks identified by deep learning and gradient boosting. *Front. Immunol.* **14**, 1177611 (2023).
30. Kalyakulina, A., Yusipov, I., Kondakova, E., Sivtseva, T., Zakharova, R., Semenov, S., Klimova, T., Ammosova, E., Trukhanov, A., Franceschi, C. & Ivanchenko, M. Inflammaging Markers in the Extremely Cold Climate: A Case Study of Yakutian Population. *IJMS* **25**, 13741 (2024).
31. Morrisette-Thomas, V., Cohen, A. A., Fülöp, T., Riesco, É., Legault, V., Li, Q., Milot, E., Dusseault-Bélanger, F. & Ferrucci, L. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. *Mechanisms of Ageing and Development* **139**, 49–57 (2014).
32. Tavenier, J., Rasmussen, L. J. H., Houlind, M. B., Andersen, A. L., Panum, I., Andersen, O., Petersen, J., Langkilde, A. & Nehlin, J. O. 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 (2020).
33. Piber, D., Olmstead, R., Cho, J. H.-J., Witarama, T., Perez, C., Dietz, N., Seeman, T. E., Breen, E. C., Cole, S. W. & Irwin, M. R. Inflammaging: Age and Systemic, Cellular, and Nuclear Inflammatory Biology in Older Adults. *The Journals of Gerontology: Series A* **74**, 1716–1724 (2019).
34. Kim, K.-A., Jeong, J.-J., Yoo, S.-Y. & Kim, D.-H. Gut microbiota lipopolysaccharide accelerates inflamm-aging in mice. *BMC Microbiol* **16**, 9 (2016).
35. Zhang, P., Catterson, J. H., Grönke, S. & Partridge, L. Inhibition of S6K lowers age-related inflammation and increases lifespan through the endolysosomal system. *Nat Aging* **4**, 491–509 (2024).
36. Kounatidis, I., Chtarbanova, S., Cao, Y., Hayne, M., Jayanth, D., Ganetzky, B. & Ligoxygakis, P. NF-κB Immunity in the Brain Determines Fly Lifespan in Healthy Aging and Age-Related Neurodegeneration. *Cell Reports* **19**, 836–848 (2017).
37. Těšický, M., Krajzingrová, T., Świderská, Z., Syslová, K., Bílková, B., Eliáš, J., Velová, H., Svobodová, J., Bauerová, P., Albrecht, T. & Vinkler, M. Longitudinal evidence for immunosenescence and inflammaging in free-living great tits. *Experimental Gerontology* **154**, 111527 (2021).
38. Mercken, E. M., Capri, M., Carboneau, B. A., Conte, M., Heidler, J., Santoro, A., Martin-Montalvo, A., Gonzalez-Freire, M., Khraiwesh, H., González-Reyes, J. A., Moaddel, R., Zhang, Y., Becker, K. G., Villalba, J. M., Mattison, J. A., Wittig, I., Franceschi, C. & De Cabo, R. Conserved and species-

specific molecular denominators in mammalian skeletal muscle aging. *npj Aging Mech Dis* **3**, 8 (2017).

39. Jiménez, A. G. Inflammaging in domestic dogs: basal level concentrations of IL-6, IL-1β, and TNF-α in serum of healthy dogs of different body sizes and ages. *Biogerontology* **24**, 593–602 (2023).
40. Schmid, S. M., Hoffman, J. M., Prescott, J., Ernst, H., Promislow, D. E. L., Dog Aging Project Consortium, Akey, J. M., Benton, B., Borenstein, E., Castelhano, M. G., Coleman, A. E., Creevy, K. E., Crowder, K., Dunbar, M. D., Fajt, V. R., Fitzpatrick, A. L., Jeffery, U., Jonlin, E. C., Kaeberlein, M., Karlsson, E. K., Kerr, K. F., Levine, J. M., Ma, J., McClelland, R. L., Ruple, A., Schwartz, S. M., Shrager, S., Snyder-Mackler, N., Tolbert, K., Urfer, S. R., Wilfond, B. S. & Creevy, K. E. The companion dog as a model for inflammaging: a cross-sectional pilot study. *GeroScience* **46**, 5395–5407 (2024).
41. Moons, L., Bollaerts, I., Van Houcke, J., Vanhunsel, S., Beckers, A., Lemmens, K. & De Groef, L. "Inflammaging" in the zebrafish visual system. *Acta Ophthalmologica* **95**, j.1755-3768.2017.03625 (2017).
42. Morabito, G., Dönertas, H. M., Sperti, L., Seidel, J., Poursadegh, A., Poeschla, M. & Valenzano, D. R. Spontaneous onset of cellular markers of inflammation and genome instability during aging in the immune niche of the naturally short-lived turquoise killifish (*Nothobranchius furzeri*). Preprint at https://doi.org/10.1101/2023.02.06.527346 (2023).
43. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. Hallmarks of aging: An expanding universe. *Cell* **186**, 243–278 (2023).
44. Baechle, J. J., Chen, N., Makhijani, P., Winer, S., Furman, D. & Winer, D. A. Chronic inflammation and the hallmarks of aging. *Molecular Metabolism* **74**, 101755 (2023).
45. Franck, M., Tanner, K. T., Tennyson, R. L., Daunizeau, C., Ferrucci, L., Bandinelli, S., Trumble, B. C., Kaplan, H. S., Aronoff, J. E., Stieglitz, J., Kraft, T. S., Lea, A. J., Venkataraman, V. V., Wallace, I. J., Lim, Y. A. L., Ng, K. S., Yeong, J. P. S., Ho, R., Lim, X., Mehrjerd, A., Charalambous, E. G., Aiello, A. E., Pawelec, G., Franceschi, C., Hertel, J., Fülöp, T., Lemoine, M., Gurven, M. & Cohen, A. A. Nonuniversality of inflammaging across human populations. *Nat Aging* (2025) doi:10.1038/s43587-025-00888-0.
46. Aronoff, J. E., Jenkins, C. L., Garcia, A. R., Koebele, S. V., Ghafoor, S., Woolard, K. L., Charifson, M., Suarez, I. M., Eid Rodriguez, D., Beheim, B., Cummings, D. K., Hooper, P. L., Kraft, T. K., Buetow, K., Finch, C. E., Franck, M., Cohen, A. A., Stieglitz, J., Gurven, M., Kaplan, H. & Trumble, B. C. Inflammaging is minimal among forager-horticulturalists in the Bolivian Amazon. *Proc. R. Soc. B.* **292**, 20251111 (2025).
47. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
48. Kotas, M. E. & Medzhitov, R. Homeostasis, Inflammation, and Disease Susceptibility. *Cell* **160**, 816–827 (2015).
49. Chovatiya, R. & Medzhitov, R. Stress, Inflammation, and Defense of Homeostasis. *Molecular Cell* **54**, 281–288 (2014).
50. Okabe, Y. & Medzhitov, R. Tissue biology perspective on macrophages. *Nat Immunol* **17**, 9–17 (2016).

51. Medzhitov, R. The spectrum of inflammatory responses. *Science* **374**, 1070–1075 (2021).
52. Meizlish, M. L., Franklin, R. A., Zhou, X. & Medzhitov, R. Tissue Homeostasis and Inflammation. *Annu. Rev. Immunol.* **39**, 557–581 (2021).
53. Kopp, E. B., Agaronyan, K., Licona-Limón, I., Nish, S. A. & Medzhitov, R. Modes of type 2 immune response initiation. *Immunity* **56**, 687–694 (2023).
54. Vasek, D., Holicek, P., Galatik, F., Kratochvilova, A., Porubska, B., Somova, V., Fikarova, N., Hajkova, M., Prevorovsky, M., Zurmanova, J. M. & Krulova, M. Immune response to cold exposure: Role of γδ T cells and TLR2-mediated inflammation. *Eur J Immunol* 2350897 (2024) doi:10.1002/eji.202350897.
55. Kogel, V., Trinh, S., Gasterich, N., Beyer, C. & Seitz, J. Long-Term Glucose Starvation Induces Inflammatory Responses and Phenotype Switch in Primary Cortical Rat Astrocytes. *J Mol Neurosci* **71**, 2368–2382 (2021).
56. Houser, M. C., Mac, V., Smith, D. J., Chicas, R. C., Xiuhtecutli, N., Flocks, J. D., Elon, L., Tansey, M. G., Sands, J. M., McCauley, L. & Hertzberg, V. S. Inflammation-Related Factors Identified as Biomarkers of Dehydration and Subsequent Acute Kidney Injury in Agricultural Workers. *Biological Research For Nursing* **23**, 676–688 (2021).
57. Kaufmann, C. C., Wegberger, C., Tscharre, M., Haller, P. M., Piackova, E., Vujasin, I., Kassem, M., Tentzeris, I., Freynhofer, M. K., Jäger, B., Wojta, J. & Huber, K. Effect of marathon and ultra-marathon on inflammation and iron homeostasis. *Scandinavian Med Sci Sports* **31**, 542–552 (2021).
58. Mosser, D. M., Hamidzadeh, K. & Goncalves, R. Macrophages and the maintenance of homeostasis. *Cell Mol Immunol* **18**, 579–587 (2021).
59. Gordon, S. & Plüddemann, A. Macrophage Clearance of Apoptotic Cells: A Critical Assessment. *Front. Immunol.* **9**, 127 (2018).
60. Maddipati, K. R. Non-inflammatory Physiology of "Inflammatory" Mediators – Unalamation, a New Paradigm. *Front. Immunol.* **11**, (2020).
61. Klotskova, H., Kidess, E., Nadal, A. L. & Brugman, S. The role of interleukin-22 in mammalian intestinal homeostasis: Friend and foe. *Immunity Inflam & Disease* **12**, (2024).
62. Liongue, C. & Ward, A. C. Evolution of the JAK-STAT pathway. *JAK-STAT* **2**, e22756 (2013).
63. Liongue, C., Taznin, T. & Ward, A. C. Signaling via the CytoR/JAK/STAT/SOCS pathway: Emergence during evolution. *Molecular Immunology* **71**, 166–175 (2016).
64. Myllymäki, H. & Rämet, M. JAK/STAT Pathway in *Drosophila* Immunity. *Scand J Immunol* **79**, 377–385 (2014).
65. Kültz, D. Evolution of cellular stress response mechanisms. *J Exp Zool Pt A* **333**, 359–378 (2020).
66. Colaço, H. G. & Moita, L. F. Initiation of innate immune responses by surveillance of homeostasis perturbations. *The FEBS Journal* **283**, 2448–2457 (2016).
67. Fontana, M. F., Shin, S. & Vance, R. E. Activation of Host Mitogen-Activated Protein Kinases by Secreted Legionella pneumophila Effectors That Inhibit Host Protein Translation. *Infect Immun* **80**, 3570–3575 (2012).
68. Ip, W. K. E. & Medzhitov, R. Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLRC4 inflammasome activation. *Nat Commun* **6**, 6931 (2015).

69. Raggi, F., Pelassa, S., Pierobon, D., Penco, F., Gattorno, M., Novelli, F., Eva, A., Varesio, L., Giovarelli, M. & Bosco, M. C. Regulation of Human Macrophage M1–M2 Polarization Balance by Hypoxia and the Triggering Receptor Expressed on Myeloid Cells-1. *Front. Immunol.* **8**, 1097 (2017).
70. Ludtka, C., Silberman, J., Moore, E. & Allen, J. B. Macrophages in microgravity: the impact of space on immune cells. *npj Microgravity* **7**, 13 (2021).
71. Lemoine, M. The Evolution of the Hallmarks of Aging. *Front. Genet.* **12**, 693071 (2021).
72. Liu, G., Zhang, H., Zhao, C. & Zhang, H. Evolutionary History of the Toll-Like Receptor Gene Family across Vertebrates. *Genome Biology and Evolution* **12**, 3615–3634 (2020).
73. Velová, H., Gutowska-Ding, M. W., Burt, D. W. & Vinkler, M. Toll-Like Receptor Evolution in Birds: Gene Duplication, Pseudogenization, and Diversifying Selection. *Molecular Biology and Evolution* **35**, 2170–2184 (2018).
74. Hughes, AustinL. Evolution of the interleukin-1 gene family in mammals. *J Mol Evol* **39**, (1994).
75. Liongue, C. & Ward, A. C. Evolution of Class I cytokine receptors. *BMC Evol Biol* **7**, 120 (2007).
76. Williams, L. M. & Gilmore, T. D. Looking Down on NF- *κ* B. *Molecular and Cellular Biology* **40**, e00104-20 (2020).
77. Boudinot, P., Bird, S., Du Pasquier, L. & Collet, B. The repertoire of vertebrate STAT transcription factors: Origin and variations in fish. *Developmental & Comparative Immunology* **116**, 103929 (2021).
78. Cañestro, C., Albalat, R., Irimia, M. & Garcia-Fernàndez, J. Impact of gene gains, losses and duplication modes on the origin and diversification of vertebrates. *Seminars in Cell & Developmental Biology* **24**, 83–94 (2013).
79. Wang, B., Wangkahart, E., Secombes, C. J. & Wang, T. Insights into the Evolution of the Suppressors of Cytokine Signaling (SOCS) Gene Family in Vertebrates. *Molecular Biology and Evolution* **36**, 393–411 (2019).
80. Bailey, J. A., Gu, Z., Clark, R. A., Reinert, K., Samonte, R. V., Schwartz, S., Adams, M. D., Myers, E. W., Li, P. W. & Eichler, E. E. Recent Segmental Duplications in the Human Genome. *Science* **297**, 1003–1007 (2002).
81. Lynch, M. & Conery, J. S. The Evolutionary Fate and Consequences of Duplicate Genes. *Science* **290**, 1151–1155 (2000).
82. Antczak, M., Cañete, P. F., Chen, Z., Belle, C. & Yu, D. Evolution of γ chain cytokines: Mechanisms, methods and applications. *Computational and Structural Biotechnology Journal* **20**, 4746–4755 (2022).
83. Shields, D. C., Harmon, D. L., Nunez, F. & Whitehead, A. S. The evolution of haematopoietic cytokine /receptor complexes. *Cytokine* **7**, 679–688 (1995).
84. Zimmerman, L. M., Bowden, R. M. & Vogel, L. A. A vertebrate cytokine primer for eco-immunologists. *Functional Ecology* **28**, 1061–1073 (2014).
85. Msweli, S., Pakala, S. B. & Syed, K. NF-κB Transcription Factors: Their Distribution, Family Expansion, Structural Conservation, and Evolution in Animals. *IJMS* **25**, 9793 (2024).

86. Stec, W., Vidal, O. & Zeidler, M. P. Drosophila SOCS36E negatively regulates JAK/STAT pathway signaling via two separable mechanisms. *MBoC* **24**, 3000–3009 (2013).
87. Boraschi, D. What Is IL-1 for? The Functions of Interleukin-1 Across Evolution. *Front. Immunol.* **13**, 872155 (2022).
88. Hilliard, S., Mosoyan, K., Branciamore, S., Gogoshin, G., Zhang, A., Simons, D. L., Rockne, R. C., Lee, P. P. & Rodin, A. S. Bow-tie architectures in biological and artificial neural networks: Implications for network evolution and assay design. *iScience* **26**, 106041 (2023).
89. Csete, M. & Doyle, J. Bow ties, metabolism and disease. *Trends in Biotechnology* **22**, 446–450 (2004).
90. Tieri, P., Grignolio, A., Zaikin, A., Mishto, M., Remondini, D., Castellani, G. C. & Franceschi, C. Network, degeneracy and bow tie. Integrating paradigms and architectures to grasp the complexity of the immune system. *Theor Biol Med Model* **7**, 32 (2010).
91. Qing, Y. & Stark, G. R. Alternative Activation of STAT1 and STAT3 in Response to Interferon-γ. *Journal of Biological Chemistry* **279**, 41679–41685 (2004).
92. Trengove, M. C. & Ward, A. C. SOCS proteins in development and disease. *Am J Clin Exp Immunol* **2**, 1–29 (2013).
93. Croker, B. A., Krebs, D. L., Zhang, J.-G., Wormald, S., Willson, T. A., Stanley, E. G., Robb, L., Greenhalgh, C. J., Förster, I., Clausen, B. E., Nicola, N. A., Metcalf, D., Hilton, D. J., Roberts, A. W. & Alexander, W. S. SOCS3 negatively regulates IL-6 signaling in vivo. *Nat Immunol* **4**, 540–545 (2003).
94. Yasukawa, H., Ohishi, M., Mori, H., Murakami, M., Chinen, T., Aki, D., Hanada, T., Takeda, K., Akira, S., Hoshijima, M., Hirano, T., Chien, K. R. & Yoshimura, A. IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. *Nat Immunol* **4**, 551–556 (2003).
95. Bode, J. G., Albrecht, U., Häussinger, D., Heinrich, P. C. & Schaper, F. Hepatic acute phase proteins – Regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF-κB-dependent signaling. *European Journal of Cell Biology* **91**, 496–505 (2012).
96. Zhang, Z. & Fuller, G. M. The Competitive Binding of STAT3 and NF-κB on an Overlapping DNA Binding Site. *Biochemical and Biophysical Research Communications* **237**, 90–94 (1997).
97. Gottschalk, R. A., Martins, A. J., Angermann, B. R., Dutta, B., Ng, C. E., Uderhardt, S., Tsang, J. S., Fraser, I. D. C., Meier-Schellersheim, M. & Germain, R. N. Distinct NF-κB and MAPK Activation Thresholds Uncouple Steady-State Microbe Sensing from Anti-pathogen Inflammatory Responses. *Cell Systems* **2**, 378–390 (2016).
98. Norkina, O., Dolganiuc, A., Catalano, D., Kodys, K., Mandrekar, P., Syed, A., Efros, M. & Szabo, G. Acute Alcohol Intake Induces SOCS1 and SOCS3 and Inhibits Cytokine-Induced STAT1 and STAT3 Signaling in Human Monocytes. *Alcoholism Clin & Exp Res* **32**, 1565–1573 (2008).
99. Hartgers, F. C., Obeng, B. B., Kruize, Y. C. M., Dijkhuis, A., McCall, M., Sauerwein, R. W., Luty, A. J. F., Boakye, D. A. & Yazdanbakhsh, M. Responses to Malarial Antigens Are Altered in Helminth-Infected Children. *J INFECT DIS* **199**, 1528–1535 (2009).
100. Harwardt, T., Lukas, S., Zenger, M., Reitberger, T., Danzer, D., Übner, T., Munday, D. C., Nevels, M. & Paulus, C. Human Cytomegalovirus Immediate-Early 1 Protein Rewires Upstream STAT3 to

Downstream STAT1 Signaling Switching an IL6-Type to an IFNγ-Like Response. *PLoS Pathog* **12**, e1005748 (2016).
101. Meizlish, M. L., Kimura, Y., Pope, S. D., Matta, R., Kim, C., Philip, N. H., Meyaard, L., Gonzalez, A. & Medzhitov, R. Mechanosensing regulates tissue repair program in macrophages. *Sci. Adv.* **10**, eadk6906 (2024).
102. Wu, Z., Pope, S. D., Ahmed, N. S., Leung, D. L., Hajjar, S., Yue, Q., Anand, D. M., Kopp, E. B., Okin, D., Ma, W., Kagan, J. C., Hargreaves, D. C., Medzhitov, R. & Zhou, X. Control of Inflammatory Response by Tissue Microenvironment. Preprint at https://doi.org/10.1101/2024.05.10.592432 (2024).
103. Kaur, A., Ecker, B. L., Douglass, S. M., Kugel, C. H., Webster, M. R., Almeida, F. V., Somasundaram, R., Hayden, J., Ban, E., Ahmadzadeh, H., Franco-Barraza, J., Shah, N., Mellis, I. A., Keeney, F., Kossenkov, A., Tang, H.-Y., Yin, X., Liu, Q., Xu, X., Fane, M., Brafford, P., Herlyn, M., Speicher, D. W., Wargo, J. A., Tetzlaff, M. T., Haydu, L. E., Raj, A., Shenoy, V., Cukierman, E. & Weeraratna, A. T. Remodeling of the Collagen Matrix in Aging Skin Promotes Melanoma Metastasis and Affects Immune Cell Motility. *Cancer Discovery* **9**, 64–81 (2019).
104. Marongiu, F., Serra, M. P., Doratiotto, S., Sini, M., Fanti, M., Cadoni, E., Serra, M. & Laconi, E. Aging promotes neoplastic disease through effects on the tissue microenvironment. *Aging* **8**, 3390–3399 (2016).
105. Linehan, E., Dombrowski, Y., Snoddy, R., Fallon, P. G., Kissenpfennig, A. & Fitzgerald, D. C. Aging impairs peritoneal but not bone marrow-derived macrophage phagocytosis. *Aging Cell* **13**, 699–708 (2014).
106. McFarlane, A., Pohler, E. & Moraga, I. Molecular and cellular factors determining the functional pleiotropy of cytokines. *The FEBS Journal* **290**, 2525–2552 (2023).
107. Orange, S. T., Leslie, J., Ross, M., Mann, D. A. & Wackerhage, H. The exercise IL-6 enigma in cancer. *Trends in Endocrinology & Metabolism* **34**, 749–763 (2023).
108. De Melo Madureira, Á. N., De Oliveira, J. R. S. & De Menezes Lima, V. L. The Role of IL-6 Released During Exercise to Insulin Sensitivity and Muscle Hypertrophy. *MRMC* **22**, 2419–2428 (2022).
109. Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N. & Slavich, G. M. Chronic inflammation in the etiology of disease across the life span. *Nat Med* **25**, 1822–1832 (2019).
110. Foy, B. H., Sundt, T. M., Carlson, J. C. T., Aguirre, A. D. & Higgins, J. M. Human acute inflammatory recovery is defined by co-regulatory dynamics of white blood cell and platelet populations. *Nat Commun* **13**, (2022).
111. Inoue, T., Komoda, H., Nonaka, M., Kameda, M., Uchida, T. & Node, K. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease. *International Journal of Cardiology* **124**, 319–325 (2008).
112. Panichi, V., Maggiore, U., Taccola, D., Migliori, M., Rizza, G. M., Consani, C., Bertini, A., Sposini, S., Perez-Garcia, R., Rindi, P., Palla, R. & Tetta, C. Interleukin-6 is a stronger predictor of total and

cardiovascular mortality than C-reactive protein in haemodialysis patients. *Nephrology Dialysis Transplantation* **19**, 1154–1160 (2004).
113. Mainous, A. G., Sharma, P. & Jo, A. Systemic inflammation among adults with diagnosed and undiagnosed cardiometabolic conditions: a potential missed opportunity for cardiovascular disease prevention. *Front. Med.* **10**, 1327205 (2024).
114. Yeh, E. T. H. & Willerson, J. T. Coming of Age of C-Reactive Protein: Using Inflammation Markers in Cardiology. *Circulation* **107**, 370–371 (2003).
115. Shen-Orr, S. S., Furman, D., Kidd, B. A., Hadad, F., Lovelace, P., Huang, Y.-W., Rosenberg-Hasson, Y., Mackey, S., Grisar, F. A. G., Pickman, Y., Maecker, H. T., Chien, Y., Dekker, C. L., Wu, J. C., Butte, A. J. & Davis, M. M. Defective Signaling in the JAK-STAT Pathway Tracks with Chronic Inflammation and Cardiovascular Risk in Aging Humans. *Cell Systems* **3**, 374-384.e4 (2016).
116. Blackstone, N. W. A food's-eye view of the transition from basal metazoans to bilaterians. *Integrative and Comparative Biology* **47**, 724–733 (2007).
117. Mori, S., Kobayashi, A., Sakamoto, H., Hamada, M., Sakamoto, T. & Nakamura, R. Model systems for discovering evolutionary singularity of bilaterian physiological regulation: lessons from studies on simple/primitive flatworms. *BIOPHYSICS* **21**, n/a (2024).
118. Monahan-Earley, R., Dvorak, A. M. & Aird, W. C. Evolutionary origins of the blood vascular system and endothelium. *Journal of Thrombosis and Haemostasis* **11**, 46–66 (2013).
119. Campbell, R. Piecing together evolution of the vertebrate endocrine system. *Trends in Genetics* **20**, 359–366 (2004).
120. Willmer, P., Stone, G. & Johnston, I. *Environmental Physiology of Animals*. (John Wiley & Sons, 2009).
121. Ye, J. & Medzhitov, R. Control strategies in systemic metabolism. *Nat Metab* **1**, 947–957 (2019).
122. Clarke, A. & Pörtner, H. Temperature, metabolic power and the evolution of endothermy. *Biological Reviews* **85**, 703–727 (2010).
123. Altringham, J. D. & Block, B. A. Why Do Tuna Maintain Elevated Slow Muscle Temperatures? Power Output Of Muscle Isolated From Endothermic And Ectothermic Fish. *Journal of Experimental Biology* **200**, 2617–2627 (1997).
124. Costa, D. P., Houser, D. S. & Crocker, D. E. Fundamentals of Water Relations and Thermoregulation in Animals. in *Encyclopedia of Life Sciences* (Wiley, 2013). doi:10.1002/9780470015902.a0003216.pub2.
125. Natochin, Yu. V. Coevolution of physiological systems. *J Evol Biochem Phys* **52**, 414–423 (2016).
126. Polakof, S., Mommsen, T. P. & Soengas, J. L. Glucosensing and glucose homeostasis: From fish to mammals. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology* **160**, 123–149 (2011).
127. Adams, T. & Covino, B. G. Racial Variations to a Standardized Cold Stress. *Journal of Applied Physiology* **12**, 9–12 (1958).
128. Bergenstal, R. M., Gal, R. L., Connor, C. G., Gubitosi-Klug, R., Kruger, D., Olson, B. A., Willi, S. M., Aleppo, G., Weinstock, R. S., Wood, J., Rickels, M., DiMeglio, L. A., Bethin, K. E., Marcovina, S., Tassopoulos, A., Lee, S., Massaro, E., Bzdick, S., Ichihara, B., Markmann, E., McGuigan, P.,

Woerner, S., Ecker, M., Beck, R. W., & for the T1D Exchange Racial Differences Study Group. Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A $_{1c}$ Levels. *Ann Intern Med* **167**, 95 (2017).

129. Ziemer, D. C. Glucose-Independent, Black–White Differences in Hemoglobin A $_{1c}$ Levels: A Cross-sectional Analysis of 2 Studies. *Ann Intern Med* **152**, 770 (2010).
130. Franceschini, N., Fox, E., Zhang, Z., Edwards, T. L., Nalls, M. A., Sung, Y. J., Tayo, B. O., Sun, Y. V., Gottesman, O., Adeyemo, A., Johnson, A. D., Young, J. H., Rice, K., Duan, Q., Chen, F., Li, Y., Tang, H., Fornage, M., Keene, K. L., Andrews, J. S., Smith, J. A., Faul, J. D., Guangfa, Z., Guo, W., Liu, Y., Murray, S. S., Musani, S. K., Srinivasan, S., Velez Edwards, D. R., Wang, H., Becker, L. C., Bovet, P., Bochud, M., Broeckel, U., Burnier, M., Carty, C., Chasman, D. I., Ehret, G., Chen, W.-M., Chen, G., Chen, W., Ding, J., Dreisbach, A. W., Evans, M. K., Guo, X., Garcia, M. E., Jensen, R., Keller, M. F., Lettre, G., Lotay, V., *et al.* Genome-wide Association Analysis of Blood-Pressure Traits in African-Ancestry Individuals Reveals Common Associated Genes in African and Non-African Populations. *The American Journal of Human Genetics* **93**, 545–554 (2013).
131. Ježek, P. & Hlavatá, L. Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism. *The International Journal of Biochemistry & Cell Biology* **37**, 2478–2503 (2005).
132. Brestoff, J. R., Wilen, C. B., Moley, J. R., Li, Y., Zou, W., Malvin, N. P., Rowen, M. N., Saunders, B. T., Ma, H., Mack, M. R., Hykes, B. L., Balce, D. R., Orvedahl, A., Williams, J. W., Rohatgi, N., Wang, X., McAllaster, M. R., Handley, S. A., Kim, B. S., Doench, J. G., Zinselmeyer, B. H., Diamond, M. S., Virgin, H. W., Gelman, A. E. & Teitelbaum, S. L. Intercellular Mitochondria Transfer to Macrophages Regulates White Adipose Tissue Homeostasis and Is Impaired in Obesity. *Cell Metabolism* **33**, 270-282.e8 (2021).
133. Pxytycz, B. & Józkowicz, A. Differential effects of temperature on macrophages of ectothermic vertebrates. *Journal of Leukocyte Biology* **56**, 729–731 (1994).
134. Mann, V., Sundaresan, A. & Shishodia, S. Overnutrition and Lipotoxicity: Impaired Efferocytosis and Chronic Inflammation as Precursors to Multifaceted Disease Pathogenesis. *Biology* **13**, 241 (2024).
135. Tabas, I., Tall, A. & Accili, D. The Impact of Macrophage Insulin Resistance on Advanced Atherosclerotic Plaque Progression. *Circulation Research* **106**, 58–67 (2010).
136. Rieger, A. M., Konowalchuk, J. D., Grayfer, L., Katzenback, B. A., Havixbeck, J. J., Kiemele, M. D., Belosevic, M. & Barreda, D. R. Fish and Mammalian Phagocytes Differentially Regulate Pro-Inflammatory and Homeostatic Responses In Vivo. *PLoS ONE* **7**, e47070 (2012).
137. Peto, R., Roe, F. J., Lee, P. N., Levy, L. & Clack, J. Cancer and ageing in mice and men. *Br J Cancer* **32**, 411–426 (1975).
138. Aktipis, C. A., Boddy, A. M., Gatenby, R. A., Brown, J. S. & Maley, C. C. Life history trade-offs in cancer evolution. *Nat Rev Cancer* **13**, 883–892 (2013).
139. Wang, A., Luan, H. H. & Medzhitov, R. An evolutionary perspective on immunometabolism. *Science* **363**, eaar3932 (2019).

140. Watanobe, H. & Hayakawa, Y. Hypothalamic Interleukin-1β and Tumor Necrosis Factor-α, But Not Interleukin-6, Mediate the Endotoxin-Induced Suppression of the Reproductive Axis in Rats. *Endocrinology* **144**, 4868–4875 (2003).
141. Hotamisligil, G. S., Murray, D. L., Choy, L. N. & Spiegelman, B. M. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proc. Natl. Acad. Sci. U.S.A.* **91**, 4854–4858 (1994).
142. Jager, J., Grémeaux, T., Cormont, M., Le Marchand-Brustel, Y. & Tanti, J.-F. Interleukin-1β-Induced Insulin Resistance in Adipocytes through Down-Regulation of Insulin Receptor Substrate-1 Expression. *Endocrinology* **148**, 241–251 (2007).
143. Weigert, C., Hennige, A. M., Lehmann, R., Brodbeck, K., Baumgartner, F., Schaüble, M., Häring, H. U. & Schleicher, E. D. Direct Cross-talk of Interleukin-6 and Insulin Signal Transduction via Insulin Receptor Substrate-1 in Skeletal Muscle Cells. *Journal of Biological Chemistry* **281**, 7060–7067 (2006).
144. García-López, S., Villanueva, R. & Meikle, M. C. Alterations in the Synthesis of IL-1β, TNF-α, IL-6, and Their Downstream Targets RANKL and OPG by Mouse Calvarial Osteoblasts In vitro: Inhibition of Bone Resorption by Cyclic Mechanical Strain. *Front. Endocrinol.* **4**, (2013).
145. Lam, J., Takeshita, S., Barker, J. E., Kanagawa, O., Ross, F. P. & Teitelbaum, S. L. TNF-α induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J. Clin. Invest.* **106**, 1481–1488 (2000).
146. Dantzer, R. & Kelley, K. W. Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity* **21**, 153–160 (2007).
147. Wdowiak, A., Gujski, M., Bojar, I., Raczkiewicz, D., Bartosińska, J., Wdowiak-Filip, A. & Filip, R. Chronic Inflammation Impairs Male Fertility—A Case-Control Study in Ulcerative Colitis Patients. *JCM* **10**, 1460 (2021).
148. Chawla, A., Nguyen, K. D. & Goh, Y. P. S. Macrophage-mediated inflammation in metabolic disease. *Nat Rev Immunol* **11**, 738–749 (2011).
149. Graham, A. L., Schrom, E. C. & Metcalf, C. J. E. The evolution of powerful yet perilous immune systems. *Trends in Immunology* **43**, 117–131 (2022).
150. Abegglen, L. M., Caulin, A. F., Chan, A., Lee, K., Robinson, R., Campbell, M. S., Kiso, W. K., Schmitt, D. L., Waddell, P. J., Bhaskara, S., Jensen, S. T., Maley, C. C. & Schiffman, J. D. Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans. *JAMA* **314**, 1850 (2015).
151. Culmsee, C., Siewe, J., Junker, V., Retiounskaia, M., Schwarz, S., Camandola, S., El-Metainy, S., Behnke, H., Mattson, M. P. & Krieglstein, J. Reciprocal Inhibition of p53 and Nuclear Factor-κB Transcriptional Activities Determines Cell Survival or Death in Neurons. *J. Neurosci.* **23**, 8586–8595 (2003).
152. Schumm, K., Rocha, S., Caamano, J. & Perkins, N. D. Regulation of p53 tumour suppressor target gene expression by the p52 NF-κB subunit. *EMBO J* **25**, 4820–4832 (2006).
153. Xie, H., Wei, L., Ruan, G., Zhang, H. & Shi, H. Inflammaging score as a potential prognostic tool for cancer: A population-based cohort study. *Mechanisms of Ageing and Development* **219**, 111939 (2024).

154. Zhou, P., Tachedjian, M., Wynne, J. W., Boyd, V., Cui, J., Smith, I., Cowled, C., Ng, J. H. J., Mok, L., Michalski, W. P., Mendenhall, I. H., Tachedjian, G., Wang, L.-F. & Baker, M. L. Contraction of the type I IFN locus and unusual constitutive expression of IFN-α in bats. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 2696–2701 (2016).
155. Irving, A. T., Ahn, M., Goh, G., Anderson, D. E. & Wang, L.-F. Lessons from the host defences of bats, a unique viral reservoir. *Nature* **589**, 363–370 (2021).
156. Downs, C. J., Dochtermann, N. A., Ball, R., Klasing, K. C. & Martin, L. B. The Effects of Body Mass on Immune Cell Concentrations of Mammals. *The American Naturalist* **195**, 107–114 (2020).
157. Nauseef, W. M. Human neutrophils ≠ murine neutrophils: Does it matter? *Immunological Reviews* **314**, 442–456 (2023).
158. Styrt, B. Species Variation in Neutrophil Biochemistry and Function. *Journal of Leukocyte Biology* **46**, 63–74 (1989).
159. Gorissen, M., De Vrieze, E., Flik, G. & Huising, M. O. STAT genes display differential evolutionary rates that correlate with their roles in the endocrine and immune system. *Journal of Endocrinology* **209**, 175–184 (2011).
160. Emes, R. D. Comparison of the genomes of human and mouse lays the foundation of genome zoology. *Human Molecular Genetics* **12**, 701–709 (2003).
161. Seok, J., Warren, H. S., Cuenca, A. G., Mindrinos, M. N., Baker, H. V., Xu, W., Richards, D. R., McDonald-Smith, G. P., Gao, H., Hennessy, L., Finnerty, C. C., López, C. M., Honari, S., Moore, E. E., Minei, J. P., Cuschieri, J., Bankey, P. E., Johnson, J. L., Sperry, J., Nathens, A. B., Billiar, T. R., West, M. A., Jeschke, M. G., Klein, M. B., Gamelli, R. L., Gibran, N. S., Brownstein, B. H., Miller-Graziano, C., Calvano, S. E., Mason, P. H., Cobb, J. P., Rahme, L. G., Lowry, S. F., Maier, R. V., Moldawer, L. L., Herndon, D. N., Davis, R. W., Xiao, W., Tompkins, R. G., the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program, Abouhamze, A., Balis, U. G. J., Camp, D. G., De, A. K., Harbrecht, B. G., Hayden, D. L., Kaushal, A., O'Keefe, G. E., Kotz, K. T., Qian, W., *et al.* Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 3507–3512 (2013).
162. Jones, O. R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C. G., Schaible, R., Casper, B. B., Dahlgren, J. P., Ehrlén, J., García, M. B., Menges, E. S., Quintana-Ascencio, P. F., Caswell, H., Baudisch, A. & Vaupel, J. W. Diversity of ageing across the tree of life. *Nature* **505**, 169–173 (2014).
163. Partridge, L. & Gems, D. Mechanisms of aging: public or private? *Nat Rev Genet* **3**, 165–175 (2002).
164. Wensink, M. J. & Cohen, A. A. The Danaid Theory of Aging. *Front. Cell Dev. Biol.* **9**, 671208 (2022).
165. Du, Z., Chakrabarti, S., Kulaberoglu, Y., Smith, E. S. J., Dobson, C. M., Itzhaki, L. S. & Kumita, J. R. Probing the unfolded protein response in long-lived naked mole-rats. *Biochemical and Biophysical Research Communications* **529**, 1151–1157 (2020).
166. Seim, I., Ma, S., Zhou, X., Gerashchenko, M. V., Lee, S.-G., Suydam, R., George, J. C., Bickham, J. W. & Gladyshev, V. N. The transcriptome of the bowhead whale Balaena mysticetus reveals adaptations of the longest-lived mammal. *Aging* **6**, 879–899 (2014).
167. Lecointre, G. & Huneman, P. Que signifie « se ressembler » en biologie? *philosophiascientiae* 75–98 (2020) doi:10.4000/philosophiascientiae.2304.

168. Huneman, P. & Lecointre, G. Postface. L'individualité–entre logique et historicité.
169. Brodin, P., Jojic, V., Gao, T., Bhattacharya, S., Angel, C. J. L., Furman, D., Shen-Orr, S., Dekker, C. L., Swan, G. E., Butte, A. J., Maecker, H. T. & Davis, M. M. Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences. *Cell* **160**, 37–47 (2015).
170. Ferrucci, L. & Kuchel, G. A. Heterogeneity of Aging: Individual Risk Factors, Mechanisms, Patient Priorities, and Outcomes. *J American Geriatrics Society* **69**, 610–612 (2021).
171. Franceschi, C., Salvioli, S., Garagnani, P., De Eguileor, M., Monti, D. & Capri, M. Immunobiography and the Heterogeneity of Immune Responses in the Elderly: A Focus on Inflammaging and Trained Immunity. *Front. Immunol.* **8**, 982 (2017).
172. Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., Franceschi, C., Lithgow, G. J., Morimoto, R. I., Pessin, J. E., Rando, T. A., Richardson, A., Schadt, E. E., Wyss-Coray, T. & Sierra, F. Geroscience: Linking Aging to Chronic Disease. *Cell* **159**, 709–713 (2014).
173. Orrù, V., Steri, M., Sidore, C., Marongiu, M., Serra, V., Olla, S., Sole, G., Lai, S., Dei, M., Mulas, A., Virdis, F., Piras, M. G., Lobina, M., Marongiu, M., Pitzalis, M., Deidda, F., Loizedda, A., Onano, S., Zoledziewska, M., Sawcer, S., Devoto, M., Gorospe, M., Abecasis, G. R., Floris, M., Pala, M., Schlessinger, D., Fiorillo, E. & Cucca, F. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. *Nat Genet* **52**, 1266–1266 (2020).
174. Hornero-Ramirez, H., Morisette, A., Marcotte, B., Penhoat, A., Lecomte, B., Panthu, B., Lessard Lord, J., Thirion, F., Van-Den-Berghe, L., Blond, E., Simon, C., Caussy, C., Feugier, N., Doré, J., Sanoner, P., Meynier, A., Desjardins, Y., Pilon, G., Marette, A., Cani, P. D., Laville, M., Vinoy, S., Michalski, M.-C. & Nazare, J.-A. Multifunctional dietary approach reduces intestinal inflammation in relation with changes in gut microbiota composition in subjects at cardiometabolic risk: the SINFONI project. *Gut Microbes* **17**, 2438823 (2025).
175. Shen-Orr, S. S. & Furman, D. Variability in the immune system: of vaccine responses and immune states. *Current Opinion in Immunology* **25**, 542–547 (2013).
176. Scott, J. F., Das, L. M., Ahsanuddin, S., Qiu, Y., Binko, A. M., Traylor, Z. P., Debanne, S. M., Cooper, K. D., Boxer, R. & Lu, K. Q. Oral Vitamin D Rapidly Attenuates Inflammation from Sunburn: An Interventional Study. *Journal of Investigative Dermatology* **137**, 2078–2086 (2017).
177. Nicklas, B. J., Ambrosius, W., Messier, S. P., Miller, G. D., Penninx, B. W., Loeser, R. F., Palla, S., Bleecker, E. & Pahor, M. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *The American Journal of Clinical Nutrition* **79**, 544–551 (2004).
178. Miller, G. E., Chen, E. & Parker, K. J. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin* **137**, 959–997 (2011).
179. Casaletto, K. B., Staffaroni, A. M., Elahi, F., Fox, E., Crittenden, P. A., You, M., Neuhaus, J., Glymour, M., Bettcher, B. M., Yaffe, K. & Kramer, J. H. Perceived Stress is Associated with Accelerated Monocyte/Macrophage Aging Trajectories in Clinically Normal Adults. *The American Journal of Geriatric Psychiatry* **26**, 952–963 (2018).

180. Glencross, D. A., Ho, T.-R., Camiña, N., Hawrylowicz, C. M. & Pfeffer, P. E. Air pollution and its effects on the immune system. *Free Radical Biology and Medicine* **151**, 56–68 (2020).
181. Castanon-Cervantes, O., Wu, M., Ehlen, J. C., Paul, K., Gamble, K. L., Johnson, R. L., Besing, R. C., Menaker, M., Gewirtz, A. T. & Davidson, A. J. Dysregulation of Inflammatory Responses by Chronic Circadian Disruption. *The Journal of Immunology* **185**, 5796–5805 (2010).
182. Li, M., Yao, D., Zeng, X., Kasakovski, D., Zhang, Y., Chen, S., Zha, X., Li, Y. & Xu, L. Age related human T cell subset evolution and senescence. *Immun Ageing* **16**, 24 (2019).
183. Becker, L., Nguyen, L., Gill, J., Kulkarni, S., Pasricha, P. J. & Habtezion, A. Age-dependent shift in macrophage polarisation causes inflammation-mediated degeneration of enteric nervous system. *Gut* **67**, 827–836 (2018).
184. Lumeng, C. N., Liu, J., Geletka, L., Delaney, C., Delproposto, J., Desai, A., Oatmen, K., Martinez-Santibanez, G., Julius, A., Garg, S. & Yung, R. L. Aging Is Associated with an Increase in T Cells and Inflammatory Macrophages in Visceral Adipose Tissue. *The Journal of Immunology* **187**, 6208–6216 (2011).
185. Basisty, N., Kale, A., Jeon, O. H., Kuehnemann, C., Payne, T., Rao, C., Holtz, A., Shah, S., Sharma, V., Ferrucci, L., Campisi, J. & Schilling, B. A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol* **18**, e3000599 (2020).
186. Claesson, M. J., Jeffery, I. B., Conde, S., Power, S. E., O'Connor, E. M., Cusack, S., Harris, H. M. B., Coakley, M., Lakshminarayanan, B., O'Sullivan, O., Fitzgerald, G. F., Deane, J., O'Connor, M., Harnedy, N., O'Connor, K., O'Mahony, D., Van Sinderen, D., Wallace, M., Brennan, L., Stanton, C., Marchesi, J. R., Fitzgerald, A. P., Shanahan, F., Hill, C., Ross, R. P. & O'Toole, P. W. Gut microbiota composition correlates with diet and health in the elderly. *Nature* **488**, 178–184 (2012).
187. Veldhuis, J. D. Aging and hormones of the hypothalamo-pituitary axis: Gonadotropic axis in men and somatotropic axes in men and women. *Ageing Research Reviews* **7**, 189–208 (2008).
188. Gupta, D. & Morley, J. E. Hypothalamic-Pituitary-Adrenal (HPA) Axis and Aging. in *Comprehensive Physiology* (ed. Terjung, R.) 1495–1510 (Wiley, 2014). doi:10.1002/cphy.c130049.
189. Pascot, A., Lemieux, S., Lemieux, I., Prud'homme, D., Tremblay, A., Bouchard, C., Nadeau, A., Couillard, C., Tchernof, A., Bergeron, J. & Després, J. P. Age-related increase in visceral adipose tissue and body fat and the metabolic risk profile of premenopausal women. *Diabetes Care* **22**, 1471–1478 (1999).
190. Kaczorowski, K. J., Shekhar, K., Nkulikiyimfura, D., Dekker, C. L., Maecker, H., Davis, M. M., Chakraborty, A. K. & Brodin, P. Continuous immunotypes describe human immune variation and predict diverse responses. *Proc. Natl. Acad. Sci. U.S.A.* **114**, (2017).
191. Kaplan, H., Thompson, R. C., Trumble, B. C., Wann, L. S., Allam, A. H., Beheim, B., Frohlich, B., Sutherland, M. L., Sutherland, J. D., Stieglitz, J., Rodriguez, D. E., Michalik, D. E., Rowan, C. J., Lombardi, G. P., Bedi, R., Garcia, A. R., Min, J. K., Narula, J., Finch, C. E., Gurven, M. & Thomas, G. S. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *The Lancet* **389**, 1730–1739 (2017).

192. Gurven, M., Blackwell, A. D., Rodríguez, D. E., Stieglitz, J. & Kaplan, H. Does Blood Pressure Inevitably Rise With Age?: Longitudinal Evidence Among Forager-Horticulturalists. *Hypertension* **60**, 25–33 (2012).
193. Rowan, C. J., Eskander, M. A., Seabright, E., Rodriguez, D. E., Linares, E. C., Gutierrez, R. Q., Adrian, J. C., Cummings, D., Beheim, B., Tolstrup, K., Achrekar, A., Kraft, T., Michalik, D. E., Miyamoto, M. I., Allam, A. H., Wann, L. S., Narula, J., Trumble, B. C., Stieglitz, J., Thompson, R. C., Thomas, G. S., Kaplan, H. S. & Gurven, M. D. Very Low Prevalence and Incidence of Atrial Fibrillation among Bolivian Forager-Farmers. *Annals of Global Health* **87**, 18 (2021).
194. Trumble, B. C., Stieglitz, J., Rodriguez, D. E., Linares, E. C., Kaplan, H. S. & Gurven, M. D. Challenging the Inevitability of Prostate Enlargement: Low Levels of Benign Prostatic Hyperplasia Among Tsimane Forager-Horticulturalists. *GERONA* **70**, 1262–1268 (2015).
195. Gatz, M., Mack, W. J., Chui, H. C., Law, E. M., Barisano, G., Sutherland, M. L., Sutherland, J. D., Eid Rodriguez, D., Quispe Gutierrez, R., Copajira Adrian, J., Bani Cuata, J., Borenstein, A. R., Walters, E. E., Irimia, A., Rowan, C. J., Wann, L. S., Allam, A. H., Thompson, R. C., Miyamoto, M. I., Michalik, D. E., Cummings, D. K., Seabright, E., Garcia, A. R., Hooper, P. L., Kraft, T. S., Finch, C. E., Thomas, G. S., Stieglitz, J., Trumble, B. C., Gurven, M. D. & Kaplan, H. Prevalence of dementia and mild cognitive impairment in indigenous Bolivian forager-horticulturalists. *Alzheimer's & Dementia* **19**, 44–55 (2023).
196. Gurven, M., Jaeggi, A. V., Kaplan, H. & Cummings, D. Physical Activity and Modernization among Bolivian Amerindians. *PLoS ONE* **8**, e55679 (2013).
197. Kraft, T. S., Stieglitz, J., Trumble, B. C., Martin, M., Kaplan, H. & Gurven, M. Nutrition transition in 2 lowland Bolivian subsistence populations. *The American Journal of Clinical Nutrition* **108**, 1183–1195 (2018).
198. Blackwell, A. D., Trumble, B. C., Maldonado Suarez, I., Stieglitz, J., Beheim, B., Snodgrass, J. J., Kaplan, H. & Gurven, M. Immune function in Amazonian horticulturalists. *Annals of Human Biology* **43**, 382–396 (2016).
199. Gurven, M., Kaplan, H., Winking, J., Eid Rodriguez, D., Vasunilashorn, S., Kim, J. K., Finch, C. & Crimmins, E. Inflammation and Infection Do Not Promote Arterial Aging and Cardiovascular Disease Risk Factors among Lean Horticulturalists. *PLoS ONE* **4**, e6590 (2009).
200. Gurven, M., Kaplan, H., Winking, J., Finch, C. & Crimmins, E. M. Aging and Inflammation in Two Epidemiological Worlds. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **63**, 196–199 (2008).
201. Horvath, S., Gurven, M., Levine, M. E., Trumble, B. C., Kaplan, H., Allayee, H., Ritz, B. R., Chen, B., Lu, A. T., Rickabaugh, T. M., Jamieson, B. D., Sun, D., Li, S., Chen, W., Quintana-Murci, L., Fagny, M., Kobor, M. S., Tsao, P. S., Reiner, A. P., Edlefsen, K. L., Absher, D. & Assimes, T. L. An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. *Genome Biol* **17**, 171 (2016).
202. Coelho, M. M., Moreira, F. C., Zuccherato, L. W., Ventura, L. H. D. A., Camatta, G. C., Starling-Soares, B., Torres, L., Durso, D. F., Sato, H. I., Da Costa, M. S., Guimarães, H. C., Barbuto, R. C., Júnior, M. L. O., Speziali, E., Tupinambas, U., Teixeira, S. M. R., Silveira-Nunes, G., Teixeira-

Carvalho, A., Maioli, T. U. & Faria, A. M. C. Living in endemic area for infectious diseases is associated to differences in immunosenescence and inflammatory signatures. *Front. Immunol.* **16**, 1547854 (2025).
203. Perry, G. H. Parasites and human evolution. *Evolutionary Anthropology* **23**, 218–228 (2014).
204. Leung, A., Gregory, N. S., Allen, L.-A. H. & Sluka, K. A. Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing interleukin-10 in mice. *Pain* **157**, 70–79 (2016).
205. Blanks, A. M., Wagamon, T. T., Lafratta, L., Sisk, M. G., Senter, M. B., Pedersen, L. N., Bohmke, N., Shah, A., Mihalick, V. L. & Franco, R. L. Impact of physical activity on monocyte subset CCR2 expression and macrophage polarization following moderate intensity exercise. *Brain, Behavior, & Immunity - Health* **2**, 100033 (2020).
206. Liu, B., Hutchison, A. T., Thompson, C. H., Lange, K. & Heilbronn, L. K. Markers of adipose tissue inflammation are transiently elevated during intermittent fasting in women who are overweight or obese. *Obesity Research & Clinical Practice* **13**, 408–415 (2019).
207. Lu, J., Fu, S., Dai, J., Hu, J., Li, S., Ji, H., Wang, Z., Yu, J., Bao, J., Xu, B., Guo, J. & Yang, H. Integrated metabolism and epigenetic modifications in the macrophages of mice in responses to cold stress. *J. Zhejiang Univ. Sci. B* **23**, 461–480 (2022).
208. Yao, Y., Zhao, X., Zheng, S., Wang, S., Liu, H. & Xu, S. Subacute cadmium exposure promotes M1 macrophage polarization through oxidative stress-evoked inflammatory response and induces porcine adrenal fibrosis. *Toxicology* **461**, 152899 (2021).
209. Yang, J., Scicluna, B. P., Van Engelen, T. S. R., Bonta, P. I., Majoor, C. J., Van'T Veer, C., De Vos, A. F., Bel, E. H. & Van Der Poll, T. Transcriptional changes in alveolar macrophages from adults with asthma after allergen challenge. *Allergy* **76**, 2218–2222 (2021).
210. Teppan, J., Schwanzer, J., Rittchen, S., Bärnthaler, T., Lindemann, J., Nayak, B., Reiter, B., Luschnig, P., Farzi, A., Heinemann, A. & Sturm, E. The disrupted molecular circadian clock of monocytes and macrophages in allergic inflammation. *Front. Immunol.* **15**, 1408772 (2024).
211. Palma, A., Jarrah, A. S., Tieri, P., Cesareni, G. & Castiglione, F. Gene Regulatory Network Modeling of Macrophage Differentiation Corroborates the Continuum Hypothesis of Polarization States. *Front. Physiol.* **9**, 1659 (2018).
212. Lavin, Y., Winter, D., Blecher-Gonen, R., David, E., Keren-Shaul, H., Merad, M., Jung, S. & Amit, I. Tissue-Resident Macrophage Enhancer Landscapes Are Shaped by the Local Microenvironment. *Cell* **159**, 1312–1326 (2014).
213. Martinez, F. O. & Gordon, S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep* **6**, (2014).
214. Strizova, Z., Benesova, I., Bartolini, R., Novysedlak, R., Cecrdlova, E., Foley, L. K. & Striz, I. M1/M2 macrophages and their overlaps – myth or reality? *Clinical Science* **137**, 1067–1093 (2023).
215. Mosser, D. M. & Edwards, J. P. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol* **8**, 958–969 (2008).
216. Murray, P. J., Allen, J. E., Biswas, S. K., Fisher, E. A., Gilroy, D. W., Goerdt, S., Gordon, S., Hamilton, J. A., Ivashkiv, L. B., Lawrence, T., Locati, M., Mantovani, A., Martinez, F. O., Mege, J.-

L., Mosser, D. M., Natoli, G., Saeij, J. P., Schultze, J. L., Shirey, K. A., Sica, A., Suttles, J., Udalova, I., van Ginderachter, J. A., Vogel, S. N. & Wynn, T. A. Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity* **41**, 14–20 (2014).

217. Fong, C. H. Y., Bebien, M., Didierlaurent, A., Nebauer, R., Hussell, T., Broide, D., Karin, M. & Lawrence, T. An antiinflammatory role for IKKβ through the inhibition of "classical" macrophage activation. *The Journal of Experimental Medicine* **205**, 1269–1276 (2008).
218. Kawakami, T., Koike, A., Maehara, T., Hayashi, T. & Fujimori, K. Bicarbonate enhances the inflammatory response by activating JAK/STAT signalling in LPS + IFN-γ-stimulated macrophages. *The Journal of Biochemistry* **167**, 623–631 (2020).
219. Ginhoux, F. & Guilliams, M. Tissue-Resident Macrophage Ontogeny and Homeostasis. *Immunity* **44**, 439–449 (2016).
220. Williams, H., Mack, C., Baraz, R., Marimuthu, R., Naralashetty, S., Li, S. & Medbury, H. Monocyte Differentiation and Heterogeneity: Inter-Subset and Interindividual Differences. *IJMS* **24**, 8757 (2023).
221. Jentho, E., Lajqi, T., Yang, K., Winkler, R., Stojiljkovic, M., Wetzker, R. & Bauer, M. Pathogen-Induced Hormetic Responses. in *The Science of Hormesis in Health and Longevity* 161–170 (Elsevier, 2019). doi:10.1016/B978-0-12-814253-0.00014-0.
222. Calabrese, E. J., Giordano, J. J., Kozumbo, W. J., Leak, R. K. & Bhatia, T. N. Hormesis mediates dose-sensitive shifts in macrophage activation patterns. *Pharmacological Research* **137**, 236–249 (2018).
223. Genard, G., Lucas, S. & Michiels, C. Reprogramming of Tumor-Associated Macrophages with Anticancer Therapies: Radiotherapy versus Chemo- and Immunotherapies. *Front. Immunol.* **8**, 828 (2017).
224. Wu, Q., Allouch, A., Martins, I., Modjtahedi, N., Deutsch, E. & Perfettini, J.-L. Macrophage biology plays a central role during ionizing radiation-elicited tumor response. *Biomedical Journal* **40**, 200–211 (2017).
225. Wu, Q., Allouch, A., Paoletti, A., Leteur, C., Mirjolet, C., Martins, I., Voisin, L., Law, F., Dakhli, H., Mintet, E., Thoreau, M., Muradova, Z., Gauthier, M., Caron, O., Milliat, F., Ojcius, D. M., Rosselli, F., Solary, E., Modjtahedi, N., Deutsch, E. & Perfettini, J.-L. NOX2-dependent ATM kinase activation dictates pro-inflammatory macrophage phenotype and improves effectiveness to radiation therapy. *Cell Death Differ* **24**, 1632–1644 (2017).
226. Willenborg, S., Sanin, D. E., Jais, A., Ding, X., Ulas, T., Nüchel, J., Popović, M., MacVicar, T., Langer, T., Schultze, J. L., Gerbaulet, A., Roers, A., Pearce, E. J., Brüning, J. C., Trifunovic, A. & Eming, S. A. Mitochondrial metabolism coordinates stage-specific repair processes in macrophages during wound healing. *Cell Metabolism* **33**, 2398-2414.e9 (2021).
227. Bauer, M., Ermolaeva, M., Singer, M., Wetzker, R. & Soares, M. P. Hormesis as an adaptive response to infection. *Trends in Molecular Medicine* **30**, 633–641 (2024).
228. Ifrim, D. C., Quintin, J., Joosten, L. A. B., Jacobs, C., Jansen, T., Jacobs, L., Gow, N. A. R., Williams, D. L., Van Der Meer, J. W. M. & Netea, M. G. Trained Immunity or Tolerance: Opposing Functional

Programs Induced in Human Monocytes after Engagement of Various Pattern Recognition Receptors. *Clin Vaccine Immunol* **21**, 534–545 (2014).
229. Li, X., Wang, Z., Zou, Y., Lu, E., Duan, J., Yang, H., Wu, Q., Zhao, X., Wang, Y., You, L., He, L., Xi, T. & Yang, Y. Pretreatment with lipopolysaccharide attenuates diethylnitrosamine-caused liver injury in mice via TLR4-dependent induction of Kupffer cell M2 polarization. *Immunol Res* **62**, 137–145 (2015).
230. Antonietta Ajmone-Cat, M., Mancini, M., De Simone, R., Cilli, P. & Minghetti, L. Microglial polarization and plasticity: Evidence from organotypic hippocampal slice cultures: Microglial Polarization and Tolerization. *Glia* **61**, 1698–1711 (2013).
231. Rattan, S. I. S. Hormesis in aging. *Ageing Research Reviews* **7**, 63–78 (2008).
232. Franceschi, C., Garagnani, P., Parini, P., Giuliani, C. & Santoro, A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14**, 576–590 (2018).
233. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
234. Mahbub, S., Deburghgraeve, C. R. & Kovacs, E. J. Advanced Age Impairs Macrophage Polarization. *Journal of Interferon & Cytokine Research* **32**, 18–26 (2012).
235. Gibon, E., Loi, F., Córdova, L. A., Pajarinen, J., Lin, T., Lu, L., Nabeshima, A., Yao, Z. & Goodman, S. B. Aging Affects Bone Marrow Macrophage Polarization: Relevance to Bone Healing. *Regen. Eng. Transl. Med.* **2**, 98–104 (2016).
236. Franck, M., De Toro-Martín, J. & Vohl, M.-C. Eco-Evolutionary Dynamics of the Human-Gut Microbiota Symbiosis in a Changing Nutritional Environment. *Evol Biol* **49**, 255–264 (2022).
237. Kerner, G., Neehus, A.-L., Philippot, Q., Bohlen, J., Rinchai, D., Kerrouche, N., Puel, A., Zhang, S.-Y., Boisson-Dupuis, S., Abel, L., Casanova, J.-L., Patin, E., Laval, G. & Quintana-Murci, L. Genetic adaptation to pathogens and increased risk of inflammatory disorders in post-Neolithic Europe. *Cell Genomics* **3**, 100248 (2023).
238. Wells, J. C. K. & Stock, J. T. Life History Transitions at the Origins of Agriculture: A Model for Understanding How Niche Construction Impacts Human Growth, Demography and Health. *Front. Endocrinol.* **11**, 325 (2020).
239. Deschamps, M., Laval, G., Fagny, M., Itan, Y., Abel, L., Casanova, J.-L., Patin, E. & Quintana-Murci, L. Genomic Signatures of Selective Pressures and Introgression from Archaic Hominins at Human Innate Immunity Genes. *The American Journal of Human Genetics* **98**, 5–21 (2016).
240. Tateno, Y., Komiyama, T., Katoh, T., Munkhbat, B., Oka, A., Haida, Y., Kobayashi, H., Tamiya, G. & Inoko, H. Divergence of East Asians and Europeans Estimated Using Male- and Female-Specific Genetic Markers. *Genome Biology and Evolution* **6**, 466–473 (2014).
241. Moreno-Mayar, J. V., Potter, B. A., Vinner, L., Steinrücken, M., Rasmussen, S., Terhorst, J., Kamm, J. A., Albrechtsen, A., Malaspinas, A.-S., Sikora, M., Reuther, J. D., Irish, J. D., Malhi, R. S., Orlando, L., Song, Y. S., Nielsen, R., Meltzer, D. J. & Willerslev, E. Terminal Pleistocene Alaskan genome reveals first founding population of Native Americans. *Nature* **553**, 203–207 (2018).
242. Deng, L., Hoh, B. P., Lu, D., Fu, R., Phipps, M. E., Li, S., Nur-Shafawati, A. R., Hatin, W. I., Ismail, E., Mokhtar, S. S., Jin, L., Zilfalil, B. A., Marshall, C. R., Scherer, S. W., Al-Mulla, F. & Xu, S. The

population genomic landscape of human genetic structure, admixture history and local adaptation in Peninsular Malaysia. *Hum Genet* **133**, 1169–1185 (2014).
243. Domínguez-Andrés, J., Kuijpers, Y., Bakker, O. B., Jaeger, M., Xu, C.-J., Van Der Meer, J. W., Jakobsson, M., Bertranpetit, J., Joosten, L. A., Li, Y. & Netea, M. G. Evolution of cytokine production capacity in ancient and modern European populations. *eLife* **10**, e64971 (2021).
244. Klimentidis, Y. C., Beasley, T. M., Lin, H.-Y., Murati, G., Glass, G. E., Guyton, M., Newton, W., Jorgensen, M., Heymsfield, S. B., Kemnitz, J., Fairbanks, L. & Allison, D. B. Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics. *Proc. R. Soc. B.* **278**, 1626–1632 (2011).
245. Aiello, L. C. & Wheeler, P. The Expensive-Tissue Hypothesis: The Brain and the Digestive System in Human and Primate Evolution. *Current Anthropology* **36**, 199–221 (1995).
246. Kristensen, T. N., Ketola, T. & Kronholm, I. Adaptation to environmental stress at different timescales. *Annals of the New York Academy of Sciences* **1476**, 5–22 (2020).
247. Egecioglu, E., Anesten, F., Schéle, E. & Palsdottir, V. Interleukin-6 is important for regulation of core body temperature during long-term cold exposure in mice. *biom rep* (2018) doi:10.3892/br.2018.1118.
248. Zhao, L., Melenhorst, J. J. & Hennighausen, L. Loss of Interleukin 6 Results in Delayed Mammary Gland Involution: A Possible Role for Mitogen-Activated Protein Kinase and Not Signal Transducer and Activator of Transcription 3. *Molecular Endocrinology* **16**, 2902–2912 (2002).
249. Zhou, X., Franklin, R. A., Adler, M., Carter, T. S., Condiff, E., Adams, T. S., Pope, S. D., Philip, N. H., Meizlish, M. L., Kaminski, N. & Medzhitov, R. Microenvironmental sensing by fibroblasts controls macrophage population size. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2205360119 (2022).
250. Foy, B. H., Petherbridge, R., Roth, M. T., Zhang, C., De Souza, D. C., Mow, C., Patel, H. R., Patel, C. H., Ho, S. N., Lam, E., Powe, C. E., Hasserjian, R. P., Karczewski, K. J., Tozzo, V. & Higgins, J. M. Haematological setpoints are a stable and patient-specific deep phenotype. *Nature* **637**, 430–438 (2025).
251. Mirantes, C., Passegué, E. & Pietras, E. M. Pro-inflammatory cytokines: Emerging players regulating HSC function in normal and diseased hematopoiesis. *Experimental Cell Research* **329**, 248–254 (2014).
252. Franceschi, C., Olivieri, F., Moskalev, A., Ivanchenko, M. & Santoro, A. Toward precision interventions and metrics of inflammaging. *Nature Aging* **5**, 1441–1454 (2025).
253. Barabási, A.-L., Menichetti, G. & Loscalzo, J. The unmapped chemical complexity of our diet. *Nat Food* **1**, 33–37 (2019).

Declaration of Interest Statement

AAC is the founder and CEO of Oken Health. The other authors declare no competing interests.

Highlights

- Inflamm-aging is universal in principle but highly variable in practice
- Inflamm-aging is a reaction norm shaped by genotype and exposome
- Defining cross-species measurands is challenging due to biological divergence
- Inflamm-aging as commonly defined in humans reflects a mismatch with modern lifestyles