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Chronic Inflammation in the Etiology of Disease Across the Lifespan

David Furman[1,2], Pedro Carrera-Bastos[3], Judith Campisi[4,5], Eric Verdin[4], Claudio Franceschi[6], Luigi Ferrucci[7], Derek W. Gilroy[8], Alessio Fasano[9], Gary W. Miller[10], Andrew H. Miller[11], Alberto Mantovani[12,13,14], Cornelia M. Weyand[15], Nir Barzilai[16], Jorg J. Goronzy[15], Thomas A. Rando[17,18,19], Rita B. Effros[20], Alejandro Lucia[21, 22], Nicole Kleinstreuer[23, 24], George M. Slavich[25]

[1]*Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, 279 Campus Drive, Stanford, California, 94306, USA*

[2]*Institute for Research in Translational Medicine (IIMT), Universidad Austral, CONICET, Pilar, Buenos Aires, B1630FHB, Argentina*

[3]*Center for Primary Health Care Research, Lund University/Region Skåne, Skåne University Hospital, Malmö, Sweden*

[4]*Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94945, USA*

[5]*Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720 USA*

[6]*IRCCS Institute of Neurological Sciences of Bologna, 40139 Bologna, Italy and Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia*

[7]*Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD, USA*

[8]*Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, United Kingdom*

[9]*MassGeneral Hospital for Children-Harvard Medical School, Boston, MA 02114-4404, USA*

[10]*Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY 10032, USA*

[11]*Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA*

[12] *Humanitas Clinical and Research Center, via Manzoni 56, 20089 Rozzano, Milano, Italy*

[13]*Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 20090 Pieve Emanuele, Milano, Italy*

[14]*William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University, London, UK*

[15]*Division of Immunology and Rheumatology, Department of Medicine, Stanford University, Stanford, CA 94305, USA*

[16]*Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, NY, USA*

[17]*Paul F. Glenn Center for the Biology of Aging, Stanford University School of Medicine, Stanford, CA 94305, USA*

[18]*Center for Tissue Regeneration, Repair and Restoration, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 90304, USA*

[19]*Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305 USA*

[20]*Department of Pathology, University of California Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA*

[21]*Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain.*

[22]*Research Institute of the Hospital 12 de Octubre (i+12), Madrid, Spain.*

[23]*Biostatistics and Computational Biology Branch, Division of Intramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA*

[24]*NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA*

[25]*Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA 90095, USA*

Correspondence to: David Furman, PhD, 279 Campus Drive, Beckman Center, B219, Stanford, CA, 94305, USA. E-mail: furmand@stanford.edu

Abstract

Although intermittent increases in inflammation are critical for survival during physical injury and infection, recent research has revealed that certain social and environmental factors can promote systemic chronic inflammation (SCI) that can lead to several costly diseases that collectively represent the leading causes of death worldwide. Indeed, more than 50% of all deaths are currently attributable to SCI-related diseases like cardiovascular diseases, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease, autoimmune and neurodegenerative conditions. In the present review, we discuss multi-level mechanisms underlying SCI and several factors that have been found to promote this health-damaging phenotype, including poor diet, physical inactivity, stress, and environmental and industrial toxicants. Although seemingly grim, the upside is that risk for SCI-related disorders can be substantially reduced by targeting factors that promote inflammation. Developing new methods for the early diagnosis, prevention, and treatment of SCI may thus not only extend life, but also reduce worldwide chronic disease burden and enhance human health.

Introduction

One of the most important medical discoveries over the past two decades has involved the realization that the body's immune system in general, and inflammatory processes in particular, are involved in not just a few select disorders but a wide variety of mental and physical health problems that dominate present-day morbidity and mortality [1-3]. Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today, with more than 50% of every deaths worldwide being attributable to inflammation-related diseases, like ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD), autoimmune and neurodegenerative conditions [4]. Risk for developing chronic inflammation can be traced back to early in life – even before birth – and its effects are now known to persist throughout the lifespan to affect adulthood health and risk of mortality [5-7]. In the present review, we summarize the substantial body of research describing these effects and outline some promising avenues for future research.

Inflammation

Inflammation is an evolutionarily conserved process characterized by the activation of immune and non-immune cells that help to keep the body biologically safe from bacteria, viruses, toxins, and infections by eliminating pathogens and promoting tissue repair and recovery [2, 8]. Depending on the degree and extent of the inflammatory response, including whether it is systemic versus local, metabolic and neuroendocrine changes can occur to conserve metabolic energy and allocate more nutrients to the activated immune system [8-11]. Specific biobehavioral effects of inflammation can thus include a constellation of energy-saving behaviors commonly known as *sickness*

behaviors, such as sadness, anhedonia, fatigue, reduced libido and food intake, altered sleep, and social-behavioral withdrawal, as well as increased blood pressure, insulin resistance and dyslipidemia [9, 12].

These biobehavioral changes can be critical for survival during times of physical or microbial threat. A normal inflammatory response is thus characterized by the time-limited upregulation of inflammatory activity that occurs when a threat is present and that resolves once the threat has passed [8, 12, 13]. As we describe below, however, the presence of certain social, psychological, environmental, and biological factors can prevent acute inflammation from resolving and, in turn, promote a state of low-grade, non-infective (i.e., "sterile") systemic chronic inflammation (SCI) that is characterized by the activation of specific immune components that are often distinct from those detected during an acute immune response [12, 14].

Shifts in the temporal nature of the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance [8, 13] and lead to major alterations in all tissues and organs, and multiple changes in normal cellular physiology, which can increase risk for various non-communicable diseases in both young and older individuals [9, 10, 15-20]. SCI can also impair normal immune function, leading to increased susceptibility to infections and tumors, and poor responses to vaccines [21-24]. Furthermore, SCI during pregnancy and childhood has developmental consequences that result in a higher rate of non-communicable diseases later in life [6, 7, 25, 26].

Systemic Chronic Inflammation and Non-Communicable Disease Risk

Although sharing some common mechanisms, the acute inflammatory response differs from SCI. As shown in Table 1, the acute inflammatory response is typically initiated during times of infection via an interaction between pattern recognition receptors (PRRs) expressed in innate immune cells and evolutionarily conserved structures on pathogens, called *pathogen-associated molecular patterns* (PAMPs) [2]. When engaged, PRRs trigger biochemical signaling cascades that result in the expression of multiple pro-inflammatory proteins, including cytokines, chemokines, and growth factors. These proteins orchestrate the host response to infection, which is characterized by a sharp increase in canonical inflammatory mediators including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α that regulate both innate and adaptive immune dynamics to help degrade inflammatory triggers (e.g., bacteria, viruses) and initiate tissue repair mechanisms, healing, and recovery [2, 8].

In contrast with the acute inflammatory response, SCI is typically triggered by physical, chemical, or metabolic noxious stimuli (i.e., "sterile" agents), such as those released by damaged cells or environmental insults that are generally called *damage-associated molecular patterns* (DAMPs) [27-29]. SCI often increases with age [27], as evidenced by a large literature showing that older individuals have higher circulating levels of cytokines, chemokines, acute phase proteins, as well as greater expression of genes involved in inflammation [16, 18, 27]. SCI is low-grade and persistent – as the name suggests – and ultimately leads to collateral damage to tissues and organs [3, 8, 16, 18].

The clinical consequences of SCI-driven damage are depicted in Figure 1. These consequences can be severe and include increased risk of the metabolic syndrome [30, 31], type 2 diabetes [30], NAFLD [30, 32], hypertension [16], cardiovascular disease (CVD) [17, 18], chronic kidney disease [18], various types of cancer [15], depression [20], neurodegenerative

and autoimmune diseases [3, 11, 19], osteoporosis [10, 33], and sarcopenia [18]. Empirical evidence that inflammation plays a causal role in disease onset or progression is strongest for metabolic syndrome, type 2 diabetes, and CVD. Indeed, it has long been known that patients with autoimmune diseases characterized by systemic inflammation exhibit insulin resistance, dyslipidemia and hypertension, and have higher rates of metabolic syndrome, type 2 diabetes, and CVD (particularly ischemic heart disease and stroke) [9, 11, 34-36]. Moreover, the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP), is a predictor of cardiovascular events in men and women [37]. In a recent meta-analysis of more than 160,000 people and 28,000 incident cardiovascular events, every one standard deviation increase in log-normalized levels of hsCRP was associated with a relative increase in risk of 1.37 for coronary heart disease and 1.55 for CVD mortality, while adjusting for covariates [38].

The most compelling evidence for an association between SCI and disease risk comes from randomized controlled trials (RCT) that have tested drugs, or *biologics*, which target specific pro-inflammatory cytokines (e.g., IL-1β, TNF-α). In a recent meta-analysis of eight RCT and 260 participants, TNF-α inhibitor administration was found to significantly reduce insulin resistance in patients with rheumatoid arthritis (RA) [standard differences in means (SDM) for scores on the Homeostatic Model Assessment for Insulin resistance = -0.148] and to improve insulin sensitivity (SDM for the Quantitative Insulin Sensitivity Check Index = 0.312) [39] . In addition, a recent double-blind RCT of the IL-1β inhibitor canakinumab that assessed more than 10,000 adults with a history of myocardial infarction and hsCR level $\geq$2 mg/L showed that the hazard ratio (HR) for patients treated with 150 mg of canakinumab subcutaneously every three months (*vs* placebo) was 0.85 for nonfatal myocardial infarction (MI), nonfatal stroke, or CVD death, despite no change in LDL cholesterol over the 48-month

study period. Canakinumab-treated patients also exhibited a significantly lower likelihood of unstable angina leading to urgent revascularization (HR for treatment *vs* placebo = 0.83) [40].

A recent large-scale cohort study obtained incidental blood samples from more than 160,000 people over eight years. Consistent with a strong role for SCI in structuring mortality risk, a combination of the inflammatory markers hsCRP (> 3 mg/L), albumin, and neutrophil count predicted all-cause mortality over the eight-year time period (HR 7.37), in addition to cancer (HR 9.32), cardiovascular (HR 4.03), and cerebrovascular (HR 3.10) mortality [41]. There is thus substantial evidence that SCI is strongly related to inflammation-related disease risk and mortality.

Biomarkers for Systemic Chronic Inflammation

Despite evidence linking SCI with disease risk and mortality [41], there are presently no standard biomarkers for indicating the presence of health-damaging chronic inflammation. In lieu of having general biomarkers for SCI, studies have shown that canonical biomarkers of acute inflammation may be used to detect age-related SCI and predict morbidity and mortality in both cross-sectional and longitudinal studies [42]. However, other research has found that some of these biomarkers – specifically IL-6, IL-1β, TNF-α, and hsCRP – are associated with aging among individuals with pathological conditions but are not related to aging more broadly. Seminal work by Roubenoff and colleagues (1998) [43] showed that in monocytes from ambulatory individuals, levels of IL-6 and IL-1ra (but not IL-1β or TNF-α) increased with age. However, no difference in IL-1 and IL-6 expression has been found between young and older individuals when the health status of older individuals is strictly controlled [44, 45].

In line with the aforementioned findings, a recent study that examined endogenous and *ex vivo* stimulated levels of 18 inflammatory markers obtained from adults across the lifespan (i.e., 20 to 77 years). Results revealed that unstimulated levels of IL-12p70 (in females only) and CRP (particularly in men) – but not IL-1β, interferon (IFN)-α, or TNF-α – were associated with older age [46]. Therefore, evidence exists that greater inflammatory activity is associated with older age, but these effects are not present for all inflammatory markers and it is possible that these associations are due, at least in part, to increases in chronic ailments and frailty that are frequently associated with age rather than to biological aging itself.

To address limitations associated with assessing only a few select inflammatory biomarkers, some researchers have employed a multi-dimensional approach that involves assaying large numbers of inflammatory markers and then combining them into more robust latent factors representing heightened inflammatory activity. In one recent study that utilized this approach, principal component analysis identified a latent construct of inflammatory activation (i.e., both pro- and anti-inflammatory markers), as well as innate immune response that significantly predicted risk for multiple chronic diseases (i.e., CVD, kidney disease, and diabetes) as well as mortality (HR/PCA unit: 1.33 and 0.87 for inflammatory activation and innate immune response, respectively) [47].

More recently, Shen-Orr and colleagues took one step further and applied a multiomics approach to examining links between SCI and disease risk. They followed 135 adults longitudinally and conducted deep molecular profiling of patients' gene expression (transcriptome), immune proteins (immunome), and cell subsets frequencies. In turn, they observed high inter-individual variability in the rates of change over time that was dictated by patients' baseline values. This allowed construction of a

high-dimensional trajectory of immune aging (IMM-AGE) that described a person's immune status better than chronological age. This new metric accurately predicted all-cause mortality, establishing its potential use in clinics for identification of patients at risk [48].

So far, these integrative, multi-level approaches appear to be promising, but more work is needed to identify best practices for selecting and analyzing SCI-related biomarkers in order to yield the most useful and predictive information for predicting age-related disease risk.

Sources of Systemic Chronic Inflammation

The SCI state in older individuals is thought to be caused in part by a complex process called *cellular senescence*, which is characterized by an arrest of cell proliferation and the development of a multifaceted senescence-associated secretory phenotype (SASP) [49]. A prominent feature of the SASP is increased secretion of pro-inflammatory cytokines, chemokines, and other pro-inflammatory molecules [49]. Senescent cells expressing a SASP can in turn promote a multitude of chronic health conditions and diseases, including insulin resistance, CVD, pulmonary arterial hypertension, chronic obstructive pulmonary disorder, emphysema, Alzheimer's and Parkinson's disease, macular degeneration, osteoarthritis, and cancer [50, 51].

How senescent cells acquire the SASP is not fully understood, but existing research points to a combination of both endogenous and environmental risk factors. Among the known endogenous causes of this phenotype are DNA damage, dysfunctional telomeres, epigenomic disruption, mitogenic signals, and oxidative stress

[52]. As we discuss in greater detail below, the known non-endogenous contributors include chronic infections, physical inactivity, lifestyle-induced microbiome dysbiosis, diet, social and cultural changes, and environmental and industrial toxicants. The fact that differences exist in the extent to which older adults exhibit SCI [48, 53] is thought to be indicative of inter-individual differences in exposure to these and other related pro-inflammatory factors.

Differences in non-communicable diseases associated with SCI are also clearly evident across cultures and countries. Most prominently, SCI-link diseases have reached epidemic proportions in most industrialized countries, even among younger individuals, but are relatively rare in non-westernized populations that adhere to diets, lifestyles, and ecological niches that more closely resemble those present during most of human evolution [54-60]. Furthermore, as we discuss in greater detail below, certain individual dietary and lifestyle habits, as well as exposure to a variety of different pollutants, can increase oxidative stress, upregulate mitogenic signaling pathways, and cause genomic and epigenomic perturbations [7, 55, 61] that can induce the SASP. Consistent with these differential effects across cultures and people, Brodin et al. argued that non-heritable factors are the strongest contributors to differences in chronic inflammation across individuals [62] and that exposure to non-endogenous environmental factors, which have been collectively called the *exposome*, are the main drivers of SCI. Simply put, the exposome refers to a person's lifelong exposure to physical, chemical, and biological elements, starting from the prenatal period onward [63]. As we discuss below, these exposures span multiple domains and include viral and bacterial infections, chronic psychological stressors, hypercaloric diets high in ultra-processed foods, excessive artificial blue light at night, tobacco smoke, air pollutants, and other environmental and industrial toxicants.

Chronic Infections

The effect of lifelong infections caused by cytomegalovirus, Epstein-Barr virus, hepatitis-C virus, and other microbes in SCI and immune dysregulation remains controversial [64-67]. In terms of aging, chronic infection with cytomegalovirus has been associated with the so-called *Immune Risk Phenotype* that has been predictive of early mortality in several longitudinal studies [68]. Interestingly, chronic infection with HIV causes premature aging of the immune system and is also associated with early cardiovascular and skeletal changes [69]. Many of these effects can be attributed to the accumulation of senescent CD8+ T cells, which produce increased levels of pro-inflammatory mediators [70].

Although several studies have reported associations between chronic infections and autoimmune diseases, certain cancers, neurodegenerative diseases, CVD, and chronic infections appear to interact synergistically with environmental and genetic factors to influence these health outcomes [65, 66, 71]. Indeed, humans coevolved with a variety of viruses, bacteria, and other microbes over the course of evolution [72], and while chronic infections appear to contribute to SCI, they are not likely the primary driver. For instance, populations of hunter-gatherers and other existing traditional societies such as the Shuar hunter-gatherers of the Ecuadorian Amazon [73, 74], Tsimane forager-horticulturalists of Bolivia [57], Hadza hunter-gatherers from Tanzania [56], subsistence-agriculturalists from Rural Ghana [75], traditional horticulturalists of Kitava (Papua New Guinea) [76] – all of whom are minimally exposed to modern environments but highly exposed to a variety of microbes – exhibit very low rates of inflammation-related chronic disease and substantial fluctuations in inflammatory markers that do not increase with age [54, 56, 57, 73, 76].

Social and Physical Environment

The distinct lack SCI-related health problems in these populations has not been attributed to genetics or a low-life expectancy, but rather to the lifestyles they lived in the social and physical environments of the time [55]. These lifestyles were characterized by high levels of physical activity [56, 60, 77], diets composed mainly of fresh or minimally processed food sources [55, 78, 79], and low exposure to environmental pollutants [55]. In addition, individuals living in these environments had circadian rhythms that were in synch with diurnal fluctuations in sunlight exposure [80] and they were also more commonly exposed to acute, intermittent stressors (e.g., being physically attacked) as opposed to the types of longer-term chronic stressors that typify modern-day social environments (e.g., chronic work or financial problems) [55].

These social and environmental characteristics are believed to have predominated during most of hominin evolutionary history until the emergence of the industrial revolution, which marked the advent of the modern era [55]. The modern era conferred many benefits, including social stability, reduced physical trauma, and improved public health measures (e.g., sanitation, quarantine policies, vaccination) and access to modern medical technology, all of which significantly decreased infant mortality rates and increased average life expectancy [55]. However, this modernization also caused radical changes in diet and lifestyle characterized by physical inactivity [81], the adoption of westernized diets [55], aberrant circadian rhythms and sleep-wake cycles [82], chronic psychological stress [55], and increased exposure to man-made chemical pollutants [7, 55]. This contemporary environment was ultimately very different from the ones that shaped human physiology for most of human evolution, thus creating an *evolutionary mismatch* marked by an increasing separation from our ecological niche. This mismatch, in turn, is hypothesized to be a major cause of SCI [54, 55, 72, 79, 83]. Below, we discuss several of these factors in greater detail – specifically, physical (in)activity,

lifestyle-induced microbiome dysbiosis, diet, social and cultural changes, and environmental and industrial toxicants.

Physical Activity

The modern lifestyle is associated with a significant decrease in physical activity, especially in most industrialized countries, although the pandemic of inactivity is also reaching low- and middle-income countries [81]. Worldwide, one-third of adults are considered *physically inactive* [81], meaning that they do not meet the minimum international recommendations for regular physical activity (i.e., ≥150 min of moderate-intensity aerobic activity per week such as walking or brisk walking). In the United States, these numbers are even higher, with approximately 50% of adults being considered physically inactive [84].

The skeletal muscle is an endocrine organ that produces and releases cytokines and other small proteins, called *myokines*, into the bloodstream. This occurs particularly during muscle contraction and can have the effect of systemically reducing inflammation [85]. Low physical activity, therefore, has been found to be directly related to increased anabolic resistance [86] and levels of CRP and pro-inflammatory cytokine levels in healthy individuals [87], as well as in breast cancer survivors [88], and patients with type 2 diabetes [89]. These effects can in turn promote several inflammation-related pathophysiologic derangements, including insulin resistance, dyslipidemia, endothelial dysfunction, high blood pressure, and loss of muscle mass [90] that have been found to increase risk for a variety of conditions, including CVD, type II diabetes, NAFLD, sarcopenia, osteoporosis, various types of cancer, depression, dementia, and Alzheimer's disease in individuals who are chronically physically inactive [85, 90].

Consistent with these effects, there is strong evidence for an association between physical inactivity and increased risk for age-related diseases and mortality. A recent meta-analysis of studies with cohorts from Europe, the United States, and the rest of the world that included 1,683,693 participants found that going from physically inactive to achieving the recommended 150 minutes of moderate-intensity aerobic activity per week was associated with lower risk of CVD mortality by 23%, CVD incidence by 17%, and type 2 diabetes incidence by 26% during an average follow-up period of 12.8 years [91]. Moreover, data from 1.44 million participants across several prospective cohort studies revealed that as compared to individuals exhibiting high levels of leisure-time physical activity (i.e., $\geq 90^{th}$ percentile), those who were physically inactive (i.e., $\leq$10th percentile) had a greater risk (>20%) for several cancers (esophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrium, and myeloid leukemia) even after adjusting for several risk factors including adiposity and smoking status (except for lung cancer) [92]. Likewise, a meta-analysis of ten studies and 23,345 older adults (70 to 80 years) who were followed for 3.9–31 years found that individuals meeting the minimum international physical activity recommendations had a 40% lower risk of Alzheimer's disease as compared to their physically inactive counterparts [93].

Finally, physical inactivity can increase individuals' risk for various non-communicable diseases because it promotes obesity [90] and, in particular, excessive visceral adipose tissue (VAT), which is a significant trigger of inflammation [94, 95]. VAT is an active endocrine, immunological, and metabolic organ composed of various cells (including immune cells, such as resident macrophages) that expands mostly through adipocyte hypertrophy, which can lead to areas of hypoxia and even cell death, resulting in activation of hypoxia-inducible factor-1α (HIF-1α), increased production of reactive oxygen species, and release of DAMPs (e.g., cell-free DNA). These events can induce

the secretion of numerous pro-inflammatory molecules, including adipokines, cytokines (e.g., IL-1β, IL-6, TNF-α), and chemokines (especially monocyte chemoattractant protein-1) by adipocytes, endothelial cells, and resident adipose tissue immune cells (e.g., macrophages) [31, 95-97]. This, in turn, will lead to the infiltration of various immune cells in the VAT, including monocytes, neutrophils, dendritic cells, B, T and natural killer lymphocytes, and a reduction in T regulatory (Treg) cells, thereby amplifying inflammation, which can eventually become systemic [98].

Furthermore, TNF-α and other molecules can cause adipocyte insulin resistance, which increases lipolysis with the resulting spillover of lipids into other organs, such as the pancreas and liver where they can contribute to beta-cell dysfunction, hepatic insulin resistance, and fatty liver [99]. Hence, visceral obesity accelerates aging and increases the risk for cardiometabolic, neurodegenerative and autoimmune diseases, as well as several types of cancer [18, 95, 100-102]. These dynamics are known to occur in adults to promote age-related disease risk, but they first emerge during childhood [25]. The childhood obesity epidemic might thus be playing a critical role in promoting inflammation and age-related disease risk worldwide [103].

Lifestyle-Induced Microbiome Dysbiosis

Obesity may also lead to SCI through gut-mediated mechanisms [104]. For example, studies conducted in moderately obese non-diabetic Danish individuals [105] and in severely obese French women [106] have observed changes in gut microbiota composition and low microbial gene richness (dysbiosis), which were correlated with increased fat mass, pro-inflammatory biomarkers, and insulin resistance. Obesity has also been associated with increased intestinal paracellular permeability and endotoxemia [107], with the latter being a suspected cause of inflammation (e.g., via activation of PRRs,

388 such as Toll-like receptors, in immune cells) and inflammation-mediated metabolic
389 conditions such as insulin resistance [108]. Interestingly, serum concentrations of zonulin,
390 a protein that increases intestinal permeability, have been found to be elevated in obese
391 children and adults [107, 109], and in persons with type II diabetes [108], NAFLD, coronary
392 heart disease, polycystic ovary syndrome, autoimmune diseases, and cancer [107]. More
393 recently, elevated serum zonulin concentrations have been found to predict
394 inflammation and physical frailty [110]. Furthermore, in older adults, the changes observed
395 in the gut microbiota seem to dictate the outcome of multiple inflammatory pathways
396 [111].

397 Therefore, a complex balance exists in the intestinal ecosystem that, if disrupted,
398 can compromise its function and integrity and, in turn, cause low-grade SCI [111]. It is
399 thus imperative to identify the triggers of dysbiosis and intestinal hyperpermeability.
400 Among these triggers are the overuse of certain drugs (e.g., antibiotics, nonsteroidal
401 anti-inflammatory drugs, and proton-pump inhibitors) [112, 113]; the lack of microbial
402 exposure induced by excessive hygiene and reduced contact with animals and natural
403 soils, which is a very recent phenomenon in human evolutionary history [72]; and the
404 reduced intake of soluble fiber and other non-digestible carbohydrates in current diets,
405 which causes a deficiency in the diversity of the gut microbiome (see below).

406 ***Diet***

407 The typical western-type diet that has become widely adopted in many countries
408 over the past 40 years is low in fruits, vegetables, and other fiber-rich foods [55, 114, 115],
409 and high in refined grains [114], alcohol [116] and ultra-processed foods, particularly those
410 containing emulsifiers [115]. All of these dietary factors may alter the gut microbiota
411 composition and function [94, 117, 118] and lead to increased intestinal permeability [117, 119]

and epigenetic changes in the immune system [117] that ultimately cause low-grade endotoxemia and SCI [117-119]. The influence of diet on inflammation is not confined to these effects, though. For example, orally absorbed advanced glycation and lipoxidation end-products that are formed during the processing of foods or when foods are cooked at high temperatures and in low humidity conditions upregulate the expression of genes that code for pro-inflammatory proteins [120]. Some of these genes can also be activated by increased oxidative stress caused with the intake of high glycemic-load foods, such as isolated sugars and refined grains [121], which are common ingredients in most ultra-processed foods.

Western diets also frequently contain high levels of trans fatty acids, another suspected trigger of inflammation [122], and excessive salt, shown to skew macrophages toward an M1 pro-inflammatory phenotype to increase the differentiation of naïve $CD4^+$ T cells into T helper (Th)17 cells, which are highly inflammatory, and to decrease the expression and anti-inflammatory activity of Treg cells [123]. In addition, high salt intake can cause adverse changes in gut microbiota composition, as exemplified by the reduced *Lactobacillus* population observed in animal models and humans fed high salt diets [123]. This specific population is critical for health as it keeps Th17 cells in balance and contributes to the integrity of the intestinal epithelial barrier, thus reducing systemic inflammation [123]. Consistent with the expected health-damaging effects of consuming these foods, a recent cohort study of 44,551 French adults who were followed for a median of 7.1 years found that a 10% increase in the proportion of ultraprocessed food consumption was associated with a 14% greater risk of all-cause mortality [124].

Several other nutritional factors can also impact inflammation and lead to SCI. These factors include deficiencies in zinc [125] and magnesium [126] that are caused by

436 inadequate food choices (e.g., eating processed or refined foods, which are low in
437 vitamins and minerals) and suboptimal omega-3 levels [127], which play a critical role in
438 the resolution phase of inflammation. For example, long-chain omega-3 fatty acids –
439 especially eicosapentaenoic acid and docosahexaenoic acid – modulate the expression
440 of genes involved in metabolism and inflammation [127]. More important, they are
441 precursors to molecules such as resolvins, maresins and protectins that are involved in
442 the resolution of inflammation [128]. A low intake of fish or high intake of vegetable oils
443 that are high in linoleic acid (which displaces omega-3 fatty acids in cell membrane
444 phospholipids) are the main contributors to the growing worldwide incidence of low
445 omega-3 status [129, 130]. In fact, a meta-analysis of nationally representative health
446 surveys and disease-specific mortality statistics from the National Center for Health
447 Statistics in the United States showed that the dietary risk factors associated with the
448 greatest mortality among American adults in 2005 were high dietary trans fatty acids
449 (estimated deaths: 82,000; 95% confidence interval [CI]: 63,000, 97,000), low dietary
450 omega-3 fatty acids (estimated deaths: 84,000; 95% CI: 72,000, 96,000), and high
451 dietary salt (estimated deaths: 102,000; 95% CI: 97,000, 107,000) [131]. Of interest, a
452 recent systematic analysis of dietary data across 195 countries revealed suboptimal diets
453 as the main risk factor for death in 2017, with excessive sodium intake being
454 responsible for more than half of diet-related deaths (estimated deaths: 3 million; 95%
455 CI: 1, 5) [132].

456 Finally, when combined with low physical activity, the adoption of a
457 hypercaloric diet (due to increased consumption of hyperpalatable processed foods that
458 are high in fat, sugar, salt, and flavor additives [133]) can cause major changes in cell
459 metabolism and lead to the increased production (and defective disposal) of,
460 dysfunctional organelles such as mitochondria, as well as misplaced, misfolded, and

461 oxidized self-molecules [27, 61, 134]. These molecules, which also increase with age [18], can
462 be recognized as DAMPs by innate immune cells through PRRs and in turn activate the
463 inflammasome machinery, amplify the inflammatory response [16, 27, 61], and contribute to
464 *inflammaging*, or "the long-term result of the chronic physiological stimulation of the
465 innate immune system" that degrades health and promotes age-related diseases [18].

466

467 ***Social and Cultural Changes***

468 In addition to physical inactivity and western-type diet, the industrial revolution
469 and modern era ushered in other inflammation-promoting changes, including increased
470 social isolation, digitally mediated social interactions that can promote social threat, and
471 disrupted sleep. These factors in turn promote SCI [135, 136], insulin resistance [137], and high
472 risk for obesity, type 2 diabetes, CVD and all-cause mortality [136-140]. Moreover,
473 stressors that are persistently present in contemporary work environments, such as high
474 job demand and low control, can cause physiologic changes [141] that disrupt the ability
475 for glucocorticoids to effectively down-regulate inflammatory activity, leading to SCI
476 [142].

477 Another core feature of modern society that has occurred very recently in human
478 evolutionary history is increased exposure to artificial light, especially the blue
479 spectrum, at atypical biologic times [82, 143]. Exposure to blue light, especially after
480 sundown, increases arousal and alertness and thus causes circadian rhythm disruption
481 [143], which in turn promotes inflammation and risk for multiple inflammation-related
482 diseases [82, 144]. As an example, night-shift work has been found to increase risk for the
483 metabolic syndrome and is suspected of being a causal factor in obesity, type II

diabetes, and CVD, as well as in breast, ovarian, prostate, colorectal, and pancreatic cancer [82].

Environmental and Industrial Toxicants

The rapid rise in urbanization over the past 200 years brought with it an unprecedented increase in humans' exposure to various xenobiotics, including air pollutants, hazardous waste products, and industrial chemicals that promote SCI [7, 145]. Each year, an estimated 2,000 new chemicals are introduced into items that individuals use or ingest daily, including foods, personal care products, prescription drugs, household cleaners, and lawn care products [https://ntp.niehs.nih.gov/]. The concomitant increase in estimated contribution of environmental chemicals to human disease burden [146] has prompted a shift toward data generation using high-throughput screening, which has been supported by initiatives like the United States Federal Tox21 Program, and to the adoption of translational systems toxicology approaches for integrating diverse data streams to better understand how chemicals affect human health and disease outcomes [147]. To date, the Tox21 Program has tested more than 9,000 chemicals using more than 1,600 assays, and has demonstrated that numerous chemicals to which people are commonly exposed greatly alter molecular signaling pathways that underlie inflammation and inflammation-related disease risk [148].

These compounds can promote inflammatory activity via multiple mechanisms. For example, they can be cytotoxic [7, 146], cause oxidative stress, or act as endocrine disruptors (starting in utero) [7]. These chemicals are thus suspected of playing a causal role in hormone-dependent cancers, metabolic syndrome, type 2 diabetes, hypertension, CVD, allergy and asthma, and autoimmune and neurodegenerative diseases [7, 146, 149].

Tobacco smoking, which remains a worldwide health problem, is yet another source of xenobiotics that is associated with a variety of inflammation-related diseases [150].

Summary

SCI can be promoted by a number of social-environmental, lifestyle, and physical factors, including physical inactivity, lifestyle-induced microbiome dysbiosis, poor diet, social and cultural changes, and environmental and industrial toxicants that either directly or indirectly upregulate inflammatory processes and, in turn, promote age-related diseases. As we have described above, a key issue underlying this phenomenon is a general mismatch between humans' long evolutionary history and the types of inflammatory triggers to which individuals are currently exposed. Indeed, the human body is now exposed to numerous inflammation-promoting factors for which there is very little genetic or psychosocial adaption, in turn causing SCI and increased inflammation-related disease risk.

Developmental Origins of Systemic Chronic Inflammation

The origins of SCI can also be viewed from a developmental perspective. For example, it is well established that childhood circumstances significantly impact metabolic and immune responses later in life that in turn promote SCI in adulthood [7, 25, 26, 151, 152]. Childhood obesity, for instance, is strongly associated with major changes in adipose tissue and metabolic dysfunction that cause metabolism related-SCI, or *metainflammation* [25]. Because obese children often become obese adolescents and adults [25], risk for exhibiting a pro-inflammatory phenotype also frequently persists into adulthood among individuals who are obese as children.

Another example of SCI being influenced by early life circumstances comes from epidemiologic studies showing that greater microbial exposure in infancy is associated with a reduced risk for chronic inflammation in adulthood [7, 151], as predicted by the hygiene or *old friends hypothesis* [72]. Additionally, there is substantial evidence that exposure to psychological stress early in life – for example, in the form of abuse, neglect, maltreatment, bullying, and living in a low socioeconomic environment – can heighten neural responses to threat that may alter immunocompetence and lead to SCI throughout lifecycle [26, 152]. Going even further back in the developmental trajectory are data showing that the immune system is programmed during the prenatal period [153] and is affected by epigenetic changes induced by maternal environmental exposures (e.g., infectious agents, diet, psychological stress, and xenobiotics) during intrauterine life and even before conception, when paternal factors may also have an epigenetic effect [25, 94, 153]. Together, these effects create the potential for the intergenerational transmission of risk for SCI across generations. In this model, which is depicted in Figure 2, SCI and disease risk perpetuate trans-generationally: a maternal inflammation during pregnancy passes an inflammatory "code" through epigenetic modifications to the offspring, who will exhibit elevated risk for SCI in childhood and adulthood, and therefore be more likely to suffer from a wide variety of inflammation-related health problems including obesity [6], CVD [6], cancer [154], and neurological illness [155], among others—only to again pass this risk on to their own offspring.

Chronic Inflammation and the Immune Response to Acute Challenges

Despite the observations that SCI increases with age, a majority of older adults experience a down-regulation of components of the immune response that lead to an increased susceptibility to viral infections and weakened responses to vaccines. This

apparent paradox depicted in Figure 3 can be explained by the mechanisms described below.

Elevated SCI can lead to a basal low-grade constitutive activation of various signaling pathways such as the Janus kinase/signal transducers and activators of transcription (JAK-STAT) system in leukocytes, which results in weakened acute responses to multiple stimuli in immune cells from chronically inflamed older adults due to a small delta in the phosphorylation of these proteins [21]. SCI has also been shown to predict hypo-responsiveness to Hepatitis B vaccine in humans [23]. Additionally, there is evidence that certain inflammatory biomarkers, such as CRP, are inversely correlated with older adults' response to other vaccines such as the Herpes Zoster vaccine [22]. Interestingly, this also seems to be true for younger individuals. Among adolescents, for example, those who respond well to typhoid vaccination have been found to exhibit lower concentration of CRP than non-responders in adulthood [24]. In sum, this research helps to explain the pro-inflammatory/anti-viral skewing that occurs as individuals age. This work also indicates that exposure to an inflammatory environment early in life is an important determinant of multiple aspects of an individual's immuno-phenotype in adulthood.

The Centenarian's Paradox

If aging is positively correlated with SCI, and if SCI is a primary driver of chronic degenerative diseases as we have argued, then healthy elderly and long-lived humans should presumably have lower SCI levels than unhealthy elderly and shorter-

lived humans. However, this does not appear to be the case, as shown by Franceschi et al. [156] who reported that centenarians have elevated concentrations of inflammatory cytokines, acute phase proteins, and coagulation factors. This scenario poses another apparent paradox – namely, how have centenarians survived to diseases of the pre-antibiotic era and avoided or postponed most of the common diseases of aging while exhibiting what appears to be a pro-inflammatory phenotype?

The explanation appears to have at least something to do with the fact that along with high levels of pro-inflammatory markers, centenarians also exhibit high levels of multiple anti-inflammatory, or counter-regulatory molecules, that confer key health benefits [27]. Interestingly, intestinal permeability actually appears to be well preserved in healthy centenarians since lower levels of serum zonulin, which correlates with increased endotoxemia and SCI, have been found in these long-lived individuals as compared to young adults with precocious CVD [157]. It is thus possible that the lower intestinal permeability and endotoxemia in healthy centenarians is due to an unusual gut microbiota in these individuals [158].

Together, these observations indicate that a low level of 'inflammaging', likely counterbalanced by a concomitant level of 'anti-inflammaging', occurs with age as a result of adaptive remodeling (rather than solely detrimental) processes, without necessarily leading to the development of major age-related diseases [159]. Centenarians provide evidence for this possibility, for while they appear to have unique genetics [160] , they have also followed a healthy and active lifestyle [156], and lived most of their lives in non-obesogenic, non-polluted environments [156]. In contrast, cumulative exposure to a diverse array of pro-inflammatory social and environmental factors can cause the 'inflammaging' phenotype to reach pathogenic levels that in turn promote a variety of

chronic, inflammation-related conditions. Although a complete account for why these biological dynamics are so health damaging is not yet available, our hypothesis is that the pro-inflammatory factors that we have described herein have been introduced too recently on the evolutionary time scale for human physiology to have fully adapted, thus creating a social-cultural/genetic mismatch that leads to SCI. Clearly, therefore, the effects of aging and 'inflammaging' on age-related diseases and longevity are highly context-dependent and must be viewed from an integrated evolutionary, ecological, and historical perspective [160].

Future Directions

Considered together, the research described above provides evidence that SCI is associated with a variety of chronic diseases that dominate present-day morbidity and mortality worldwide, and that cause enormous amounts of human suffering. At the same time, there are several key avenues that could be pursued to help strengthen this work and translate the research into effective strategies for improving human health. First, there is a clear need for additional studies that collect data on multiple sources of SCI in order to form a more comprehensive picture of how exposures and experiences at different levels of analysis combine to affect SCI and inflammation-related disease risk. Second, the field sorely needs robust biomarkers of SCI that go beyond combining a few canonical biomarkers of acute inflammation. These biomarkers – which have primarily included CRP, IL-1β, IL-6, and TNF-α–have been useful for demonstrating that inflammatory activity is related to disease and mortality risk, but they provide only limited mechanistic information (given how complex the inflammatory response actually is), do not speak anti-inflammatory regulatory pathways, and do not focus specifically on components of the response that may be most relevant for age-related

disease risk. Constructing latent factors that represent inflammatory activity or immune regulation/dysregulation could be useful avenues to pursue in this regard, as could applying multi-omics approaches to studying multi-level, SCI-related mechanisms.

Finally, although many of the SCI-promoting factors that we have described herein are modifiable, at least partly – including physical inactivity, poor diet, nighttime blue light exposure, psychological stress, tobacco smoking, and environmental and industrial toxicants exposure – the number of studies that have successfully targeted these risk factors and shown reductions in SCI levels is extremely limited. This has occurred despite the fact that associations between inflammation and chronic disease is now widely recognized and healthcare systems are buckling due to the enormous cost of treating a worldwide population that is heavily burdened by SCI-related chronic health problems. Therefore, the time to start seriously studying how to prevent and treat SCI-related disease risk in both children and adults is now.

Conclusion

SCI has become a primary cause of human disease burden and mortality worldwide. Rates of inflammation-related diseases and conditions like obesity, type 2 diabetes, hypertension, CVD, and various types of cancer have reached epidemic proportions, and whereas these age-related diseases were once primarily evident in adults, drastic changes in social and cultural habits of children and adolescents – including physical activity levels, diet, stress, and sleep –now mean that more young people than ever are suffering from inflammation-related health problems. As a result, there is now general consensus in both the medical and research communities that SCI should be classified as a clinical condition that requires our immediate attention.

At the same time, we have a long way to go to fully understand the role that SCI plays in biological aging and mortality. For example, no study to date has assessed the entire human exposome over the entire developmental trajectory, starting in the uterus and including maternal lifestyle (type of delivery, early-life nutrition, and lifelong antibiotic use, vaccinations, infectious diseases) and continuing throughout life with xenobiotic exposures, social-psychological stressors, and individual lifestyle including dietary habits. Moreover, only a limited number of studies have investigated how modifying SCI-related processes can yield benefits for human health and longevity. As a result, although SCI is a highly modifiable process in principle, we have a long way to go before we start realizing the potential benefits associated of reducing chronic inflammation to improve human health.

659

	Acute Inflammation	**Systemic Chronic Inflammation (SCI)**
Trigger	PAMPs (infection), trauma	DAMPs ("exposome", metabolic dysfunction, tissue damage)
Duration	Short-term	Persistent, non-resolving
Magnitude	High-grade	Low-grade
Outcome(s)	Healing, trigger removal, tissue repair	Collateral damage
Age-related	No	Yes
Biomarkers	IL-6, TNF-**α**, IL-1**β**, CRP	Silent – No canonical standard blood markers

Notes: PAMP = pathogen-associated molecular pattern; DAMP = damage-associated molecular pattern

660 **Table 1 | Acute inflammation versus systemic chronic inflammation**

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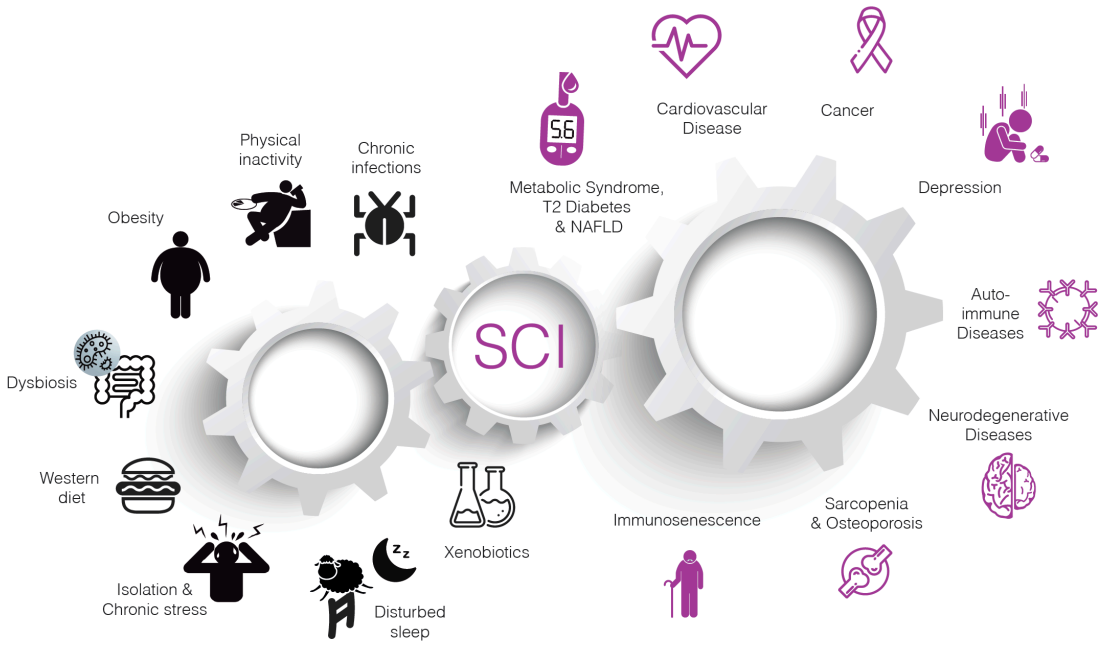

Figure 1 | Causes and consequences of low-grade systemic chronic inflammation

Several causes of low-grade systemic chronic inflammation (SCI) and their consequences have been identified. As shown on the left, the most common triggers of SCI (in counter-clockwise direction) include chronic infections, physical inactivity, (visceral) obesity, intestinal dysbiosis, a western-like dietary pattern, social isolation, psychological stress, disturbed sleep, disrupted circadian rhythm, and exposure to xenobiotics such as air pollutants, hazardous waste products, industrial chemicals, and tobacco smoking. As shown on the right, the consequences of SCI (in clockwise direction) include metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, cancer, depression, autoimmune diseases, neurodegenerative diseases, sarcopenia, osteoporosis, and immunosenescence.

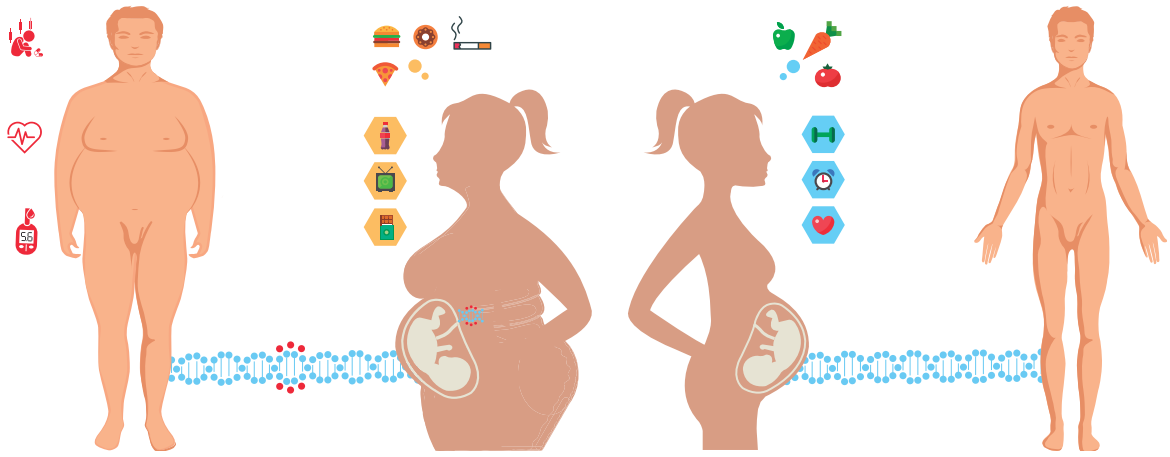

Figure 2 | The maternal exposome and low-grade systemic chronic inflammation

Maternal lifestyle and environmental exposures—collectively referred to as the *exposome*—comprises diet, physical activity, psychological stress, and exposure to various xenobiotics, including pollutants and smoking during intrauterine life. These factors in turn program the immune system of the offspring, leading to a more pro-inflammatory phenotype. Left panel: an obese, and sedentary mother, who smokes and follows an unhealthy diet giving birth to a fetus with epigenetic marks that increases the child's risk for obesity, low-grade systemic chronic inflammation, and its associated consequences (e.g., neuropsychiatric illnesses, cardiovascular disease, type 2 diabetes, etc.; see Figure 1) in adolescence and adulthood. Right panel: a healthy mother giving birth to a healthy baby, without epigenetic changes related to low-grade systemic chronic inflammation, who eventually grows into a healthy adolescent and adult.

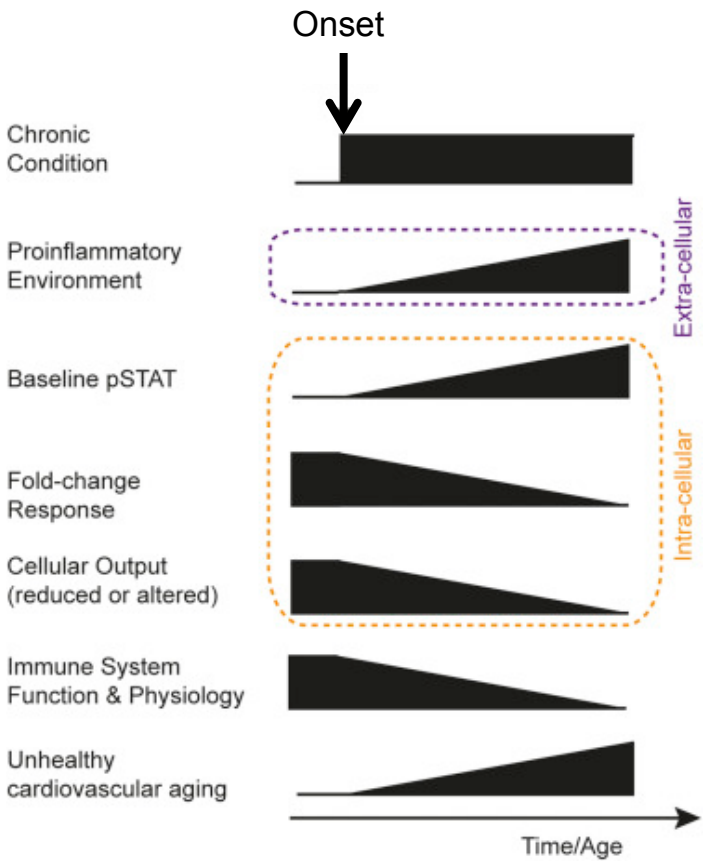

Figure 3 | Inflammatory model of immunosenescence and chronic disease

This proposed model associates elevated baseline phosphorylated STAT (pSTAT) levels with cellular unresponsiveness and chronic pro-inflammation. The model involves an elevation of baseline pSTAT levels and its association with hallmark phenomenon of immunosenescence, an increased pro-inflammatory environment, unresponsive cells, and a clinical impact on immune response. (Adapted from Shen-Orr, S et al., 2016 Cell Systems 3(4):374-384 with permission)

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