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Aging, Inflammation and the Environment

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Abstract

The aging process is driven by interrelated mechanisms that lead to the emergence of characteristic phenotypes that include changes in body composition, energy production and utilization imbalance, homeostatic dysregulation, and neurodegeneration and loss of neuroplasticity. Mainstream theories of aging all recognize that the aging phenotypes result from an imbalance between stressors and stress buffering mechanisms and a resultant loss of compensatory reserve leading to accumulation of unrepaired damage. This in turn results in increased disease susceptibility, reduced functional reserve, reduced healing capacity and stress resistance, unstable health and finally failure to thrive. The resultant physical and cognitive decline that culminates with the frailty syndrome is a tipping point of healthspan and implies a high risk of system decompensation and death. Preserving physical and cognitive function is the main focus of geriatric and gerontological research, but it is important to recognize that accomplishing this goal requires a profound understanding of the molecular, cellular and physiological mechanisms that ultimately determine functional changes. In this context, the pro-inflammatory state of aging plays a major role. Longitudinal studies have shown that with aging most individuals tend to develop a chronic low-grade pro-inflammatory state, and that such a state is a strong risk factor for multi-morbidity, physical and cognitive disability, frailty and death. A number of environmental factors may play an important role in modifying the pro-inflammatory state. We explore processes and mechanisms of aging that affect human biology and the possible links of inflammation and the environment to aging, especially those related to metabolism. We point out that longitudinal studies with a life course approach are needed to gain further mechanistic insight on the processes

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that lead to functional decline with aging, and the role played in this process by inflammation and environmental challenges.

Keywords

Aging; Inflammation; Environment; Inflamm-aging; longitudinal studies

1. Introduction

Aging is the strongest risk factor for most chronic diseases. The number of coexistent chronic diseases, usually defined a as multi-morbidity, increase with aging and this observation has been consistently confirmed in large population studies (Marengoni et al., 2011; Vetrano et al., 2017; Yancik et al., 2007). There is some evidence that the accumulation of multiple chronic disease in some older individuals deviates from the distribution expected based on the compound probability of having each single disease, even when diseases not pathophysiologically correlated are considered. This has been interpreted as suggesting that some individuals experience “accelerated” aging and that multi-morbidity severity can be thought as a proxy measure of the “force of aging”. There have been many attempts to identify characteristics associated with multi-morbidity progression. Overall, central obesity and inflammation have consistently been found to be strongly associated with the severity of multi-morbidity and with future risk of severe multi-morbidity. Based on these studies, it has been suggested that the pro-inflammatory state of aging may be a proxy biomarker of the pace of aging. Despite the strong epidemiological evidence that high levels of pro-inflammatory markers in older people are associated with risk of developing most of the diseases typical of aging as well as multiple chronic diseases (Fabbri et al., 2015; Stepanova et al., 2015), why older people tend to have a pro-inflammatory state as well as the specific mechanisms that connect inflammation with chronic diseases remain unclear. Progress in this field is essential if we want to target inflammation in interventions that promote healthy and successful aging.

We propose that more insight can be gathered by studying the confluence between inflammation and the environment and their effects on aging and healthspan. Once co-morbidities arise, these interactions appear to lead to decreased longevity and physical and cognitive decline. Here, we explore processes and mechanisms of aging that affect human biology and possible links of inflammation and the environment to aging, especially related to metabolism. We propose that these mechanisms are best explored in the context of longitudinal studies.

2. Systemic Effects of Aging

The systemic consequences of aging on the development of the aging phenotypes can be roughly summarized into four major domains that include dimensions that change in all animals, from worms to humans (Figure 1): 1) changes in body composition; 2) imbalance between energy availability and demand; 3) dysregulated signaling networks that maintain homeostasis; and 4) neurodegeneration with impaired neuroplasticity.

2.1 Changes in Body Composition

Changes in body composition with age are among the most apparent and unavoidable effects of aging. Overall, weight increases until late middle age and will decline in men between the ages 65 and 70 and slightly later in women (Ferrucci et al., 2010). Lean body mass, on the other hand, decreases steadily after the third decade (Ferrucci et al., 2010), while fat mass increases in middle age and then declines following the trajectory of weight change (Ferrucci and Studenski, 2012). Visceral fat, which is responsible for much of obesity-related pathology and is an independent risk factor for coronary artery disease, stroke and death (Folsom et al., 1993), continues to accumulate and is reflected in waist circumference increasing throughout life (Ferrucci and Studenski, 2012). Higher total body fat mass and lower total lean mass, in particular, are predictive of a faster decline in muscle quality (strength-to-mass ratio) with age (Fabbri et al., 2017). The loss of muscle quality that at least in part is due to the accumulation of intra-myocellular lipids can lead to morbidity and mortality through both metabolic dysregulation and mobility limitations, falls and fractures (Ferrucci et al., 2014). It is evident that all organs experience some change in tissue composition through life and these age-related changes are directly connected to sub-clinical and clinical pathology, including neurodegeneration (Camandola and Mattson, 2017), physical frailty, increase in fibro-connective build-up in muscle, and demineralization and loss of strength of bone (Ferrucci et al., 2014).

2.2 Energy Production and Utilization Imbalance

The balance between energy availability and energy demand is tightly regulated; the phosphate release from ATP provides cells with the energy necessary for many essential biological functions and its continuous re-synthesis maintains the ATP concentration virtually stable even in the most energetically demanding tissues, such as the cardiac muscle and the brain (Du et al., 2008; Ferrucci and Studenski, 2012; Yaniv et al., 2013). ATP is constantly resynthesized since the storage of ATP is enough for only a few seconds (Casey and Greenhaff, 2000). In muscle cells and neurons such stability is co-adjuvated by the phosphocreatine buffering system that accumulate chemical energy to be promptly used when the demand suddenly increases (Christie, 2007). Most of the energy used by muscle is generated through aerobic metabolism (though some is generated through anaerobic glycolysis) and, hence, energy consumption can be estimated indirectly by oxygen consumption (indirect calorimetry). Fitness, or the maximum energy that can be produced by a person, can hence be estimated indirectly from peak oxygen consumption (MV_{o2peak}) using a maximal treadmill test. MV_{o2peak} declines with age (Fleg et al., 2005) and is accelerated with chronic disease or those who are sedentary (Ferrucci et al., 2010). Older individuals with multiple co-morbidities have lower available energy and require more energy at rest and during physical activity. This can be manifested as fatigue and through exercise tolerance measured by a walking test (Ferrucci and Studenski, 2012). The amount of energy used at rest, the resting metabolic rate, decreases with age in large part because of a loss of lean body mass but will decline less in those with multiple chronic conditions (Ferrucci et al., 2010; Ruggiero and Ferrucci, 2006). Hence, sick older individuals will use most of their available energy in the performance of essential activities of daily living (Ferrucci et al., 2010), and when the energy “produceable” becomes even lower, they may no longer be able to maintain autonomy even for simple, self-care activities. As mentioned

above, resting metabolic rate progressively declines with aging, and such a decline is explained in part, but not fully, by the age-related decline of lean body mass. The decline occurs even in persons who remain very healthy in late life and has been confirmed in individuals who experience extreme longevity, such as centenarians (Pereira da Silva et al., 2016).

2.3 Homeostatic Dysregulation

In all living organisms, a status of homeostatic equilibrium in spite of continuous challenges is maintained through a complex signaling system that includes hormones, inflammatory mediators, and anti-oxidants; all of which are affected by aging. Hormones such as testosterone (Harman et al., 2001), growth hormone, insulin growth factor I, 25(OH) vitamin D, aldosterone, and melatonin decline characteristically with age in both men and women; while cholecystokinin, cortisol, prolactin, norepinephrine and insulin go up with age (Ferrucci and Studenski, 2012). A mild pro-inflammatory state, discussed below, develops in most aging individuals reflected in high levels of pro-inflammatory markers such as interleukin 6 (IL-6) and c-reactive protein (CRP) (Ferrucci et al., 2005). Oxidative stress damage also increases with aging because of the increase in production of reactive oxygen species (ROS) and perhaps because of a decrease in the concentration and effectiveness of antioxidant buffers (Ferrucci and Studenski, 2012). These hormones, inflammatory biomarkers, and antioxidants are part of complex signaling networks that control homeostasis and individual biomarker levels could reflect adaptation within homeostatic feedback loops rather than be a reflection of causative factors. Also important in the homeostatic regulation of metabolism are micronutrients such as vitamins like vitamin D, minerals such as magnesium and selenium, and antioxidants such vitamins D and E. Reduced amounts of micronutrients have been implicated with accelerated aging and increased risk of disease (Ferrucci and Studenski, 2012). Interestingly, except for vitamin D, supplementation has not been clearly associated with better health.

2.4 Neurodegeneration and neuroplasticity

The number of neurons decline throughout life as neurons in general stop reproducing shortly after birth (Ferrucci et al., 2010). Atrophy occurs in various parts of the brain at different rates especially after the age of 60 years (Raz et al., 2007). Brain atrophy, for instance in the thalamus, is often accompanied by microglial activation and neuroinflammation and may be a contributor to cognitive age-related declines as well as some brain diseases such as Alzheimer’s disease (Cagnin et al., 2001). With aging, microglia acquire a predisposition to reactive inflammation and the brain tissue from older persons contains a higher level of pro-inflammatory cytokines and a lower level of anti-inflammatory cytokines than the brain of younger individuals. Higher inflammation has been associated with lower cognition and reduced neuronal plasticity, expressed as a reduced capacity of adaptation and compensation (Norden and Godbout, 2013). Because the brain is capable of reorganization and compensation, extensive neurodegeneration may occur without any clinically evident functional consequence. Brain pathology such as amyloid plaques and neurofibrillary tangles considered the hallmarks of Alzheimer’s disease are found in autopsy of many older individuals who were cognitively normal (Ferrucci and Studenski, 2012). How the brain changes and adapts with age is still the subject of intense

research. For instance, in one representative fMRI study, while there was significant activation of the left hippocampus in young participants during autobiographical event memory retrieval, there was significant bilateral hippocampi activation in older individuals suggesting that older adults may be compensating in recall by recruiting additional neural circuits (Maguire and Frith, 2003).

2.5 The Phenotype of Aging Common Pathway

The systemic changes of aging (changes in body composition; balance between energy availability and demand; signaling networks that maintain homeostasis; and neurodegeneration and neuroplasticity) all will lead in some combination to increased disease susceptibility, reduced functional reserve, reduced healing capacity and stress resistance, unstable health and finally failure to thrive. Ultimately, physical and cognitive decline will result, leading to frailty (Figure 1). In turn, frail older persons tend to develop multiple chronic diseases resulting in a vicious cycle of increased multimorbidity and worsening frailty (Vetrano et al., 2017).

3. Chronic Inflammation

Aging is characterized by the development of a mild pro-inflammatory state (Howcroft et al., 2013; Morrisette-Thomas et al., 2014). Dysregulation of inflammation with age is found in almost every living organism. However, exact mechanisms of such dysregulation are not well understood. In normal situations, inflammation is essential to health since it helps organisms to fight the invasion of microorganisms and it plays essential roles in repair and maintenance of organs. When inflammation is transient, meaning it rises when needed and fades down when it is no longer needed, there are no long-term consequences. However, when inflammation becomes prolonged, either because of an intrinsic dysregulation of the immune system, or because the cause that triggered the inflammatory reaction is not removed, inflammation can lead to the accumulation of damage that eventually becomes manifest as pathology. This state of chronic inflammation that correlates with aging but with substantial heterogeneity across individuals, is sometimes referred to as “inflamm-aging” and is a strong risk factor for the occurrence, progression, and complication of many chronic diseases including obesity, cardiovascular disease, and neurodegenerative diseases (Bektas et al., 2017; Franceschi and Campisi, 2014; Franceschi et al., 2007). Hence, the causal pathways and molecular mechanisms that connect inflamm-aging and chronic diseases remain very little understood. Clinically, inflamm-aging is characterized by increased blood levels of several inflammatory biomarkers, including CRP, IL-6, IL-18 and tumor necrosis factor-α (TNF-α) (Scheller et al., 2011). Importantly, IL-6 serum levels also predict incident disability and frailty (Soysal et al., 2016). In particular, the risk of developing mobility disability appears to be increasing linearly for IL-6 levels higher that 2.5 pg/ml and these findings have been replicated in multiple studies, although there is some uncertainty on the specific value for the critical threshold (Ferrucci et al., 1999). Also, elevated levels of IL-6 have been tied to many of the systemic changes of aging. High IL-6 scores are related to lower walking speeds, which is consistent with multifactorial origin of this phenotype (Ferrucci et al., 2002).

4. Mechanisms of Aging and the Environment

Influences of the environment on chronic inflammation and the other above-described domains of the aging phenotypes probably impact physiological and functional trajectories of aging across the whole lifespan. The role of the environment can be examined in the context of specific processes influencing inflamm-aging using the novel framework described by Lopez-Otin et al. as hallmarks of aging (Lopez-Otin et al., 2013). The hallmarks of aging are considered biological mechanisms that in model organisms have been associated with biological and physiological changes that are typical of the aging process. Although it is currently unknown where these same mechanisms drive aging in mammals, and particularly in humans, nonetheless they represent a useful platform for research. Specific hallmarks include genomic instability, epigenetic alterations, telomere attrition, mitochondrial dysfunction, loss of proteostasis, cellular senescence, altered intercellular communication, stem cell exhaustion, and dysregulated nutrient sensing (Lopez-Otin et al., 2013). An “American version” of the same topic was published soon after, and included inflamm-aging as one of the “pillars” of aging (Kennedy et al., 2014).

There is no doubt that environmental stressors, especially those that affect inflammation and metabolism, can strongly affect the “hallmarks” (or pillars) of aging. Chemical, biologic, and physical agents can challenge the stability and integrity of DNA, while intrinsic DNA replication errors and ROS further increase the risk of internal genetic lesions (Hoeijmakers, 2009). Genetics and diet have been shown to be associated with DNA damage levels and DNA repair capacity in individuals (Slyskova et al., 2014). Levels of DNA damage were found to be associated with sex (higher in women), fruit consumption (inversely associated) and *XPG* genotype; while DNA repair capacity (nucleotide excision repair) was increased with higher plasma levels of ascorbic acid and α-carotene. Evidence supports that epigenetic changes, such as enrichment of enhancer and insulator regions of genes with functional CpG methylation sites (Peters et al., 2015), accompany aging, and perturbations such as DNA methylation and histone modifications, which in general are environmentally sensitive, can provoke progeroid syndromes, and experimental manipulation in animal models can either extend or decrease lifespan (Lopez-Otin et al., 2013). For instance, a reduction of SIRT6, which through histone H3K9 signaling regulates genomic stability, NF-κB signaling and glucose homeostasis, can reduce longevity in mice (Mostoslavsky et al., 2006), while an increase of SIRT6 can increase lifespan (Kanfi et al., 2012). MiRNAs, which are epigenetic regulators that circulate in the blood, appear to change with age (Franceschi et al., 2017). Several have been linked to inflammation (inflamma-miRs), including miR-21, -126 and -146a which target the NF-κB pathway (Olivieri et al., 2013). Metabolic changes also can have a profound effect on epigenetic alterations that have been linked to aging (Lopez-Otin et al., 2016). Peters et al. (Peters et al., 2015) showed that the difference between the calculated “transcriptomic age” of an individual based on gene expression profiles and chronological age was associated with signs of the metabolic syndrome including high blood pressure, elevated cholesterol levels, abnormally high fasting glucose, and being overweight or obese. Telomeres are particularly susceptible to age-related deterioration through exogenous or endogenous damage (Blackburn et al., 2006) and through inflammation (Jurk et al., 2014). Anti-inflammatory diets such as the Mediterranean diet have been shown to

slow leukocyte telomere length shortening and to be associated with reduced cardiovascular disease and mortality (Garcia-Calzon et al., 2015). Interestingly, obesity and in particular central obesity (which is at the core of the metabolic syndrome) is one of the strongest known correlates of inflamm-aging (Schrager et al., 2007).

Mitochondrial dysfunction has been shown to lead to accelerated aging in various mouse models (Kujoth et al., 2005; Trifunovic et al., 2004; Vermulst et al., 2008) and to the overproduction of amyloid precursor protein and oxidative damage in the brain with memory loss in a mouse model of Alzheimer's disease (Morley et al., 2012). Human aging is similarly thought to be linked to mitochondrial deterioration (Wang and Hekimi, 2015). Patients with mitochondrial diseases can have signs or symptoms related to age-related diseases including muscle weakness, diabetes, and sensorineural hearing loss, frequently are multisystem in nature, and often affect the heart, liver and kidney (DiMauro et al., 2013). The role of ROS generation, DNA damage, and inflammation associated with mitochondrial dysfunction has been well-studied especially in relation to insulin resistance and cardiovascular disease (Faria and Persaud, 2017). The mitochondrial-derived peptide MOTS-c, for instance, regulates, in mice, insulin sensitivity and metabolic homeostasis via AMPK, and prevents age-dependent and high fat diet-induced insulin resistance and diet-induced obesity (Lee et al., 2015). A polymorphism of MOTS-c may be involved in increased longevity of the Japanese (Fuku et al., 2015). Obesity and insulin resistance are altered in advancing age and together are linked to chronic low grade inflammation, leading to age-related systemic metabolic dysfunction, physical limitations and frailty (Stout et al., 2017). Mitochondrial hormesis (mitohormesis) may also play a role in aging, where mild mitochondrial toxicity may trigger beneficial compensatory responses that improve cellular fitness (Lopez-Otin et al., 2013; Schulz et al., 2007). Possible examples of this include resveratrol and metformin that inhibit cellular energy metabolism through increase of AMP, activation of AMPK, and decreased oxygen uptake (Hawley et al., 2010). Metformin, a biguanide hypoglycemic, promotes lifespan in *C. elegans* through peroxiredoxin-2 by which oxidative stress is translated into a downstream prolongevity signal (De Haes et al., 2014). Also, metformin mitohormesis retards aging in *C. elegans* by altering microbial folate and methionine metabolism (Cabreiro et al., 2013). It appears that metformin's effect on diabetics is mediated by short-chain fatty acid production and an increase in *Escherichia* species with a depletion of butyrate-producing taxa in their human gut microbiome (Forslund et al., 2015). Resveratrol, a polyphenol found in wine, and metformin importantly have anti-inflammation effects (Bektas et al., 2016; Saisho, 2015).

Maintaining the stability and functionality of proteins are paramount to the proper functioning of all organisms. Protein homeostasis (proteostasis) involves mechanisms to avoid and correct errors in transcription, splicing and translation, as well as disaggregate and refold misfolded proteins, and degrade damaged, misfolded, or aggregated proteins by the ubiquitin-proteasome system or lysosome (Lopez-Otin et al., 2013; Sala et al., 2017). There is some evidence that proteostasis is dysregulated by aging (Koga et al., 2011) and protein impairment contributes to the development of age-related diseases such as cataracts, Alzheimer's disease and Parkinson's disease (Powers et al., 2009). Healthy centenarians are able to maintain high levels of proteasomal activity (Chondrogianni et al., 2000). Proteolytic systems such as the autophagy-lysosomal system and the ubiquitin-proteasome system

decline with aging (Rubinsztein et al., 2011; Tomaru et al., 2012) and defects in these and other disposal systems for organelles or cellular debris may contribute to inflamm-aging through increased production of pro-inflammatory compounds (Franceschi et al., 2017). Both dietary/nutrient supplementation of a macroautophagy inducer, the polyamine spermidine, and gut flora producing spermidine lead to increased longevity in mice (Matsumoto et al., 2011; Soda et al., 2009) while dietary supplementation of omega-6 polyunsaturated fats increases longevity through autophagy activation in *C. elegans* (O'Rourke et al., 2013). Autophagy plays an important role in modulating inflammation, mostly through the regulation of inflammasome activation. There is evidence that damaged mitochondria release ROS and other signaling molecules that activate the inflammasome and results in caspase-1-dependent secretion of the inflammatory cytokines IL-1β and IL-18. Adequate recycling of dysfunctional mitochondria through autophagy prevents such pro-inflammatory mechanistic responses (Netea-Maier et al., 2016). In addition, other inflammatory pathways are affected by autophagy including a reduction of NF-κB activation by degradation of BCL10 complexes (Paul et al., 2012). Genetic variations in genes linked to autophagy, such as *IRGM*, are linked to chronic inflammatory disorders, like Crohn's disease, and in the case of *ATG5* are linked to autoimmune disorders, such as systemic lupus erythematosus (Netea-Maier et al., 2016).

Chronic cellular stressors including those from a persistent DNA damage response, telomere shortening, and de-repression of the CDKN2A locus (producing $p16^{INK4A}$ and *ARF)* with age, lead to chronic cellular senescence, a persistent hyporeplicative state (Childs et al., 2015; He and Sharpless, 2017). A meta-analysis of over 300 genome-wide association studies has identified the *INK4a/ARF* locus as being the genomic locus linked to the highest number of age-associated diseases including cardiovascular disease, diabetes, and Alzheimer's disease (Jeck et al., 2012). Other genes associated with cellular senescence and advancing age in man, include *ATM*, a regulator of the DNA damage response pathway, which was found to have an inhibitory role in expression of certain splicing factors (Holly et al., 2013). Overall, the number of senescent cells more than doubles in very old mice to ~17% but varies between tissues with some tissues such as the heart, skeletal muscle, and kidney showing no change (Wang et al., 2009). Strong evidence that senescent cells accumulate with aging in humans is limited to the skin, and has not been associated with important age-related outcomes such as Alzheimer's disease and intervertebral disk degeneration (Childs et al., 2017), with the exception of skin appearance, though causal links of age-related diseases and cellular senescence are being explored (Childs et al., 2017). Cells that become senescent undergo profound alterations of their secretome which becomes highly enriched for pro-inflammatory cytokines, matrix metalloproteinases, and growth factors: a change known as "senescence-associated secretory phenotype" (SASP) (Childs et al., 2015). SASP result from a DNA damage response which induces inflammation and senescence by inhibiting autophagy of GATA4. GATA4 accumulates in multiple tissues and likely contributes to aging through its associated inflammation (Kang et al., 2015). The removal of senescent cells in a mouse model reduces inflamm-aging (Baker et al., 2016) but the extent to which accumulation of senescent cells causes inflamm-aging in humans is unknown.

Intercellular communication such as that of neurohormonal signaling (e.g. insulin-IGF1 and renin-angiotensin signaling) becomes deregulated in aging and corresponds to an increase in inflammatory reactions and declines in immunosurveillance (Lopez-Otin et al., 2013). Inflamm-aging contributes to increased activation of the NLRP3 inflammasome and other pro-inflammatory processes, which leads to increased secretion of IL-1β, interferons, and tumor necrosis factor (Salminen et al., 2012). Individuals with atherosclerosis have increased aortic expression of NLRP3 that correlated with coronary severity (Zheng et al., 2013) and there was increased expression of NLRP3 in peripheral blood monocytes from patients with coronary artery disease (Wang et al., 2014). Genetic ablation of the NLRP3 inflammasome in mouse models was shown to reduce age-associated inflammation and consequent insulin resistance, cognitive decline, and frailty (Goldberg and Dixit, 2015). Aging has also been linked to changes in circadian control. Decreases in circadian oscillation of the “respiratory exchange ratio” reflecting the relative use of carbohydrates or lipids for energy metabolism correlate with aging with a preference of old mice for lipids and a loss of “metabolic flexibility” (Lopez-Otin et al., 2016). Decreased circadian oscillations in transcriptional processes in the aging brain have also been noted (Chang and Guarente, 2013). It has also been demonstrated that polyamines are involved in communication between circadian clocks and metabolic pathways influencing feeding behavior and age-related reduction in polyamines that have been linked to increased circadian periodicity can be reversed with polyamine supplementation (Zwighaft et al., 2015).

The ability for the body to be able to regenerate cells and tissues is important for maintaining homeostasis and can be strongly affected by aging. For example, the phenomenon of immunosenescence which is characterized by chronic inflammation, and inadequate dynamic response to pro-inflammatory stimuli is considered a defect of intercellular signaling (Bektas et al., 2017). An important role in the impairment of tissue repair and renewal is played by loss of potential of stem cells with aging which has been found in nearly all adult stem cell compartments and has been associated with DNA damage, *INK4a*, telomere shortening, and chronic inflammation (Lopez-Otin et al., 2013). More recently, metabolic ties to stem cell exhaustion involving the balance between glycolysis, oxidative phosphorylation and response to oxidative stress has been explored (Shyh-Chang et al., 2013) and autophagy and deregulated nutrient sensing including the insulin receptor, mTORC1, and AMPK may play a role (Lopez-Otin et al., 2016). Rapamycin, for instance, which inhibits mTORC1 and mimics a state of limited nutrient availability, has been shown to postpone aging through improving proteostasis and affecting deregulated nutrient sensing and appears to improve stem cell function in the epidermis, hematopoietic system and the intestine (Lopez-Otin et al., 2013), all compartments with rapid cell turnover.

Various signaling pathways, especially the insulin and IGF1 signaling pathway, that monitor and regulate the compartmentalization of nutrients appear to be deregulated in aging and also in metabolic disorders and many studies have shown that caloric restriction which suppresses the insulin and IGF1 signaling pathway, coupled with activation of members of the FOXO protein family, and mTOR inhibition extend lifespan (Efeyan et al., 2015; Lopez-Otin et al., 2016). Polymorphisms in the *IGF-1* receptor gene, in female centenarians (Barzilai et al., 2010), and especially a polymorphism in *FOXO3A*, which has been

replicated in eight independent groups (Barzilai et al., 2012), have been linked to longevity in humans. It should be noted that two other nutrient sensors, AMPK and sirtuins, signal nutrient scarcity and catabolism, rather than nutrient abundance and anabolism as the insulin and IGF1 signaling pathway and mTOR do (Lopez-Otin et al., 2013). Interestingly, the CALERIE study, the only randomized controlled trial of caloric restriction in humans demonstrated that a 25% calorie restriction significantly reduced several biomarkers of inflammation in the circulation (Fontana et al., 2016).

Though many environmental factors influence these mechanisms of aging, it is clear that DNA damaging agents, ROS, and metabolic factors influenced by diet or the microbiome play a seminal role. For instance, many metabolic interventions through nutrient manipulation have extended health span or lifespan in mice. These include acarbose (a-glycosidase inhibitor), branched amino acid mix (valine, leucine, isoleucine), butyrate supplementation, D-glucosamine (glycolysis inhibitor), methionine restriction, metformin, nicotinamide mononucleotide, protein restriction, rapamycin, resveratrol, spermidine, and tryptophan restriction (Lopez-Otin et al., 2016).

In the previous part of this text we have described evidence from the literature that inflammation is involved in the molecular, phenotypic and functional consequences of aging. Although most of the available evidence in humans is correlational, nonetheless questions arise of whether the pro-inflammatory state of aging can be modulated by interventions and whether reducing inflammation can prevent the aging phenotypes and their functional consequences. One logical place to start is to examine lifestyle factors. Diet, microbiome changes, vitamin D deficiency, stress and dioxins are all examples that can lead to pro-inflammatory factors such as obesity, altered gut microbiota, defective immunoregulation, and pro-inflammatory cytokines (Rook, 2010). Gene-environment interactions have been found between polymorphisms in genes coding for pro-inflammatory cytokines such as IL-1β and air pollution (NO_2 exposure) which are correlated to inflammation and increase the likelihood of Parkinson's disease diagnosis (Lee et al., 2016). Persistent organic pollutants that are stored in adipose tissues have been linked to inflammatory pathway genes involved in metabolic pathways (Kim et al., 2012). Epigenome (DNA methylation) - environment interactions have linked, in the elderly, traffic-related pollutants (NO_2, CO, black carbon, PM (2.5) and sulfite) with fibrinogen (a marker of coagulation), CRP, and endothelial function markers intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Bind et al., 2012). Many examples of environmental links to chronic inflammation and age-related diseases have been shown including, as a recent example, total urinary phthalate concentration that has been shown to be associated with CRP, IL-6 and TNF-α levels and cardiovascular disease, type-2 diabetes and hypertension (Bai et al., 2017). A recent theory known as the "hygiene hypothesis" poses that the recent increase in chronic inflammatory disorders may be partially a result of immune-dysregulation that results from the lack of exposure to microorganisms that play key roles in immune system function (Rook, 2010). Preliminary studies suggest that consumption of probiotic bacteria such as those found in yogurt and other fermented milk products can alter the composition of the gut microbiome beneficially altering the hosts metabolism (Wen and Duffy, 2017).

5. Why Longitudinal Studies

Caleb Finch (Council, 2008) and others (Kuh and New Dynamics of Ageing Preparatory, 2007) have argued that aging begins at the beginning of life, including the period prior to birth. Supporting this view, life course and historical cohort studies have shown that environmental processes in early life, including in utero, influence adult function and the propensity to acquire age-related chronic diseases (Gluckman and Hanson, 2004; Kuh and New Dynamics of Ageing Preparatory, 2007).

5.1 Dealing with Different Lifetime Exposures

Chronic diseases are caused by more than an individual's genetic variants (Chakravarti and Little, 2003), and most likely result from environmental and behavioral stressors interacting with genetic predisposition (Manolio et al., 2006). Inflamm-aging can be viewed as a reactive response positioned at the cross-road between genetic susceptibility and intervening stressors that are behavioral and environmental in nature. The inflammatory cytokine IL-6 is strongly affected by genetic factors (Bektas et al., 2013; Lin et al., 2014; Pilling et al., 2015) and can theoretically be examined also in a behavioral and environmental context. While most scientists would agree with this theoretical view, empirical evidence supporting it in humans is lacking because clinical studies, especially cross-sectional ones, have limitations in detecting gene-environment interactions (Manolio et al., 2006). Longitudinal and prospective cohort studies can characterize exposures and risk factors before disease onset, therefore reducing some common biases of case-control studies and also the assessment of environmental risk factors (Manolio et al., 2006). Some markers of inflammation though have been validated in cross-sectional as well as longitudinal studies. For instance, IL-6 has been shown to be both a cross-sectional and longitudinal predictor of comorbidity. Cross-sectionally, higher levels of IL-6 are correlated with a higher number of chronic diseases, however a high baseline of IL-6 is associated with a faster increase in IL-6 over time and a higher number of chronic diseases (Fabbri et al., 2015). Also high IL-6's correlation with lower walking speed cross-sectionally is also correlated with a greater decrease in walking speed over the following three years (Ferrucci et al., 2002). It is difficult to link all the manifestations of aging with dysregulated inflammation and high levels of cytokines, especially at the cellular level. However, it is a fact that many of the phenotypic changes as well as many biological changes at the cellular and tissue levels that occur with aging have been associated with inflammation in the literature. In addition, it is possible that part of the pro-inflammatory state often found in older persons are reactive to "normal" daily activities such as eating behaviors and physical activity. However, the evidence that these behaviors contribute to chronic inflammation is still limited and need further consideration in longitudinal studies.

The power of analyses conducted on longitudinal studies can be summarized by the extraordinary productivity of the Baltimore Longitudinal Study of Aging (BLSA), a prospective cohort study following a pool of individuals who reside in the Baltimore, MD-Washington, DC area since 1958. For example, a study was conducted that examined white blood counts (WBC) in 1,298 adults over the years. Noteworthy, patterns of WBC were different among the age groups, but the pattern was also influenced by a secular trend

(personal communication). There is a declining pattern between individuals age 20–40 years old compared to those ages 81 years and older for the cohorts measured in 1958–1970 and 1971–1980; whereas there is a rising pattern of WBC counts between individuals age 20–40 years old compared to those ages 81 years for cohorts measured in 1991–2000 and 2000+. WBC count has been shown to correspond to CRP and an age-independent rise of inflammatory score (CRP) or WBC has been shown to be related to the number of chronic diseases and hence be indicative of accelerated aging (Stepanova et al., 2015). The total WBC level has also been shown to be associated with significant stepwise increases in four escalating quartiles of IL-6 levels (Leng et al., 2005) and high WBC counts and IL-6 levels were independently associated with prevalent frailty in older women (Leng et al., 2007).

5.2 Example Longitudinal Studies

There are many studies that can be exploited to examine how environmental exposures and inflammation additively and synergistically affect the aging process. For example, the BLSA, the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT), Health ABC, InCHIANTI Study (Invecchiare in Chianti, aging in the Chianti area) and the Women's Health and Aging Study (WHAS) are studies funded by the National Institute on Aging (NIA), National Institutes of Health (NIH) that are particularly suited for this purpose. The Environmental Polymorphisms Registry (EPR) at the National Institute of Environmental Health Sciences Institute (NIEHS), NIH is another example. Many of these studies are partially archived in public domains and have developed mechanisms for investigators to access them. Although none of these studies is "ideal" for testing the hypotheses delineated above, nonetheless, they can be extremely useful to test selective hypotheses about the role of inflammation in the development of the aging phenotype. The study that we need to fully test the notion that inflammation is a hallmark of aging has not been designed and conducted. Ideally, this study will include measures of the hallmarks of aging, the major phenotypes of aging and comprehensive measures of the consequences of aging on cognitive function, physical function, mental health and mood. This study will also include a comprehensive inventory of all the behavioral and environmental factors (exposome) that can affect and modulate the aging process. At the current state of knowledge and technology, such a study can be conceptualized but not designed. We do not have the capacity to measure in humans some of the biological mechanisms that theoretically are important for aging (including measures of resilience). Developing and validating these measures is perhaps the most important step in the research agenda toward the clarification of the intrinsic mechanism of aging. Given the literature described above, working on reliable and valid measures of inflammation and inflammatory response (resilience) would be a good place to start. Questions which these longitudinal studies can answer include: How do early exposures lead to genetic adaptation or later adaptation and ultimately result in a chronic inflammatory state? What are the effects of intrinsic aging versus what are the effects of the challenges of the environment for chronic inflammation? Is chronic inflammation a mechanism by which the body maintains homeostasis despite challenging conditions or is it rather a sign of intrinsic immunodysregulation? Only by studying aging cohorts and collecting extensive information on the contextual environment, may we be able to respond, at least partially, to these questions.

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Highlights

- The systemic consequences of aging on human biology can be divided into four major domains: changes in body composition; imbalance between energy availability and demand; dysfunction of the signaling networks that maintain homeostasis; and neurodegeneration and reduced neuroplasticity.
- These systemic changes lead to increased disease susceptibility, reduced functional reserve, reduced healing capacity and stress resistance, unstable health and finally the emergence of frailty characterized by rapidly progressing physical and cognitive decline and high mortality rates.
- Chronic inflammation, inflamm-aging, may be the common mechanism predisposing individuals to chronic age-related diseases.
- Many mechanisms of aging interact with environmental factors especially in the context of metabolism.
- Longitudinal studies are an important method to study aging and link in the same interpretative framework lifetime exposures, biological changes (both loss of function and compensation), the emergence of aging phenotypes and their functional consequences on the maintenance of function and survival.

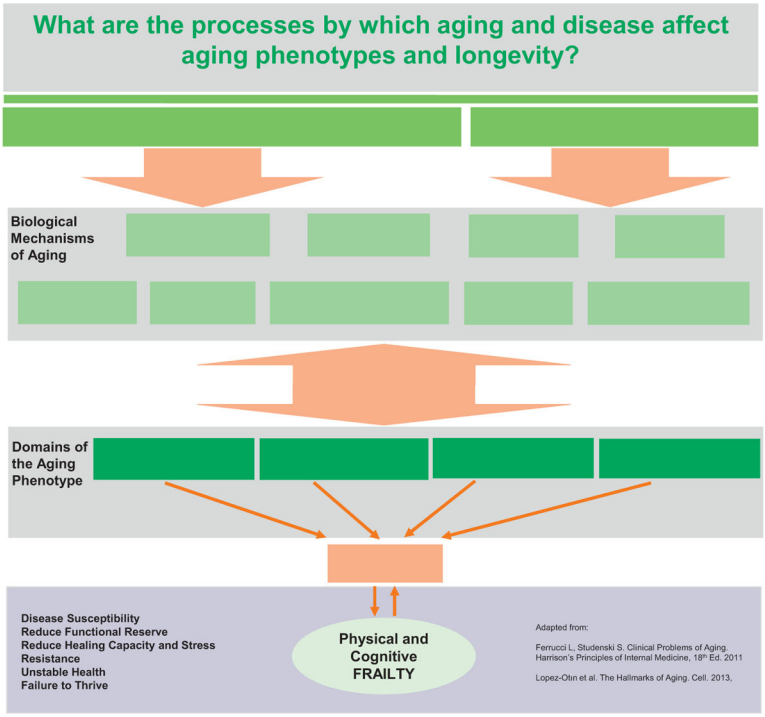

Figure 1.