Time and the Metrics of Aging

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The study of aging relates to changes in physical and functional dimensions that occur over time in living organisms. Yet, a model that establishes the hierarchical relationship and interlaced time courses of molecular, phenotypic, and functional hierarchical domains of aging in humans has not been established. We propose that studying the mechanisms and consequences of aging through the lens of these hierarchical domains and their connections will provide clarity in semantics and enhance a translational perspective. The study of human aging would be the most informative from a life course, longitudinal perspective, given that manifestations of aging are already detectable early in life at the molecular level, yet the phenotypic responses remain masked by compensatory/resiliency mechanisms. Understanding the nature of these mechanisms is paramount for developing interventions that reduce the burden of disease and disability in older people.

Hierarchical Model of the Metrics of Aging

It is customary to think about human aging as a set of characteristics that change over time and signify someone as older or younger. Consistent with the traditional tenants of biology, these changes occur at hierarchically organized levels—namely molecular, cellular, physiological, and functional levels. Perturbations at the molecular level are buffered by homeostatic mechanisms that delay their influence on the phenotypic and functional manifestations of aging. When such perturbations reach a certain severity, they then cause evident changes in anatomic and physiological parameters, eventually constraining physical and cognitive function. We can conceptually define these hierarchical levels as the metrics of aging and, for the purpose of this discussion, describe them (Figure 1) as follows: biological aging, the changes that occur with aging at the molecular, cellular, and intercellular levels; phenotypic aging, the interconnected changes in body structure/composition, energetics, homeostatic control mechanisms, and neuronal function/plasticity that occur in all aging individuals over time and may contribute to clinical diseases; functional aging, the age-associated decline in physical, cognitive, emotional, and social functions that may be either so subtle as to be evident only under challenge or so severe that they curtail performance of basic activities of daily living and contribute to loss of independence.

Hallmarks or Pillars of Aging as Drivers of Age-Related Diseases

Most research on human aging aims to elucidate the connections between longitudinal changes at the molecular, cellular, and functional levels. For example, the stiffening of heart ventricles and large arteries occurs over a wide range of severity between aging individuals. The impact of this stiffening is not purely speculative because this condition affects cardiovascular performance, leading to limitations in physical capacity.[1] Developing new interventions that reduce stiffness requires understanding the molecular mechanisms that cause arterial stiffness and its progression with aging. Similarly, the importance of understanding the most basic mechanisms of aging biology is grounded in connections between the biological mechanisms of aging, aging phenotypes, pathologies, and functional limitations. The basic hallmarks of biological aging were described in a landmark article published in 2013 by Fernando Lopez-Otin and include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.[2] Most research that supports the existence of these hallmarks derives from animal models. However, measures of these hypothetical mechanisms of aging in humans have been recently developed. Indeed, there is some evidence that these mechanisms contribute to the development of aging phenotypes, age-related diseases, and functional limitations. Herein, we provide several examples.

Expanded clonal populations of leukocytes, detected in ≈10% of older people, is perhaps the best evidence that genomic instability occurs with aging, causing the accumulation of somatic mutations in human hematopoietic stem cells. This phenomenon is defined as age-related clonal hematopoiesis even though there is little evidence that it is a risk factor for malignancy or acts as a causative driver of aging.[3] Of note, the somatic mutation accumulation hypothesis of aging cannot be accurately addressed with cross-sectional data because people of different ages may be differentially exposed to environmental genotoxic factors, making it impossible to segregate the true effects of aging from secular trends. Currently, no published studies have evaluated the longitudinal burden of genomic instability in humans and established a connection with aging phenotypes, diseases, or functional impairments.

Average telomere length declines slightly with age, and shorter telomeres in blood cells have been associated with a higher risk of developing diabetes mellitus, cardiovascular

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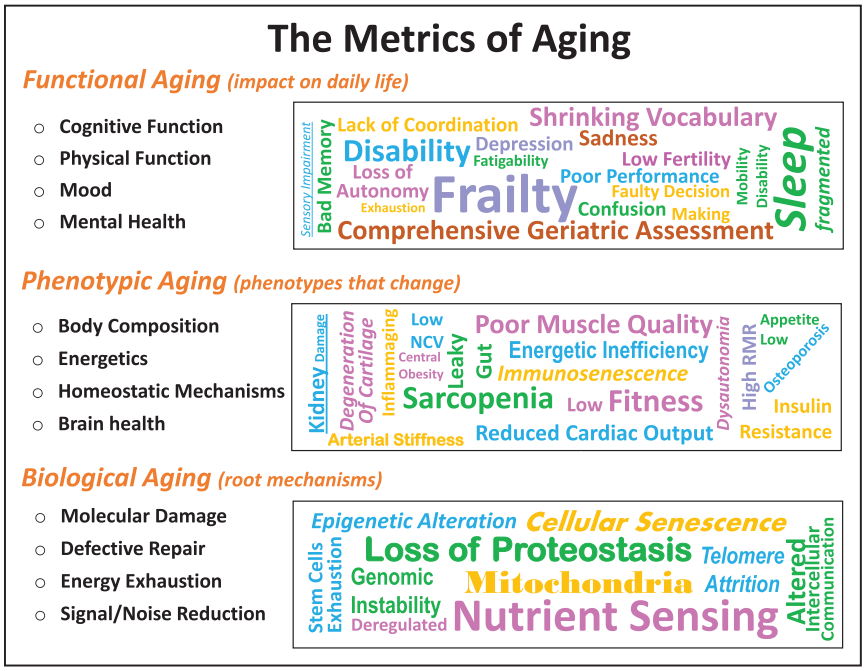

Figure 1. The metrics of aging. Note that the specific measures included in the 3 boxes are only examples of a much larger inventory of measures that belong to the 3 categories. RMR indicates resting metabolic rate.

disease, and all-cause mortality, although the causal nature of these associations and whether telomere shortening affects the aging process have been questioned.[4,5]

Predictable changes in DNA methylation—a fundamental epigenetic mechanism—track chronological age in humans, as well as phenotypic changes that occur during the lifespan and predict risk of incident coronary artery disease and cardiovascular mortality, as well as a wide range of adverse outcomes.[6,7] Why this specific methylation pattern emerges with aging and how it relates to pathology remains unknown.

Genetic animal models have revealed that defects in autophagy or mitophagy cause cardiovascular disorders, including cardiac myopathy and heart failure.[8] Evidence of defective autophagy is present in cardiac myocytes isolated from humans with ischemic heart disease and heart failure, but whether autophagy is an epiphenomenon or a causative factor is unclear. Autophagy flux has been assessed recently using human lymphocytes, demonstrating that activation-induced autophagy is preserved in CD4+ (cluster of differentiation 4) T cells in individuals from families with exceptional longevity compared with age-matched controls. These effects are also associated with higher T-cell functioning.[9]

The age-related decline in mitochondrial oxidative capacity is associated with insulin resistance, decreased muscle strength, and diminished walking performance, with some evidence of a causal association.[10,11] However, there is little longitudinal data that connects age-related changes in mitochondrial dysfunction with phenotypic and pathological changes in aging.

Senescent cells accumulate with aging in multiple tissues.[12] Studies from animal models suggest that senescence traits contribute to the whole atherosclerosis process, from senescent foamy macrophages accumulating in the subendothelial space, to the production of atherogenic and inflammatory cytokines, to the appearance of senescent vascular smooth muscle cells that promote plaque instability. Unfortunately, little of this research has been translated to humans.[13] The association between the number of senescent cells in blood or other tissues and the risk of cardiovascular diseases in humans is unknown.

Several lines of evidence suggest that the number of functional stem cells declines with aging, including reduced marrow cellularity; reduced cell number, viability, and proliferating potential; reduced tolerance to chemotherapy; and poor prognosis of grafts from old donors.[14] However, the role of these changes in affecting aging at the physiological and pathological levels is controversial.

The examples reported above suggest that the hallmarks of aging may be causative factors in age-related diseases, but much work remains to demonstrate their role in human aging. We do not know, for example, whether these hallmarks evolved independently or represent facets of the same underlying mechanism. The hypothesis of a common mechanism is consistent with inflammation being a pillar that is downstream of other mechanisms of aging, in addition to being a strong risk factor for cardiovascular disease and multimorbidity.[15]

Aging Phenotypes

In the Baltimore Longitudinal Study of Aging, we hypothesized that the major aging phenotypes can be grouped into 4 domains, namely body composition changes, energetics, homeostatic mechanisms, and neuronal control/plasticity.[16] Changes that occur during the life span in these domains, as well as their impact on functional aging, have been extensively studied. A connection between the biological mechanisms of aging and aging phenotypes has been established in a few relatively small studies. For example, the number of senescent cells in the subfascial adipose tissue of skeletal muscle is associated with slower walking speed and lower muscle strength[17]; defective autophagy contributes to immunosenescence[18]; and impaired mitochondrial function explains, at least in part, the decline in muscle strength and walking speed with aging.[10]

The evidence from these studies is relatively weak because they rely on cross-sectional comparisons and may be affected by secular trends and reverse causality. Indeed, although extensive data exist on age-related longitudinal trajectories of aging phenotypes, the availability of longitudinal data on the biological mechanisms of aging in humans is extremely limited. To address this limitation, measures of the putative biological mechanisms of aging must be developed for use in human studies. This would need to be further supported by demonstrating that individuals who have steeper longitudinal changes in these measures—compared with the general population—also show accelerated changes in aging phenotypes (including higher risk for developing multiple chronic diseases) and accelerated functional decline.

Functional Aging

The main objectives of medical interventions for older people should focus on (1) maximizing the ability of an individual to function in his/her environment and (2) maintaining autonomy and maximizing quality of life. Therefore, functional aging has been the focal target of geriatric research in recent years, and the bulk of the related literature suggests that all of the main phenotypes of aging may affect differential areas of function. For example, low ankle-brachial index within the normal range, compensated insulin resistance, and poor muscle strength are all associated with physical or functional decline in large population studies. Under the assumption that these phenotypes reflect accelerated aging, measures of biological aging could be used to identify asymptomatic individuals who would otherwise require in-depth medical examination aimed at discovering medical problems in the preclinical state. This would allow for early treatment of these conditions, which would hypothetically be more efficacious than later treatment. In addition, and possibly even more interesting, if specific biological hallmarks of aging can be utilized to capture biological aging, measuring these hallmarks could track the efficacy of interventions aimed at slowing biological aging, thereby also potentially slowing phenotypic and functional aging.

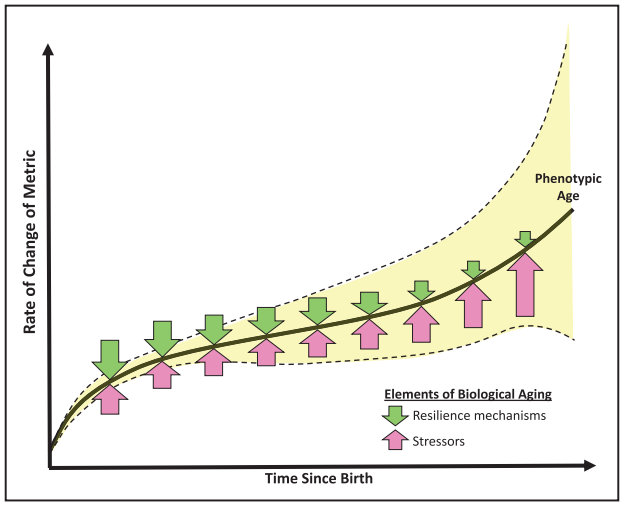

Figure 2. Graphic representation of the trajectory of aging and the interaction between entropic and compensatory mechanisms in affecting the rate of aging. Note that the trajectory shows little variability early in life, whereas the variability expands substantially later in life.

Building Connections Between the Metrics of Aging

In Figure 2, we depict the life course using a summary line that represents the anatomic and physiological changes that occur during the life span. Rapid and massive changes occur from the time of conception to full development. These changes follow a rigid sequence of events driven by a robust genetic program. After the initial growth spurt, adulthood is characterized by a period of apparent stability, free of disease and with a subtle decline in health, as well as diminished physical and cognitive function that becomes evident only if elicited by extreme stress or challenges. The intensity of the challenge required to detect this decline progressively decreases over time until functional impairment becomes evident, even in the absence of a challenge.

Some individuals show signs of aging earlier than others. Conceptually, the global rate of aging can be imagined as a dynamic equilibrium between entropic stresses (red arrows

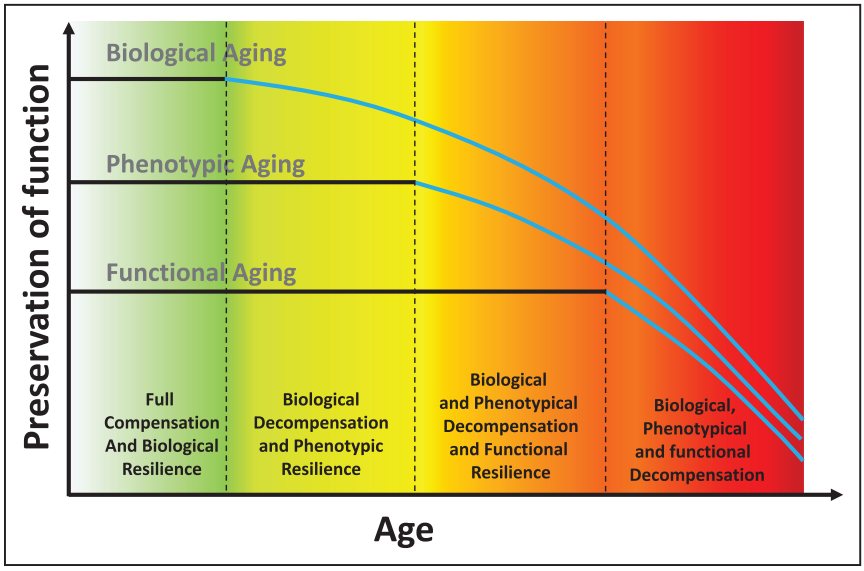

Figure 3. Trajectories of biological, phenotypic, and functional aging and their interaction during the life span. Of note, functional aging occurs only when all resilience mechanisms of the biological and phenotypic aging domains are exhausted.

in Figure 2) and homeostatic mechanisms that constantly restore order (green arrows). The resilience mechanisms that constantly perform maintenance and repair are evolutionarily conserved and allow humans to maintain health and function for many years. However, their efficiency eventually fades and allows entropy to result in frailty and death. The nature of these compensatory mechanisms must be understood to develop effective therapies in slowing aging, thereby preventing or delaying the burden of disease and disability that comes with it. This approach is a drastic departure from the traditional model of medicine, which is based on measuring damage and risk factors, in contrast to assessing functional reserve and boosting resiliency.

Temporal Hierarchy of the Metrics of Aging

The temporal relationship between the 3 metrics of aging is depicted in Figure 3. Within each level, buffering mechanisms and redundancies exist that contrast the propagation of damage from one metric of aging to the other. For example, misfolded proteins can be refolded by chaperons or eliminated by autophagy and replaced by newly synthetized proteins; damaged mitochondria can be repaired through alternating cycles of fission and fusion or eventually eliminated by mitophagy and replaced by new mitochondria; damage to nuclear or mitochondrial DNA is corrected by efficient processes that involve the coordination of dozens of proteins; apoptosis or senescence can thwart the propagation of genomic damage; adaptive epigenetic mechanisms are likely implemented as allostatic mechanisms, responding to the accumulation of intrinsic and environmental stimuli; stem cells generate new cells that replace those that are damaged, thereby maintaining the integrity and function of tissues. Assays for assessing these and other biological resilience mechanisms in humans are notably few and unreliable. Theoretically, when accumulating damage overcomes compensatory mechanisms, the effects on phenotype become progressively more evident, but because we cannot measure these resilience mechanisms, we cannot predict the degree to which a physiological system is close to decompensation. Similarly, redundancies and resilience mechanisms (ie, buffering mechanisms) exist at the phenotypic level such that a certain degree of physiological decline can occur without substantially affecting function. For example, because of the development of collaterals, gait independence can be preserved in spite of femoral artery occlusion, but the biological and phenotypic underpinnings that predict functional impairment in peripheral artery disease have not been fully identified.[19]

Environmental, behavioral, and societal compensatory mechanisms play important roles in humans, buffering the effect of underlying declines in functional aging, but their exact roles cannot be inferred from animal models. Importantly, the presence of a caregiver, owning a home equipped with assistance devices, or receiving meals on wheels may significantly compensate for phenotypic losses. These mechanisms of extrinsic resilience vary across generations through their own peculiar evolutionary processes aimed at protecting aging individuals by establishing cultural institutions. Understanding how these entities affect biological mechanisms is an important area of research that requires further development.

Summary

The different metrics of aging are mutually and longitudinally correlated, although their trajectories are not synchronous and occur with a certain time lag. In other words, biological aging takes many years before it finally translates into the deterioration of physical and cognitive function. This opportunity for prevention should be eagerly embraced because this has extraordinary translational potential. There is overwhelming evidence that frailty and disability are powerful risk factors for multiple adverse health outcomes, such as nursing home admission, disability, and mortality.[20] This is not surprising, considering that functional aging only occurs when the resilience mechanisms of biological and phenotypic aging are exhausted. Concordant with this view, frailty and other measures of functional aging have been successfully used to identify patients most likely to develop severe side effects after aggressive medical and surgical treatments, although technological progress has allowed for invasive interventions—such as hip replacement and aortic valve replacement—to be successful in old and frail patients. In spite of their success as prognostic indicators, frailty and other measures of functional aging are still rarely used in day-to-day medical practice, mostly because of inadequate evidence that frailty can be prevented or reversed. Developing methods to measure the biological mechanisms of aging in humans may enable identification of individuals on a trajectory of accelerated aging early in the process, who then can be screened for subclinical diseases and thereby targeted for future interventions that globally affect the aging rate and effectively delay frailty. Ultimately, interventions that effectively slow or delay the mechanisms of aging in subjects diagnosed with accelerated aging will need to be identified and properly tested. To foster this research agenda, new methods for measuring putative mechanisms of biological aging need to be fully developed, validated, and included in large cohort studies. This is in addition to the major phenotypes of aging, including information on chronic diseases and risk factors, as well as robust and sensitive measures of functional assessment, potentially including response to challenge.

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