Cell

Geroscience: Linking Aging to Chronic Disease

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Mammalian aging can be delayed with genetic, dietary, and pharmacologic approaches. Given that the elderly population is dramatically increasing and that aging is the greatest risk factor for a majority of chronic diseases driving both morbidity and mortality, it is critical to expand geroscience research directed at extending human healthspan.

The NIH mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." NIH-funded research is structured to address the major diseases driving morbidity and mortality. Interrogating and developing therapeutics for one disease at a time has often been productive. Will, however, the success of this approach be sustainable for the chronic aging diseases, such as neurodegenerative and metabolic syndromes, most cancers, and cardiovascular disease? Findings in the last few decades have made it impossible to ignore the integrative nature of human physiology. Pathologies thought to be disparate are now understood to be connected. This awareness raises the possibility that the stated goals in the NIH mission statement are best achieved by novel integrated approaches to health and disease, with the understanding that biological systems change with age.

Basic aging research has always been intriguing but until recently seemed to hold few concrete solutions to advance health. Despite limited resources, the field recently erupted and now offers routes to achieve a new and ambitious goal—a substantial extension in health life expectancy, or "healthspan." The lynchpin is that aging itself is the predominant risk factor for most diseases and conditions that limit healthspan. Moreover, interventions that extend lifespan in model organisms often delay or prevent many chronic diseases. This knowledge launched the era of geroscience, which strives to understand how aging enables chronic disease and seeks to develop novel multi-disease preventative and therapeutic approaches.

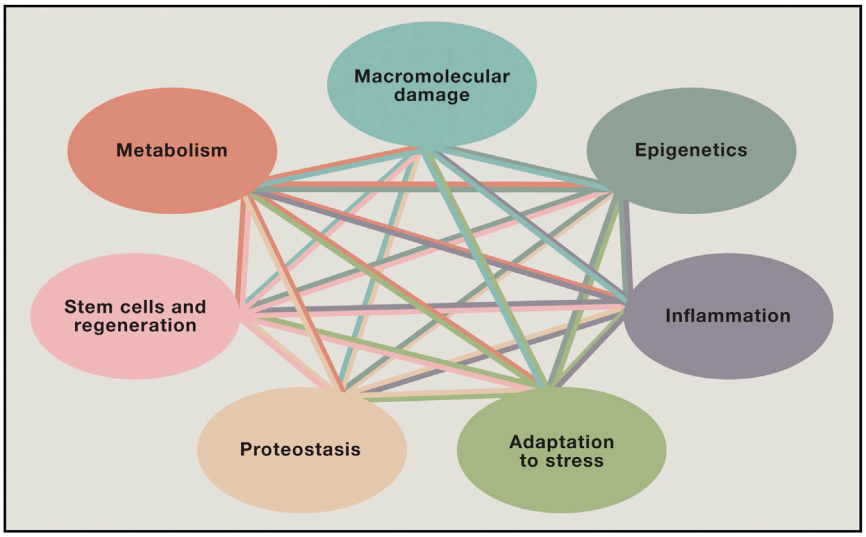


Figure 1. The Seven Pillars of Aging

The trans-NIH Geroscience Interest Group (GSIG) held a recent summit where the mechanistic relationships between aging and chronic diseases were discussed. An executive session was tasked with identifying strategies to: (1) develop a systematic understanding of aging mechanisms; (2) elaborate mechanistic links between aging and chronic disease; and (3) recommend pathways to identify and develop therapies or preventative approaches for age-associated diseases. Here, we describe the summit's conclusions, emphasizing the needs for a concerted effort to understand the aging process and to exploit this knowledge to extend human healthspan.

The Pillars of Aging

Attempts to define the causes of aging have been impeded by the complexity of the phenotype coupled with the costs and duration of longevity studies. Recently, progress has accelerated, bringing geroscience to the forefront. First, invertebrate models have identified conserved molecular pathways impacting aging. Second, mammalian studies have generated a more detailed understanding of age-associated pathologic changes. Third, several interventions that extend lifespan have been shown to also improve aspects of healthspan—long-lived mutants are often resistant to age-related chronic diseases. Finally and urgently, the global population is aging, with looming dire economic and societal impacts. While life expectancy continues to rise, healthspan is not keeping pace because current disease treatment often decreases mortality without preventing or reversing the decline in overall health. Elders are sick longer, often coping with multiple chronic diseases simultaneously. Thus, there is an urgent need to extend healthspan.

Key themes emerged regarding processes that promote aging, with recent reviews describing overlapping sets of five to ten processes processes (López-Otín et al., 2013; Mahmoudi and Brunet, 2012). Seven pillars were discussed at this recent summit (Figure 1). Specific recommendations for each pillar emerged (Table 1), but, more importantly, their connectedness was striking. The themes were not seven independent factors driving aging; rather, they were highly intertwined processes, and understanding the interplay between these seven pillars is critical.

An Aging Research Initiative

Collectively, chronic diseases comprise the majority of global disease burden and are the most common causes of mortality (http://www.healthmetricsandevaluation.org/tools/data-visualizations). Medical research has historically targeted diseases separately, assuming that organ systems act independently. Yet, optimal functionality for any single system requires overall organismal health, impelling inquiries into the interdependence of these relationships to develop multiscale network models that incorporate the physiologic changes accompanying aging. Targeting diseases individually for an aging population is also complicated because most elders have multiple morbidities that interact, confounding therapeutic strategies. By understanding how aging enables pathology, new therapeutics will arise for multiple chronic diseases, providing an opportunity to extend human healthspan by targeting aging directly. There is cause for optimism; however, much must happen to achieve this goal, including an infusion of resources to accelerate research and regulatory changes that push medical care toward chronic disease prevention. Here, we focus on a limited set of short- and intermediate-term scientific goals that will accelerate geroscience and will launch novel approaches to reduce the impact of the major global healthcare burden: the chronic diseases of aging.

Merge Geroscience with Research on Human Chronic Disease States

The mouse has emerged as a primary mammalian model to understand aging and disease. Although mice develop only some pathologies approximating human aging, other pathologies can be modeled through transgenic or genome-editing approaches. There are, however, concerns about the validity of mouse models, as preclinical studies often identify therapeutics that fail in humans. Given that mouse studies provide much of the evidence for delayed aging, pro-longevity interventions that extend healthspan may also not achieve human validation. Yet, a key difference between aging studies and many disease models is that aging can be studied in normal mice or other species; therefore, evolutionarily conserved interventions can be identified that cut across species.

Focus in three areas may improve consistency between mice and humans. First, mouse studies generally fail to use aged mice—most human chronic diseases rise with age, yet murine models invoke pathology in young mice. Aging creates a distinctive systemic milieu; drugs that show efficacy in the young may not work in the aged. Therefore, aging should be incorporated into animal

Table 1. Critical Areas of Aging Research and Important Goals

Areas of Aging Research	Important Goals
Adaptation to stress	Bridge continuum from psychological to molecular stresses Differentiate hormesis from toxic stress Better align human and animal studies
Epigenetics	Biomarker development: chronologic vs. biologic aging Link age-related environmental inputs to epigenetic signatures Test small molecules that regulate enzymes controlling epigenetic events
Inflammation	Differentiate adaptive and maladaptive inflammatory responses Define age-related inflammatory sources and their systemic effects Determine how obesity and metabolic dysfunction alter inflammation with age
Macromolecular damage	Generate systems-level understanding of the types of macromolecular damage and their roles in chronic disease states Understand how stochastic damage influences the variability of aging
Metabolism	Define role of signal transduction pathways linked to metabolism in the aging process Understand contribution of circadian clocks to aging and metabolism Connect metabolic dysfunction with tissue-specific decline in aging
Proteostasis	Identify proteostatic pathways that are overwhelmed in specific chronic disease states Examine crosstalk between proteostasis machineries Understand non-cell-autonomous signaling and activation of proteostasis pathways
Stem cells and regeneration	Determine whether declining adult stem cell function drives aging and chronic disease Examine how aging and associated disease impair adult stem cell function Determine how macromolecular damage accumulates in aging adult stem cell pools

chronic disease models, a recommendation increasing time and cost but also likely yielding results that will translate more accurately to humans and will thus provide long-term savings.

A second goal is to employ whenever possible genetically outbred lines to introduce natural population variation, better mimicking human diversity. A third is to incorporate mild stress into mouse studies to more accurately reflect the human condition. These stresses should include low-level chronic stress, including psychological sources. Many animal studies use acute stresses that are not experienced by humans. It will also be essential to distinguish stresses that induce a hormetic response, protecting from later acute stress, from those unconditionally deleterious.

Though aging promotes disease, new findings suggest the reciprocal may also be true: diseases and/or their treatments may accelerate aging pathologies. For instance, long-term cytomegalovirus (CMV) infection can induce chronic inflammation and exhaust the adaptive immune response, accelerating unrelated age-associated pathologies (Pawelec et al., 2012). This is also observed in human immunodeficiency virus (HIV) patients, attributable either to virus-induced inflammation or, ironically, treatment modalities (Pathai et al., 2014). Similarly, children subjected to chemotherapies often present with accelerated aging features decades later (Robison and Hudson, 2014). These findings highlight relationships between disease and aging, calling for a thorough analysis in humans and animal models.

Expand Interventions that Extend Lifespan and Healthspan

Mammalian lifespan, and also healthspan, can be modified by dietary, genetic, and pharmacologic interventions. Several drugs are reported to extend mouse lifespan and healthspan (Kennedy and Pennypacker, 2014), raising the possibility that human aging can be delayed. Although obstacles exist, the repertoire of aging interventions should be greatly expanded. For instance, dietary restriction is long known to extend rodent lifespan, though not easily adapted to humans. Understanding links between diet and aging, as well as approaches like intermittent fasting, may yield practical strategies. Moreover, given that different mouse strains respond variably to dietary restriction, it may be necessary to design personalized diets optimizing healthspan based on individual genetics and lifestyle.

The role of the microbiome in response to diet and aging also requires elaboration. Preliminary data suggest that the gut microbiome change dramatically with age (Heintz and Mair, 2014), although causes and effects remain undetermined. This area is particularly important for understanding obesity and metabolic diseases. In addition, it should be determined whether altering the microbiome offsets features of aging. Though early, the therapeutic hurdles to altering the gut microbiome may be more easily surmountable than those using standard pharmacology.

Exciting findings have demonstrated that aging in rodents can be accelerated, stalled, or reversed simply by altering the systemic environment (Rando and Wyss-Coray, 2014). These findings were initially spotlighted by heterochronic parabiosis experiments, in which the circulation of old and young mice was coupled. More recent findings from multiple labs now indicate that hallmarks of aging can be modulated by circulatory factors, which are beginning to be identified. This growing line of inquiry may offer tractable routes to extend healthspan.

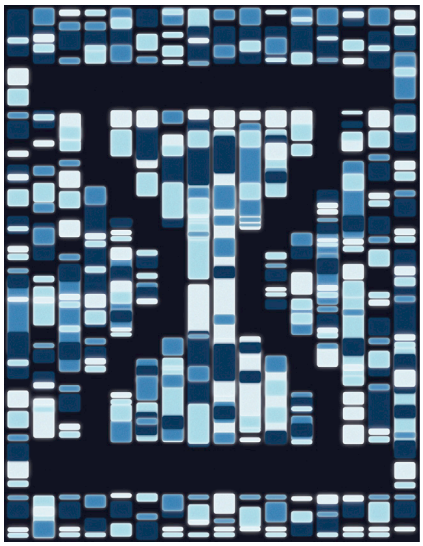
Rapamycin was the first drug shown to robustly extend mouse lifespan (Johnson et al., 2013), a finding repeated in different

backgrounds. It also increases healthspan in most studies and is protective in many age-related disease models. Other drugs, including metformin and acarbose, also extend mouse lifespan (Harrison et al., 2014; Martin-Montalvo et al., 2013). Continued efforts should be directed at identifying and optimizing new molecules with these properties and understanding those already identified (Kennedy and Pennypacker, 2014). Ultimately, drug combinations may be optimal. Further, many aging drugs approved for a single chronic disease (e.g., metformin, rapamycin) may have efficacy because they target basic aspects of aging. Therefore, a thorough analysis of drugs clinically approved for chronic diseases should be performed to identify those with the potential to increase healthspan.

Elaborate Environmental and Stochastic Factors Driving Aging

Conserved longevity pathways have been identified across disparate eukaryotic species. However, aging also depends on environmental factors, which may be modifiable. Yet, the specific environmental influences on aging, aside from obvious culprits such as smoking and obesity, remain poorly understood. Moreover, stochasticity plays a major role in aging processes. There is enormous variability in longevity traits among genetically identical individuals across all species tested. The causes of this stochasticity and its role in aging and age-related diseases remain poorly understood.

Numerous aging genes have been identified in nonvertebrates, which now should be used to develop a systems-level understanding of aging, including both genetic and environmental influences. Studies should incorporate multiple assessments of cellular and organismal function, including transcriptomics, proteomics, and metabolomics, as well as readouts of macromolecular damage and activation of stress response pathways. Achieving a holistic view of aging in organisms such as yeast, worms, and flies will likely impact our understanding of vertebrate aging, as did the identification of single genes in those organisms. It is also critical in mammals to assess the relationship among genetics, environment, and drug interventions to predict responses in human healthspan trials.



Integrate Human Genetic and Epigenetic Studies with Animal Models

Human genome association studies have identified aging-associated gene variations from either genome-wide unbiased or gene-targeted studies, examining orthologs of animal aging genes (Deelen et al., 2013). Working between mouse and human genetics will accelerate identification of human aging genes and their mechanisms. Strategies should include generating orthologous or identical human mutant alleles in mice, modeling rare variants in genes from conserved longevity pathways.

The lack of validated molecular biomarkers of human aging has impeded progress. However, recent studies have uncovered promising candidates that, if validated, could be used to test interventions. Epigenetic studies are among the most exciting, with reports indicating that human age can be predicted by analyzing DNA methylation status. It remains unclear whether these markers forecast chronologic or biologic age, which are likely distinct. If they indeed measure biologic age, then a major hurdle to initiating human studies will be overcome. Also, if similar DNA methylation sites are identified in mice, they could be validated by determining whether interventions such as rapamycin delay the appearance of an aging profile and whether chronic stressors accelerate it. Other avenues to molecular biomarkers, including metabolomic and proteomic approaches, are also yielding promising candidates and deserve equal attention.

Compare and Contrast Inflammation in Aging and Disease

Increasingly, inflammation is being linked to aging and chronic disease (Salvioli et al., 2013). Acute inflammatory responses to insults such as injury and infection are critical for organismal health and recovery. However, the basal inflammatory response rises with age, leading to low-level chronic inflammation that is likely maladaptive, promoting aging. There is a need to identify (1) the pathways by which adaptive and chronic inflammation are induced and (2) the outcomes of ''inflammaging.'' Interventions designed to reduce chronic inflammation while maintaining an effective adaptive response may have broad benefits.

Senescent cells accumulate in multiple tissues during aging and have a unique senescence-associated secretory profile (SASP) that includes many proinflammatory cytokines (Coppé et al., 2008). Cell senescence, whereby cells irreversibly cease proliferation in response to stress, was long suspected of driving organismal aging. However, the number of senescent cells in most aged tissues is limited. The SASP potentially explains how a few senescent cells can have broad, adverse effects by secreting proinflammatory factors with autocrine, paracrine, and endocrine activities. It is important to understand the in vivo consequences of senescent cells and identify interventional strategies that may mitigate their effects. Recent genetic strategies to ablate senescent cells in mice set the stage for determining to what extent they drive aspects of normal aging (Baker et al., 2011).

Metabolic dysregulation accompanies aging and is exacerbated by chronic diseases such as type II diabetes. Among the critical questions to be addressed is how overnutrition and obesity affect the aging metabolome, whether pro-longevity interventions suppress age-related metabolic dysfunction, and how these interventions act in individuals with type II diabetes. These issues are relevant to inflammation as well, as adipose tissue

is a major source of inflammatory cytokines. Determining how the proinflammatory response in adipose tissue is initiated and propagated and the systemic effects of this response on aging should be a high priority. Links between altered metabolism and inflammation may underlie connections between aging pathways previously thought to be independent.

Develop New Animal Models of Aging

Though yeast, worms, flies and mice have been powerhouse aging models, there are fundamental gaps in the knowledge they provide. Understanding the diversity of biological processes that can accelerate or protect against age-related decline is critical and is best achieved by investment in new model organisms that accentuate other aspects of aging.

A major limitation in aging research is the lack of primate and other vertebrate models for preclinical testing. Primates, often rhesus monkeys, are intermediate between rodents and clinical trials in humans. However, rhesus monkeys live three to four decades, making aging studies long and expensive. One solution is to develop a second primate model—the marmoset, whose lifespan is much shorter. Other short-lived vertebrates such as the African killifish may be useful for the same reason: aging and disease studies can be performed more rapidly than current counterparts like zebrafish and mice. Although human genetic data on aging and age-related diseases is exploding, the speed of hypothesis testing in current vertebrate models is lagging, and a short-lived vertebrate may provide a solution. Another model to consider is dogs, which live in their owner's environment, are well understood with regard to aging and disease, and comprise a wide range of pedigrees, providing genetic diversity. Finding strategies to extend healthspan in dogs may be an excellent prelude to achieving the same goals in humans.

Exceptionally long-lived species also offer promise. Though several species such as clams are intriguing, the naked mole rat has recently garnered interest. These rodents are approximately the same size as mice but reach 30 years of age and are apparently devoid of cancer. Comparative studies and genome sequencing have suggested possible mechanisms that underlie their extreme longevity. One particularly informative research path may be to engineer naked mole rat longevity mechanisms into mice.

Conclusions

The goal of slowing aging has fascinated humankind for millennia but has only recently acquired credibility. Recent findings that aging can be delayed in mammals raise the possibility of prolonging human healthspan. There is near consensus among aging researchers that this is possible, but only if resources are available to accomplish goals in areas ranging from basic biology to translational medicine.

Here, we list a set of important areas of future endeavor that aim to identify: (1) the proximal causes of aging, (2) the mechanisms by which aging enables disease, and (3) a broad set of interventional strategies for human testing. The current approach to treating chronic diseases is inadequate and fragmentary. By the time chronic diseases are diagnosed, much damage is done and undoing it is difficult. Although understanding the unique features of any given disease is laudatory and is potentially of therapeutic value, approaches to understand a common cause, aging, will be uniquely important. If we can understand how aging enables disease, it may be possible (and even easier) to target this common component of disease. Targeting aging may allow early intervention and damage avoidance, maintaining vigor and activity while offsetting the economic burdens of a burgeoning aging population hampered by multiple chronic diseases.

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