REVIEW

Healthy aging: The ultimate preventative medicine

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Age is the greatest risk factor for nearly every major cause of mortality in developed nations. Despite this, most biomedical research focuses on individual disease processes without much consideration for the relationships between aging and disease. Recent discoveries in the field of geroscience, which aims to explain biological mechanisms of aging, have provided insights into molecular processes that underlie biological aging and, perhaps more importantly, potential interventions to delay aging and promote healthy longevity. Here we describe some of these advances, along with efforts to move geroscience from the bench to the clinic. We also propose that greater emphasis should be placed on research into basic aging processes, because interventions that slow aging will have a greater effect on quality of life compared with disease-specific approaches.

The major focus of biomedical research has traditionally been the pathogenesis and treatment of individual diseases, particularly those with substantial effects on morbidity and mortality. Within the U.S. National Institutes of Health (NIH) there are institutes dedicated to research toward treatments for cancer (National Cancer Institute); eye disease (National Eye Institute); heart, lung, and blood disease (National Heart, Lung, and Blood Institute); infectious disease (National Institute of Allergy and Infectious Diseases); arthritis, musculoskeletal, and skin diseases (National Institute of Arthritis and Musculoskeletal and Skin Diseases); neurological disease and stroke (National Institute of Neurological Disorders and Stroke); and diabetes, digestive disease, and kidney disease (National Institute of Diabetes and Digestive and Kidney Diseases). Even at the National Institute on Aging (NIA), more than one-third of the 2014 research budget was allocated for a single target—Alzheimer's disease—and this percentage has increased to more than 50% in 2015. This disease-specific focus has unquestionably had a profound effect on medical care and human health; many new treatments have been developed that are helping people live longer today than ever before. However, despite notable advances in management, we have been largely unsuccessful at postponing, ameliorating, or preventing the accumulation of morbidities during aging. As a consequence, people are living longer but often suffering from multiple diseases or disabilities of aging. This has important societal and economic implications. Many families struggle to care for elderly relatives who survive for years or even decades with reduced quality of life, while nations devote an increasing proportion of finite resources toward medical care for aging populations.

Introducing geroscience

These issues have, in part, spurred efforts to increase recognition of the importance of basic research on the biology of aging. This has resulted in a series of major advances in a field once known as biogerontology but which has recently become known as geroscience. Such work has demonstrated that biological aging is modifiable and has provided tangible approaches to enhance healthy longevity. A promising new initiative, the NIH Geroscience Interest Group, has been created to expedite collaborative efforts to discover the mechanisms of aging that constitute the major risk factor for virtually all of their focused disease interests (*1*). The underlying hypothesis is that delaying the rate of biological aging would simultaneously delay the onset and progression of each of these diseases, a prediction supported by experimental data in laboratory models (*2*). This has at least two major implications for translational biomedical research. First, it is critical to account for the biological effects of aging when developing therapies for chronic disease, something that is often not appropriately managed in preclinical studies that use young animal models. Consider, for example, the efficacy of vaccine therapies, which generally work potently in young animals but poorly in the context of an aged immune system. Most preclinical studies in this area involve young animals, yet the corresponding clinical applications are, in many instances, targeted toward the elderly. A specific case for which this may have important implications is in the development of cancer immunotherapies (*3*).

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The second and most profound implication from the link between aging and disease is that successful modifications of the intrinsic rates of aging will provide a much more effective approach for improving healthy longevity, relative to strategies aimed at treating or curing an individual disease. This will occur because therapies aimed at a single chronic disease, even when maximally successful, are generally unable to affect other diseases of aging. The added value from targeting the underlying processes of aging directly, and thereby delaying multiple age-related declines in function, has been referred to as the "longevity dividend" (*4*). Efforts to quantify this dividend, based on projections from preclinical experimental data, predict substantial benefits in individual quality of life (health span), as well as important society-wide economic and productivity gains (*5*).

It is clear that directly targeting aging is theoretically superior to treating individual chronic diseases, but until recently, translational approaches to achieve this goal have been just that—purely theoretical. This is now changing. Over the past decade, numerous studies have identified key mechanisms of aging (*6*), along with targeted interventions that modulate those mechanisms and extend healthy longevity in laboratory model systems. Within the past few years, we have begun to see the first steps toward translation of these laboratory discoveries into clinical applications.

Translational geroscience

Now we will focus on the initial forays into translational geroscience and the major challenges and opportunities they present. We have identified several interventional strategies for which there is evidence of attenuating or reversing the biological aging process in model systems; therefore, these strategies may have translational potential for improving human health span (Box 1). Our list is not exhaustive, nor does it predict precisely where the field will go; rather, it indicates those areas that currently appear most promising for the development of effective interventions to enhance a person's quality of life by delaying aging. To determine the broad utility of a particular intervention for improving healthy longevity in people, several questions must be addressed, including: (i) Is it relatively easy to implement? (ii) Can it be effective when started in mid-life (or later)? (iii) Do the benefits outweigh the risks?

However, there are at least two major hurdles to overcome before clinical interventions in aging can be rigorously validated in people. The first is the time scale over which human aging occurs. One way to assess the efficacy of an intervention for delaying biological aging is to demonstrate substantial improvements in the progression of aging-related conditions. Yet, unless there are intermediate outcomes, this method may require very long clinical trials, because many aging-related conditions progress over decades. Recent advances toward the development of true biomarkers of biological aging rate (i.e., epigenetic or metabolomic signatures) may provide surrogate measures,

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Box 1. Geroscience interventions with translational potential.

Dietary restriction: Dietary restriction (DR) is the most studied intervention for delaying aging (*16*). Although not universally effective, a majority of studies have documented significant increases in both life span and health span when DR is applied in laboratory models, including nonhuman primates (*17*). Limited studies also indicate important health benefits, including reversal of disease risk factors (*16*), in people who practice DR. Although DR is not a viable translational approach at the population level, research in this area has incited the search for alternative dietary modifications (e.g., low-protein diets) or small-molecule DR mimetics (e.g., mTOR inhibitors, see below) that can provide the health benefits of DR without requiring reduced food consumption.

Exercise: A large body of literature provides evidence that the health benefits of exercise are consistent with the enhancement of health span (*18*, *19*). However, poor compliance, especially in the elderly population, makes this intervention challenging to apply. Thus, there is high interest in developing pharmacologic interventions that would synergize with lower levels of exercise.

mTOR inhibitors: Rapamycin extends life span and promotes health span in mice, as well as in simpler organisms. Treatment beginning late in life is sufficient to extend life span, reverse cardiac decline, and improve immune function in mice (*20*). A recent study also reported that a rapamycin derivative significantly boosts immune function in elderly people (*10*).

Metformin and acarbose: Metformin and acarbose are widely used antidiabetes drugs. Metformin improves health span in mice and may slightly extend life span (*21*), whereas acarbose markedly extends life span in male mice and modestly extends life span in female mice (*22*). In a nonrandomized retrospective analysis, diabetic patients taking metformin have reduced mortality compared with diabetic patients not receiving metformin, and they may live longer than nondiabetics not receiving metformin (*23*).

NAD precursors and sirtuin activators: As discussed by Verdin in a companion Review (*24*), nicotinamide adenine dinucleotide (NAD) precursors such as nicotinamide riboside and nicotinamide mononucleotide have been reported to improve health span in mouse models of muscle aging and cognitive decline. The mechanism of action is not clear, but it may involve activation of sirtuin NAD-dependent protein deacetylases, along with enhanced mitochondrial function (*25*). Other, possibly more specific, sirtuin activators also improve health span and slightly extend life span in mice (*26*).

Modifiers of senescence and telomere dysfunction: Senescent cells accumulate during aging and secrete factors that promote inflammation and cancer (*27*). As discussed in the companion Review by Blackburn *et al*. (*28*), telomere dysfunction is a major cause of cell senescence, and strategies to enhance telomerase function offer promise for improving health span (*29*), although the possibility of increased cancer risk must be addressed. Likewise, genetic and pharmacological strategies to target and kill senescent cells enhance both life span and markers of health in short-lived mice with high levels of senescent cells (*30*, *31*).

Hormonal and circulating factors: Age-related changes in important hormones (including sex-steroids, growth hormone, and insulin-like growth factor 1) are well documented; however, the risks and benefits of hormone supplementation in aging remain largely controversial (*32*). As discussed in the companion Review by Goodell and Rando (*33*), heterochronic parabiosis experiments in which the circulatory system of an aged mouse is shared with that of a young mouse suggest that additional, more subtle humoral factors affect age-associated declines in several tissues, including the brain, muscle, liver, and heart (*34*). Some progress has been made toward defining these factors (*35*), and an effort is under way to determine whether transfusion of young plasma can delay Alzheimer's disease (*36*).

Mitochondrial-targeted therapeutics: As discussed in the companion Review by Wang and Hekimi (*37*), mitochondrial dysfunction is a major contributor to aging and age-related diseases, although the mechanisms are more complex than initially suggested by the Harman's free radical theory of aging (*38*). Attention is now being directed to interventions that augment mitochondrial function, energetics, and biogenesis, including mitochondrial-targeted antioxidants and NAD precursors (*39*).

although these will also need to be validated, at least initially, in a similar manner. These strictures are greatly relaxed, however, if the intervention can be shown to reverse physiological parameters of aging. Although this is a higher bar to reach, there is evidence that it may be achieved by some interventions that target mechanisms of aging. For example, mTOR inhibitors such as rapamycin (Box 1) can partially rejuvenate immune stem cell (*7*) and cardiac (*8*, *9*) function in mice and can perhaps also restore immune function in elderly people (*10*). The second major challenge for clinical assessment of interventions that modify biological aging is a regulatory one, at least in the United States. At present, efforts to target the basic processes of biological aging do not have a defined regulatory path at the U.S. Food and Drug Administration (FDA). Thus, it may not yet be possible to receive FDA approval for an intervention whose primary indication is to delay the onset, rates, or progression of aging. However, in consultation with the FDA, a strategy has recently been proposed that would enable researchers to partially bypass these hurdles and assess the efficacy of metformin against human aging in a randomized, double-blind clinical trial over 5 to 6 years. The Targeting Aging with Metformin (TAME) clinical trial seeks to enroll individuals who have already been diagnosed with any age-associated condition for the purpose of determining whether metformin is effective at delaying the diagnosis of other age-associated conditions (*11*). Because the time between diagnosis of the first and second age-associated conditions will be compressed, the study is expected to detect delays on the order of 15 to 30% (depending on the specific age-related condition). Should the results prove to substantially delay the onset of aging disorders, the TAME study may provide a possible regulatory path for clinical trials of agents designed to retard biological aging.

As an intermediate to human clinical studies, one option is to apply translational geroscience to companion (pet) dogs (*12*). Dogs suffer from many of the same age-associated diseases and functional declines that affect humans, albeit at an accelerated rate, and veterinary practitioners are adept at recognizing and diagnosing geriatric diseases in dogs. Dogs also have substantial genetic and phenotypic diversity. Moreover, companion dogs and cats share the human environment to an extent unmatched by any other nonhuman animal. Substantial increases in healthy longevity in companion dogs would not only provide important insights into similar efforts in people but would also directly improve the quality of life for pet dogs and their owners. A pilot study assessing the effects of short-term rapamycin treatment on cardiac aging in middle-aged companion dogs is under way (*13*), and a longer-term intervention study has been proposed that would also assess the effects of rapamycin treatment on cancer incidence, cognitive decline, immune function, mobility, and life expectancy in middle-aged dogs (*12*).

Future prospects

We have briefly outlined the case for concerted efforts to determine the mechanisms by which intrinsic processes of aging lead to many of the most devastating human health disorders, including heart disease, diabetes, cancer, and dementia. We have also pointed to promising advances in

translational research that have the potential to delay or conceivably prevent most such disorders. However, there is a caveat that requires more thorough investigation: the degree to which interventions that retard aging and delay the onset of age-related disorders will be accompanied by a compression of morbidity. In other words, will such interventions regularly lead to an increase in the ratio of health span to life span? Will our medicated centenarians lead fulfilling lives with eventual sudden collapse, or will they suffer from proportionally protracted durations of chronic disease? Although some research on centenarians suggests a compression of morbidity (*14*)—and rapamycin, in particular, appears to disproportionately enhance many measures of health span in mice (*15*)—future progress in geroscience interventions will need to be carefully monitored.

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REVIEW

Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection

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Telomeres are the protective end-complexes at the termini of eukaryotic chromosomes. Telomere attrition can lead to potentially maladaptive cellular changes, block cell division, and interfere with tissue replenishment. Recent advances in the understanding of human disease processes have clarified the roles of telomere biology, especially in diseases of human aging and in some aging-related processes. Greater overall telomere attrition predicts mortality and aging-related diseases in inherited telomere syndrome patients, and also in general human cohorts. However, genetically caused variations in telomere maintenance either raise or lower risks and progression of cancers, in a highly cancer type–specific fashion. Telomere maintenance is determined by genetic factors and is also cumulatively shaped by nongenetic influences throughout human life; both can interact. These and other recent findings highlight both causal and potentiating roles for telomere attrition in human diseases.

The telomere is a highly regulated and dynamic complex at chromosome ends, consisting of a tract of tandemly repeated short DNA repeats and associated protective proteins (Fig. 1) (*1*).

The telomere protects the genomic DNA through various mechanisms. One function is to prevent the end of the linear chromosomal DNA from being recognized as a broken end. This prevents processes—such as DNA end-joining, DNA recombination, or DNA repair—that would lead to unstable chromosomes. The general chromosomal DNA replication machinery cannot completely copy the DNA out to the extreme ends of the linear chromosomes. Over the course of cell divisions, this leads to attrition of chromosome ends. This deficiency can be resolved in eukaryotes by the cellular ribonucleoprotein enzyme telomerase, which can add telomeric repeat sequences to the ends of chromosomes, hence elongating them to compensate for their attrition (*2*).

Other damage-causing mechanisms can also contribute to telomere-shortening processes; these include nuclease action, chemical (such as oxidative) damage, and DNA replication stress. To offset these various processes, telomerase, as well as recombination between telomeric repeats, can act to replenish telomere length (*3*).

In many human cell types, the levels of telomerase (or of its action on telomeres) are limiting, and in humans, telomeres shorten throughout the life span. The degree of shortening is roughly proportionate to risks of common, often comorbid, diseases of aging as well as mortality risk. Inherited telomere syndromes (*4*, *5*) have been highly informative for dissecting the roles and interactions of telomere maintenance defects in the general population's human aging and age-related diseases. Declining telomere maintenance has pathophysiological effects on cells that can lie upstream of, as well as interact with, a number of the cellular hallmarks of aging (*6*). Because the effects of compromised telomere maintenance in humans play out in cell- and tissue-specific ways, they consequently differ between

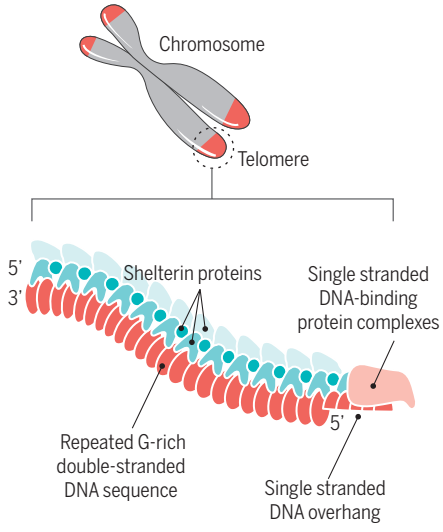

Fig. 1. Telomere structure. The human telomere complex consists of a chromosomal-terminal tract of a tandemly repeated DNA sequence bound by protective shelterin component proteins, with additional protective proteins on the overhanging single-stranded end region of the telomeric DNA repeat. This simplified schematic does not indicate details of the protein structures or of the architecture of the telomeric complex.

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