VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Aging as a Biological Target for Prevention and Therapy

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Viewpoint

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Chronic health problems related to the unprecedented aging of the human population in the 21st century threaten to disrupt economies and degrade the quality of later life throughout the developed world. Fortunately, research has shown that fundamental aging processes can be targeted by nutritional, genetic, and pharmacologic interventions to enhance and extend both health and longevity in experimental animal models. These findings clearly demonstrate that the biological rate of aging can be slowed.

The geroscience hypothesis, for which there is abundant evidence in animal models, links these biological discoveries to human health by proposing that targeting biological aging processes will prevent, or at a minimum delay, the onset and progression of multiple chronic diseases and debilities that are typically observed in older adults.[1,2] For example, interventions that extend the life span of mice often also prevent or slow the progress of several types of cancer, reduce atherosclerotic lesions, improve heart function, alleviate normal age-related cognitive loss, and even improve vaccine response.

Aging Is the Major Common Risk Factor for Chronic Diseases and Disabling Conditions

The US government annually publishes the rate of death from individual diseases stratified by age.[3] What is striking about these reports is that the rate of death increases logarithmically with advancing age for virtually all major causes of death, including heart disease, cancer, stroke, chronic obstructive pulmonary disease, chronic kidney diseases, type 2 diabetes, and Alzheimer disease. Furthermore, the incidence of multimorbidity, defined as 3 or more concurrent disease conditions from a list of 20 US Department of Health and Human Services–reported conditions, also increases exponentially with age.[4] Thus, increasing numbers of individuals are being treated for at least 3 different diseases with at least 3 different treatments, each with potential adverse effects and potential adverse drug interactions. Efforts focused on preventing individual diseases will have limited net effect on population health because one disease will be exchanged for another. If biological aging processes are the fundamental cause of virtually all major medical diseases and conditions in individuals, then targeting those processes holds promise to ameliorate many of these diseases and conditions as a group.

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Aging Processes Can Be Targeted

One of the main geroscience accomplishments is to highlight a small number of major "pillars," interacting molecular and physiological processes that underlie the biology of aging, for instance, metabolism, proteostasis, macromolecular damage, inflammation, adaptation to stress, epigenetics, and stem cells and their regeneration.[1] The key feature of this conceptual framework is that these processes are understood to be tightly interrelated. These findings have emerged from the remarkable progress made in recent years in dissecting aging processes in model organisms.

The discovery of cellular and molecular pathways that modulate healthy aging in diverse species across great evolutionary distances offers an unprecedented opportunity for intervention. In animal models, both health and longevity have been extended by multiple genetic and dietary interventions.[2] For example, knocking out the *rps6kb1* gene extends the life and health of female mice, whereas overexpressing Sirt6 makes male mice live longer, and reducing caloric intake or methionine levels makes both mouse sexes live longer.

Health and longevity have also been extended by drugs. The National Institute on Aging–funded Interventions Testing Program (ITP) evaluates drugs to determine whether they prevent disease and extend life in genetically heterogeneous (outbred) mice.[5] These studies are conducted independently at 3 centers to control for laboratory-specific environmental differences and to provide immediate experimental confirmation. The ITP has shown that of 26 candidate drugs evaluated to date, 6 (nordihydroguaiaretic acid, aspirin, acarbose, Protandim, rapamycin, and 17α-estradiol) extend life in at least 1 mouse sex. The largest overall longevity increase has been found using a combination of rapamycin and metformin, indicating that combination therapy may be applied for synergistic effects. A remarkable finding from these and other such studies suggests that interventions as late as the mouse-equivalent of older than 70 years of age could significantly extend life by more than 20 years and increase health span even more substantially.[6]

The ITP studies also confirmed that simultaneous modulation of several of the pillars of aging is possible and that improvement of one of them often has a positive effect on the others. For example, restoring proteostasis, the cellular surveillance systems responsible for protein and organelle quality control, improves cellular metabolism, reduces macromolecular damage, and enhances the ability to adapt to stress. Most of the genetic and chemical interventions shown to extend life span exert an activating effect on autophagy, one of the key components of the proteostasis system that has also been shown to malfunction in many age-related diseases.

A connection with age-related disorders has also been established for *cellular senescence*, a program that many cells activate in response to damage and stress. During aging and in many pathologic processes (such as in idiopathic pulmonary fibrosis), senescent cells are not efficiently cleared by the immune system, and their persistent presence maintains a state of chronic inflammation that contributes to tissue dysfunction. Recent advances have resulted from the realization that many human pathologic conditions are associated with the presence of senescent cells. Interventions aimed at eliminating those senescent cells, commonly called senolytic, have also been shown to improve health and extend life in various mouse disease models.[7]

Targeting Human Aging

Maximal life expectancy for humans is theorized to be about 115 years. Since the average life expectancy in the United States is currently approximately 80 years old, 35 years have yet to be realized. Centenarians not only live longer than most individuals, they also have an extra 20 to 30 years of health as well as a shorter period of morbidity at the end of life. Some of the mechanisms underlying these extra health years have been discovered.[8] Diet, exercise, and other lifestyle factors can certainly extend health, but to achieve the extraordinarily extended health of centenarians, drugs will likely be necessary. Some of the drugs mentioned above have shown interesting effects in humans. For example, acarbose not only prevents diabetes, it also prevents hypertension and cardiovascular events.[9] Rapamycin use improves vaccine response in the elderly, demonstrating that this age-targeting drug may have a specific indication in immune deficiency of older persons. Metformin has shown particular promise in humans as well as in animal models, with published clinical trials and cohort studies reporting substantial reductions (up to 30%) in the risk of type 2 diabetes, cardiovascular disease, and cognitive decline.[10] Similar reductions have been reported for cancer, dementia, and total mortality in observational studies. Metformin has shown an excellent safety profile across more than 60 years of use and is an inexpensive generic drug for treatment of type 2 diabetes.

Challenges in Targeting Aging

While geroscience has been exciting for the biological community and has resulted in important studies in experimental animal models, its significance has trickled only slowly to the medical community at large. One major challenge for improving human health by treating aging processes is that from a regulatory perspective (eg, the US Food and Drug Administration) there is no indication that is similar to targeting aging. Even if safe and effective drugs are available, health care payers will be reluctant to pay for such treatment without regulatory approval. Consequently, for now, drug companies are reluctant to invest in treatments targeting aging. Regulatory changes and further development of more drugs and drug combinations will be needed to start making major strides in improving human health. In the meantime, the so-called antiaging therapies are not regulated and may cause more harm than help because they are unsupervised and lack clinical data support. This is a challenge that geroscientists have taken up in the hope of changing the aging process in the next decades.

ARTICLE INFORMATION

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