Biology of Aging

Aging is accompanied by gradual changes in most body systems. Research on the biology of aging focuses on understanding the cellular and molecular processes underlying these changes as well as those accompanying the onset of age-related diseases. As scientists learn more about these processes, experiments can be designed to better understand when and how pathological changes begin, providing important clues toward developing interventions to prevent or treat disease. A great deal has been learned about structural and functional changes that occur in different body systems, and progress is ongoing. Research has expanded our knowledge, too, of the biologic factors associated with extended longevity in humans and animal models. This section of the NIA's narrative discusses some recent advances in the biology of aging, on cloning and transplantation and on lifespan itself. Selected future research directions are described as well, including continuing efforts to find biologic interventions to promote healthy aging, to understand the genetic basis of aging, and to explore the potential of adult stem cells and cell replacement for reducing disease and improving function.

Cloning and Transplantation Strategies

There is enormous interest in the potential uses of cloning, gene therapy, and adult stem cell transplantation, as well as tissue transplantation, to combat diseases of aging. Cloning cells or animals could lead to new advances in medicine and agriculture, and each of these new techniques could lead to strategies to replace tissues and organs lost through disease.

Cloning Resets the Telomere Clock in Cattle. An important question in cloning research is whether cloned cells or organisms created from old or senescent cells will be biologically older than their normal counterparts. Telomeres are highly repetitive DNA sequences located at the end of chromosomes, and telomere length is associated with cell age. As cells divide, telomere length gets progressively shorter until eventually, proliferation stops entirely. Such cells, which have ceased dividing, are called senescent. In a recent study, nuclei from senescent bovine fibroblasts were transferred into egg cells from which the nucleus had been removed. The nuclei were reactivated and the egg cells were implanted into cows. Healthy calves were born, and were found to have telomere lengths that are more typical of young than old animals. Thus, telomere length was reset during gestation. Whether this will affect the lifespan of the cloned calves will not be known for many years; however it does appear from these data that cloned offspring in some, if not all, species will not be biologically older than normal offspring. Such information will be useful in developing cell replacement intervention strategies to restore cells damaged or lost through disease.

Cell Transplantation and Aging. An alternative to tissue or organ transplantation that appears to have great potential is formation of functional tissue from cell transplants. Recent research has shown that isolated cow or human adrenal gland cells inserted into immunodeficient mice formed functional adrenal tissue that resembles normal adrenal gland. This approach may potentially be used for any organ, either to study its functional regeneration in a living organism with age or to therapeutically regenerate lost function as in a case, for example, when defective genes might be replaced in cells isolated from a patient and then placed back into the same patient for tissue regeneration. This technique can also reduce the need for immunosuppressive therapies and offers an alternative to adult stem cell therapies.

Understanding and Extending the Lifespan

In order to understand the aging process, it is important to identify those factors that affect the overall lifespan of an organism. In mammals, there is a progressive physiologic decline with aging that is often accompanied by disease and disability. Understanding the responsible physiological mechanisms and, further, identifying ways to slow down age-related changes are important. Beyond any gains in lifespan, studies in this area are aimed more importantly at developing interventions to keep older people healthy and free of disease and/or disability as long as possible. Experiments in a number of animal models are providing valuable insights.

Extension of Average Lifespan of Nematodes by Pharmacological Intervention. It is widely accepted that oxidative stress is a factor in aging. To date, however, it has not been demonstrated convincingly that natural antioxidants such as vitamins C and E or ß-carotene extend lifespan in model experiments with mice, fruit flies, or nematodes (a kind of worm). Varied results have been obtained in genetically altered fruit flies over-expressing either superoxide dismutase (SOD) or SOD and catalase, enzymes that reduce oxidative damage. Now, an artificial compound, EUK-134, which mimics both SOD and catalase activity, has been shown to increase the average lifespan of nematodes by about 50%. EUK-134 also reversed premature aging in a nematode strain subject to elevated oxidative damage. These results strongly suggest that oxidative stress is a major factor in rate of aging in the nematode, and that this rate can be slowed by pharmacological intervention. It may be that similar compounds could lessen oxidative stress in humans and delay or reduce age-related pathology.

Genetically Mimicking Caloric Restriction (CR) Significantly Extends Yeast Lifespan. CR has been shown to significantly extend lifespan in a variety of organisms. In organisms studied to date (yeast, nematodes, fruit flies, mice and rats), CR increased both mean and maximum lifespan, as well as significantly reducing signs of disease. In all species examined, the extended longevity and health of the animals was accompanied by changes in the regulation of energy metabolism. Recent research has determined that genetic manipulation of glucose availability, metabolism, and signaling pathways can mimic the longevity-extending effects of CR in the yeast model. This discovery makes the yeast model of aging and longevity a powerful tool for uncovering the underlying cellular and molecular mechanisms responsible for increased longevity and health span, with a view to developing effective interventions.

CR Increases Neurotrophic Factor Production in the Brain and Protects Neurons. Beyond extending lifespan, CR also reduces development of age-related cancers, immune and neuroendocrine alterations, and motor dysfunction in rodents. Recent animal model studies of neurodegenerative disorders provide the first evidence that CR can also increase resistance of neurons to age-related and disease-specific stresses. One possible mechanism is that the mild metabolic stress associated with CR induces cells to produce proteins that increase cellular resistance to disease processes. Indeed, CR increases production of one such protein, a neuronal survival factor, BDNF. BDNF signaling in turn plays a central role in the neuroprotective effect of CR. This work suggests that CR may be an effective approach for reducing neuronal damage and neurodegenerative disorders in aging, providing insight into the design of approaches that might mimic CR's beneficial consequences.

Use of Gene Expression Microarrays in Aging Research. Aging is normally accompanied by changes in expression, or activity, of a large number of genes, but it is not clear which of these changes are critical in the aging process. Gene expression microarrays, which allow profiling the activity of many thousands of genes at once, provide an opportunity to obtain a more complete picture of what these changes are, and to design tests of whether these changes are causally associated with aging. In three recent studies, investigators looked at differences in gene expression patterns in young and old mouse skeletal muscle, liver, and brain tissue and also made several observations on changes brought about by caloric restriction. Though the data analyses are complex, some initial observations are: (1) aging results in lower levels of activity of metabolic and biosynthetic genes; (2) aging is accompanied by patterns of gene expression that are indicative of stress responses, including inflammatory and oxidative stress; (3) many, but not all, age-related changes in gene expression in mouse liver and skeletal muscle are slowed by caloric restriction; and (4) caloric restriction appears to increase expression of genes for repairing and/or preventing damage to cellular macromolecules. Microarray technology is proving to be an efficient approach to answering longstanding important questions about molecular mechanisms of aging and how these may be manipulated, for example, by calorie restriction. Profiling changes in gene activity may eventually provide useful biomarkers of the aging process itself, markers that might be important in assessing the effectiveness of strategies to retard aging-related processes.

Selected Future Research Directions in the Biology of Aging

Biological Interventions To Promote Healthy Aging. Counteracting the effects of aging by hormonal and dietary supplements, including estrogen, testosterone, human growth hormone, melatonin, and DHEA (dehydroepiandrosterone), is an area of active study. There are concerns that many middle-aged and older people may be taking such agents, before safety and efficacy of these substances for so-called "anti-aging" purposes have been adequatelyassessed. Although levels of some hormones may decline with age, maintaining levels that are normal at younger ages may not be needed, or even desirable, as a person grows older. Even if effective, supplementation may entail risks. More research is needed to determine how the biologic action of these hormones changes in older people and to assess whether replacement of these hormones will improve health.

CR is another biological intervention that may promote healthy aging. Some of CR's effects on longevity have been linked to changes in specific metabolic pathways. Studies are now planned to define the role of energy metabolism and metabolic regulation in mammalian aging, longevity and age-related disease, and uncover the cellular and molecular mechanisms that may be regulating aging processes, including those affected by CR. Most recently, researchers have identified changes in physiologic function in calorically restricted rhesus monkeys that suggest delays in aging-related decline. At this point, the effects of voluntary CR on lifespan and development of age-related diseases in humans are unknown. Preliminary human intervention studies are being designed to determine whether CR and physical activity differ in their long-term effects on obesity, body composition, prevention and susceptibility to age-related diseases.

Understanding the Genetic Basis of Aging, Longevity, Disease, and Behavior. Interactions between genetic and environmental factors are major determinants of aging and longevity in many species, including humans. NIA studies have begun to reveal the biologic factors associated with extended longevity in humans and animal models, implicating numerous genes in normal aging processes, age-related pathologies and diseases, and longevity. Some of these genes are associated with dramatic extension of lifespan. Using advanced technology, the NIA plans to accelerate its efforts to discover additional age- and longevity-related genes and to characterize their biological function. A new research initiative will extend studies of longevity-associated genes, changes in gene expression patterns, and the genetic epidemiology of human longevity. The ultimate goal of this effort is to develop interventions to reduce or delay age-related degenerative processes in humans. In addition, revolutionary advances in the fields of quantitative and molecular genetics hold great promise in the search for the genetic determinants of complex behaviors. Studies in humans can help identify the relative contributions of environment and heredity to dementia, cognitive abilities, physical functioning, well being, and social aging. New techniques can track the developmental course of genetic contributions to behavior, identify genetic heterogeneity, and explore genetic links between the normal and abnormal. Basic research will explore error accumulation in DNA with age and how the cell repairs such damage.

Exploring the Potential of Adult Stem Cells and Cell Replacement in Aging. Stem cells in adult human tissues retain the capacity for self-renewal and the potential to become many of the cell types in the human body. This capacity holds enormous potential for cell replacement or tissue repair therapy in many degenerative diseases of aging, including AD, PD, stroke, myocardial infarction, musculoskeletal disorders, immune system dysfunction, and diabetes. Emerging research findings suggest that it may be possible to harness the multipotential nature of adult stem cells to maintain tissue structure and function in aging. Much remains to be learned, however, about the basic biology of stem cells in animal models before effective cell therapy can be realized. The NIA is developing an research initiative on changes in stem cells and their environment with aging in animal models and in human nonfetal tissues. This research initiative will complement as well as encourage collaboration with other components of NIH.

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