infoaging guides

BIOLOGY OF AGING

ANIMAL MODELS IN AGING RESEARCH

An introduction to aging science brought to you by the American Federation for Aging Research

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THE IMPORTANCE OF ANIMAL MODELS

Research into the processes of aging carries unique challenges. Although we have a distinct interest in understanding human aging, our already long life span makes designing experiments that use people as subjects cumbersome and largely impractical. Ethical questions also arise in human studies. Can scientists ethically withhold promising treatments in order to have a control group for comparisons? Can we rely on results obtained when no control group exists?

And so scientists have turned to animal models. Exciting research is taking place in a variety of species, from yeast to our nearest animal relatives, the primates. Through such work, researchers are elaborating on their theories of how and why we age. They are beginning to develop therapeutic or treatment models that modify aging in these other life forms in the hope of finding similar treatments for the diseases of human aging.

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WHICH ANIMAL MODELS OF AGING ARE USED IN RESEARCH?

Several species of animals have figured prominently in aging research. Much of this research has focused on the genetic basis of aging, and on learning more about physiological pathways that regulate the rate of aging and set the stage for age-related illnesses. Aging is a process that involves both a decline in the function of an organism and a greater risk of the diseases associated with growing older. Researchers have identified animal genes that influence life span, some of which modify the aging process as a whole, others of which act by increasing or decreasing diseases of aging. Some of the most well studied organisms include:

Yeast

Baker's yeast (*Saccharomyces cerevisiae*) is a much-studied primitive organism. Although yeast is not an animal (it is a single-celled fungus), it shares so much in common with animals, at least at the cellular and genetic levels, that it serves as a useful model. Because of its short life span, yeast makes an ideal research subject. Scientists have known for some time that restricting caloric intake will increase life span in a number of animal species; recent work has shown that this is also true in yeast. New genetic studies that are looking at every yeast gene, one at a time, have found evidence for yeast genes that delay aging in dividing yeast, in resting yeast

cells, or in both. Some of these make the yeast cells resistant to oxidative damage (in a process similar to rusting) and to other kinds of stress, consistent with evidence that stress-resistance genes might influence aging in multicellular organisms as well.

Mammals have genes that correspond to some of those associated with longer life in yeast, and an understanding of the workings of the yeast genes should further our understanding of the mammalian ones.

The development of genomic methods for studying yeast longevity represents another significant advance in aging research. These methods, which look across the entire genetic makeup of an organism rather than the relatively small number of genes previously identified as being associated with aging, are already yielding results. For example, They have already identified several cell signaling pathways as having an important effect both on lifespan and on the number of times a yeast cell can replicate. A signaling pathway is a complex set of communications that help control basic cellular activities.

Roundworms

Caenorhabditis elegans is a roundworm with a 20-day life span, making it a good subject for research. More than 400 genes that extend lifespan in roundworms have been described. Among the genetic controls studied are a series of interacting proteins that act like insulin and control reproduction and longevity. Investigators have also looked at a mechanism controlled by a group of genes called clock genes. These regulate metabolism in the roundworm and affect lifespan. The roundworm genes that seem to confer increased longevity do so by supporting resistance to external stresses, such as bacterial infections, high temperatures, radiation, and oxidative damage. Oxidative damage results when the toxic byproducts of oxygen metabolism damage the components of cells (see Oxidative Damage Research Center).

Some research in roundworms has focused on the gene that regulates the activity of COQ7, a particular type of protein that plays a crucial role in electron transport within cellular organs (organelles) called mitochondria that produce energy. Investigators have discovered that mutations that diminish COQ7 lead to a modest increase in life span. These mutations have a bigger effect when combined with other mutations, such as those in the insulin pathway mentioned above, and affect resistance to oxidative damage.

Other research has examined different gene-protein combinations. For example, Thomas Johnson, a scientist at the Institute of Behavioral Genetics, University of Colorado at Boulder, has studied a variant of roundworms that possess a gene labeled DAF-16. These mutant worms carry large amounts of DAF-16 in their nuclei, which cause the worms to live longer than worms without an excess of DAF-16. Although the explanation for this phenomenon is still unknown, it does offer an opportunity to screen drugs to see if they increase nuclear levels of DAF-16. If certain drugs can increase the amount of DAF-16, then they might be beneficial in increasing life span.

The correlation between the existence of roundworm genes and their mammalian counterparts suggests that the roundworm will continue to be a valuable animal model for the study of aging.

Fruit flies

Drosophila melanogaster, or the fruit fly, is a favorite subject for studies on longevity. Researchers have identified one gene that they have named Methuselah, which can increase fruit fly life span by 35 percent. Molecular physiologist Xin-Yun Huang of Cornell University's Weill Medical College in New York City has been conducting research to uncover what activates the Methuselah protein. Huang and his team found that

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another protein, the Sun protein, binds to Methuselah and alters fly longevity. Flies with a disabled copy of the Sun gene lived 50 percent longer than control flies.

A number of studies on a fruit fly gene called Indy (for "I'm Not Dead Yet") have been published. Various mutations in that gene result in a doubling of the average life span, without any loss of fertility or physical activity. Loss of the mutation returns life span to a normal length. The protein that the Indy gene produces is closely related to a human protein active in energy production. Because the fruit fly has genes such as Indy that produce proteins very much like human proteins, it makes an excellent animal model for aging research.

Rodents

Mice and rats are favorite subjects of scientists interested in human aging. Because they are mammals, they are more closely related to us than yeast, flies, or worms, and their relatively small size and short life span make them easier to study than long-lived animals. Much of the excitement in recent aging research has come from discoveries that aging can be postponed in mice or rats by very low calorie diets, and by discoveries of mutant genes that can extend life span by as much as 50 percent. (For comparison, the complete conquest of cancer would extend average human life span by about 3 percent.) Some of these genes interfere with responses to certain hormones, while others make cells within the mouse more resistant to injury and death. Studies of these slow-aging mice and rats might prove helpful in the development of drugs that could prevent late-life diseases and disabilities by mimicking the effects seen in the mice.

Through targeted genetic manipulation, researchers have already created genetic lines of mice that model Werner's syndrome (premature aging), Alzheimer's disease, other neurodegenerative conditions, atherosclerosis, diabetes, immune dysfunction, musculoskeletal disorders, oxidative stress, and many other medical conditions associated with aging. These mouse models are currently providing novel insights into aging processes.

Other studies are using mice engineered to make them particularly vulnerable to DNA damage or to damage to their mitochondria (energy producing "organs" inside cells). By studying these vulnerable mice, scientists are gathering new clues to the ways in which DNA or mitochondrial damage might contribute to the diseases of aging.

The growing interest in mouse aging and genetics has been strongly stimulated by the sequencing of the mouse and human genomes and by the realization that most human genetic diseases can be modeled by changes in equivalent genes in these rodents. The fact that aging can be slowed by dietary or genetic changes in mice is fueling new enthusiasm for the use of this model mammal as a guide to human aging.

Nonhuman Primates

The discovery that fruit flies and roundworms carry genes that affect their longevity is exciting, particularly because many of those genes have human counterparts. However, the fact remains that the complexity of human physiology can't be replicated in simpler organisms such as fruit flies and roundworms. But our DNA is very similar to that of nonhuman primates such as monkeys and apes. And it is nearly identical to that of chimpanzees. The National Institute on Aging (NIA) is sponsoring an extensive series of experiments into aging and longevity using primate models, including rhesus and squirrel monkeys. Rhesus monkeys are particularly useful because the rate of aging in rhesus monkeys is three times as fast as the rate in humans. For this reason and because rhesus monkeys are well adapted for laboratory research, the NIA supports colonies of aging rhesus monkeys at five primate research centers in the United States. Research at these NIA sites is complemented by ongoing longitudinal studies taking place at the Wisconsin National Primate Research Center and the University of Maryland, Baltimore.

Primate studies are ongoing in neurobiology, skeletal deterioration, reproductive aging, and other age-related diseases such as heart disease and diabetes. Results from studies of caloric restriction and its impact on aging in primates are starting now becoming available.

Birds
Studies of aging in birds have disproved the old assumptions about metabolic rates and aging. Birds have very high metabolic rates, body temperatures and blood sugar levels, and yet some species are among the most long-lived of all animal species. Some seabird species show very slow age-related declines in survival and in reproductive success. Some researchers believe that birds age slowly because they mature late, and because some species have low fecundity. Research is coming out that suggests that birds have mechanisms to protect them from oxidative damage and that they can regenerate some neurons in their brains. However, even though birds seem to age slowly, their patterns of aging and of disease development are in many ways similar to those of mammals, and so studying them may uncover revelations about the aging process in humans.

Until recently, modern biomedical research was unable to perform targeted genetic manipulations in birds. But the discovery of the whole genome sequence of two bird species and the development of new genetic engineering techniques is helping scientists over this barrier.

At least five bird species deserve special attention for development as models of successful aging:

- Budgerigars
- Canaries
- Zebra finches
- European starlings
- House sparrows

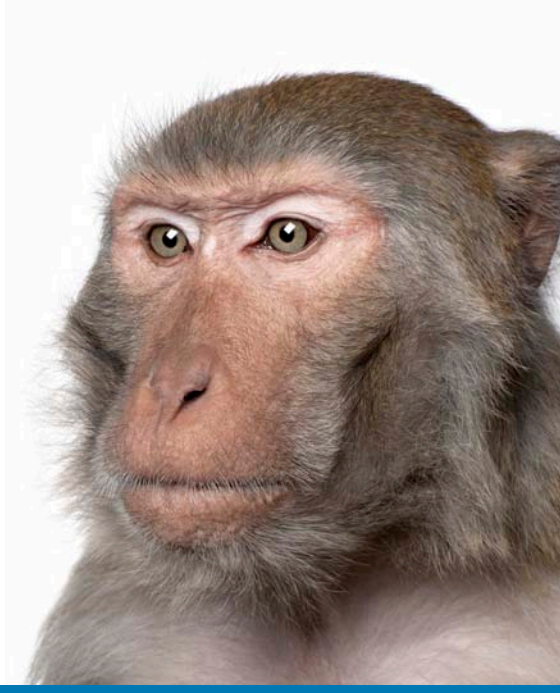
THE FUTURE OF ANIMAL MODELS

A greater understanding of the mechanisms of caloric restriction that slow aging could help scientists understand how to accomplish the same physiological changes without diminishing caloric intake. One solution involves developing a calorie restriction mimetic (CRM)—a pill that mimics the physiological effects of eating less without actually forcing the organism to starve itself.

The National Institute on Aging has established the Interventions Testing Program to test substances predicted to "extend lifespan and delay disease and dysfunction." So far, about a dozen agents have been investigated, with results ranging from good to mixed. The program uses three test sites (the University of Michigan, the Jackson Laboratories and the University of Texas Health Sciences Center at San Antonio). Each candidate compound is tested for longevity effects in a sufficient sample size of mice to detect a 10 percent change in mean lifespan.

Scientists will continue to use animal models in researching the causes and treatment of specific age-related illnesses. Including cancer, cardiovascular disease, osteoarthritis, osteoporosis, Alzheimer's disease, kidney disease, and others.

Finally, much of the aging process in humans and other animals involves a loss of function. For example, we lose muscle mass with age. Animal models that permit us to understand this process might permit us to develop useful treatments or better still, preventive measures.



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