

Aging Theory Card 1

Tracking Down a Longevity Gene

“Investigators are finding clues to aging and longevity in yeast, one-celled organisms that have some intriguing genetic similarities to human cells. In a laboratory at Louisiana State University Medical Center in New Orleans, Michal Jazwinski has found genes that seem to promote longevity in these rapidly dividing, easy-to-study organisms.

Yeast normally have about 21 cell divisions or generations. Jazwinski observed that over the course of that "life span," certain genes in the yeast are more active or less active as the cells age; in the language of molecular biology, they are differentially expressed. So far, Jazwinski has found 14 such genes in yeast.

Selecting one of these genes, Jazwinski tried two different experiments. First, he introduced the gene into yeast cells in a form that allowed him to control its activity. When the gene was activated to a greater degree than normal, or overexpressed, some of the yeast cells went on dividing for 27 or 28 generations; their period of activity was extended by 30 percent.

In his second experiment, Jazwinski mutated the gene. When he introduced this non-working version into a group of yeast cells, they had only about 12 divisions.

The two experiments made it clear that the gene, now called LAG-1, influences the number of divisions in yeast or, according to some researchers' ways of thinking, its longevity. (LAG-1 is short for longevity assurance gene.) But how it works is still a mystery. One small clue lies in its sequence of DNA bases -- its genetic code -- which suggests that it produces a protein found in cell membranes. One next step is to study the function of that protein. Similar sequences have been found in human DNA, so a second investigative path is to clone the human gene and study its function. If there turns out to be a human LAG-1 counterpart, new insights into aging may be uncovered.”

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In the Lab of the Long-Lived Fruit Flies

“A laboratory at the University of California, Irvine, is the home of thousands of *Drosophila melanogaster* or fruit flies that routinely live for 70 or 80 days, nearly twice the average *Drosophila* life span. Here evolutionary biologist Michael Rose has bred the long-lived stocks by selecting and mating flies late in life.

To begin the process of genetic selection, Rose first collected eggs laid by middle-aged fruit flies and let them hatch in isolation. The progeny were then transferred to a communal plexiglass cage to eat, grow, and breed under conditions ideal for mating. Once they had reached advanced ages, the eggs laid by older females (and fertilized by older males) were again collected and removed to individual hatching vials. The cycle was repeated, but with succeeding generations, the day on which the eggs were collected was progressively postponed. After two years and 15 generations, the laboratory had stocks of *Drosophila* with longer life spans.

The next question is what genes and what gene products are involved? Since the first experiments, Rose has bred longer life spans into fruit flies by selecting for other characteristics, such as ability to resist starvation, so the flies' long life spans are not necessarily tied to their fertility late in life.

One possibility is that the anti-oxidant enzyme, superoxide dismutase (SOD), is involved. In another laboratory at Irvine, the late Robert Tyler discovered that the longer-lived flies had a somewhat different form of the SOD gene, which was more active than its counterpart in the flies with average life spans. This finding has given a boost to the hypothesis that anti-oxidant enzymes like SOD are linked to aging or longevity.”

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Aging Theory Card 2

Scientists extend the life span of human cells

DALLAS -- Jan. 13, 1998 --

Researchers at UT Southwestern Medical Center at Dallas and their colleagues at Geron Corp., Menlo Park, Calif., say they have figured out how to overcome the mechanisms that control cellular aging and extend the life span of human cells.

In the Jan. 16 issue of *Science*, Drs. Woodring Wright and Jerry Shay, UT Southwestern professors of cell biology and neuroscience, and their collaborators report finding that the enzyme telomerase -- which UT Southwestern scientists call a "cellular fountain of youth" -- causes human cells grown in the laboratory to retain their "youth" and continue to divide long past the time when they normally stop dividing.

Normal human cells have a limited capacity to proliferate. After a certain finite number of cell divisions, time on the biological clock runs out; the cells "age" and stop dividing. Time remaining in a cell's life correlates with the length of the telomeres -- repeated sequences of DNA on the ends of chromosomes that protect the tips from degradation. In normal cells, telomeres shorten with each cell division. Although some have thought that this telomere shortening might be the biological clock's control mechanism, the hypothesis was controversial. The research now proves that human cells grow older each time they divide because their telomeres shorten.

Specialized reproductive cells and most cancer cells appear to divide indefinitely. They contain the enzyme telomerase, which adds back telomeric DNA to the ends of chromosomes. Most normal cells do not have this enzyme.

"We have found that cellular aging can be bypassed by the introduction of the catalytic component of the immortalizing enzyme telomerase," Shay said. The expression of telomerase in normal human cells should extend their lifespan indefinitely. From a basic research point of view, we could begin to replace the abnormal tumor-cell lines now being used to study biochemical and physiological aspects of growth and differentiation with normal, yet immortal cell lines.

The scientists introduced telomerase into normal human cells to see if the cells' life spans could be prolonged. The cells with telomerase extended the length of their telomeres, divided for 20 additional generations past the time they normally would stop dividing and are continuing to divide. The cells also grew and divided in a normal manner, giving rise to normal cells with the normal number of chromosomes. By all accounts these cells had found their fountain of youth.

"The extension of normal cell lifespan in a youthful state by telomerase is a dramatic confirmation of the telomere hypothesis and one that presents numerous opportunities for biotechnology and medicine," said Dr. Calvin Harley, Geron vice president and chief scientific officer.

One immediate use of finding that telomere shortening controls cellular aging may be in the area of producing engineered products in human cells. Instead of using uncharacterized primary human-cell cultures to produce vaccines or other biological products, one should now be able to produce products in a re-engineered normal human cell-type that does not change, Wright said.

"This research raises the possibility that we could take a patient's own cells, rejuvenate them, then modify the cells as needed and give them back to the patient to treat a variety of genetic and other diseases," Wright said. "The potential long-term applications are simply staggering."

Other investigators on the project included Drs. Andrea Bodnar, Maria Frolkis, Choy-Pik Chiu, Gregg B. Morin, Calvin Harley and Serge Lichtsteiner of Geron Corp.; and Drs. Michel Ouellette and Shawn Holt, research fellows in UT Southwestern's Department of Cell Biology and Neuroscience. The research was funded in part by the National Institutes of Health.

Reprinted from
The University of Texas Southwestern Medical Center at Dallas
<http://www.swmed.edu/news/lifespan.htm>

Aging Theory Card 3

“Demolishing proteins and damaging nucleic acids, oxygen radicals are thought to be the villains in the day-to-day life of cells. The free radical theory of aging, first proposed by Denham Harman at the University of Nebraska, holds that damage caused by oxygen radicals is responsible for many of the bodily changes that come with aging. Free radicals have been implicated not only in aging but also in degenerative disorders, including cancer, atherosclerosis, cataracts, and neurodegeneration.

A free radical is a molecule with an unpaired, highly reactive electron. An oxygen-free radical is a byproduct of normal metabolism, produced as cells turn food and oxygen into energy.

In need of a mate for its lone electron, the free radical takes an electron from another molecule, which in turn becomes unstable and combines readily with other molecules. A chain reaction can ensue, resulting in a series of compounds, some of which are harmful. They damage proteins, membranes, and nucleic acids, particularly DNA, including the DNA in mitochondria, the organelles within the cell that produce energy.

But free radicals do not go unchecked. Mounted against them is a multilayer defense system manned by anti-oxidants that react with and disarm these damaging molecules. Anti-oxidants include nutrients -- the familiar vitamins C and E and beta carotene -- as well as enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. They prevent most, but not all, oxidative damage. Little by little the damage mounts and contributes, so the theory goes, to deteriorating tissues and organs.

Support for the free radical theory comes from studies of anti-oxidants, particularly SOD. SOD converts oxygen radicals into the also harmful hydrogen peroxide, which is then degraded by another enzyme, catalase, to oxygen and water.”

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Anti-Oxidants and Aging Gerbils

“A boost for the hypothesis that high levels of anti-oxidants can slow the aging process comes from a study of N-tert-butyl-alpha-phenylnitrone or PBN in gerbils. Although it does not occur naturally in the body, PBN works in much the same way as beta-carotene and other anti-oxidants by binding and neutralizing free radicals.

Older gerbils had been shown to have increased levels of oxidized protein in their brains by two researchers, Robert A. Floyd at the Oklahoma Medical Research Foundation and John M. Carney at the University of Kentucky. Curious about the effects of anti-oxidants in older animals, Floyd and Carney designed an experiment to learn whether PBN could lower oxidized protein levels in gerbils' brains. Over a period of 14 days they gave PBN to two groups of gerbils, one made up of young adults, the other of older adults.

As the older gerbils were treated with PBN, their levels of oxidized protein decreased until they were nearly comparable to levels found in the younger animals. After treatment ended, oxidized protein gradually returned to pretreatment levels. PBN had no effect on the young gerbils.

While it is only one study and more are needed, this investigation supports the idea that maintaining anti-oxidant defense levels may be critical during aging. It also suggests that an intervention such as PBN may someday provide the means.”

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Aging Theory Card 4

Research on Sunlight May Help Explain What Happens to Skin as We Age

“As anyone who reads beauty magazines knows, sunlight damages skin in ways that seem similar to aging. It causes wrinkles, to begin with. And in both normal aging and photoaging -- the process initiated by sunlight -- the skin becomes drier and loses elasticity. Although gerontologists think that the normal or intrinsic aging process is probably not the same as photoaging, there are enough similarities to make this a tantalizing field of study.

The process of photoaging may hold clues to normal aging because many of the same cells are affected. Photoaging, for example, damages collagen and elastin, the two proteins that give skin its elasticity. These proteins decline as we age, along with the fibroblast cells that manufacture them. In addition, the enzymes that break down collagen and elastin increase.

Other changes occur in keratinocytes, upper-layer skin cells that are shed and renewed regularly. In the normal aging process the turnover of keratinocytes slows down and in photoaging, they are damaged. Still other skin cells, called melanocytes, are also affected by both processes: they decline with normal aging, are killed in photoaging. (Stopped in their tracks by sunlight, these normally migratory cells show up as freckles in light skin.)

What we don't know yet is exactly how photoaging damages cells. Ultraviolet light can damage DNA and could be the culprit. Free radicals could be involved in some way. Researchers continue to explore these and other factors in the effort to understand photoaging.”

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Heat Shock Proteins

“Despite their name, heat shock proteins (HSPs) are produced when cells are exposed to various stresses, not only heat. Their expression can be triggered by exposure to toxic substances such as heavy metals and chemicals and even by behavioral and psychological stress.

What attracts aging researchers to HSPs is the finding that the levels at which they are produced depend on age. Old animals placed under stress -- physical restraint, for example -- have lower levels of a heat shock protein designated HSP-70 than young animals under similar stress. Moreover, in laboratory cultures of cells, researchers have found a striking decline in HSP-70 production as cells approach senescence.

Exactly what role HSPs play in the aging process is not yet clear. They are known to help the cell disassemble and dispose of damaged proteins and to facilitate the making and transport of new proteins. But what proteins are involved and how they relate to aging is still the subject of speculation and study.

Researchers like Nikki Holbrook at the NIA's Gerontology Research Center in Baltimore, Maryland, are investigating the action of HSP-70 in specific sites, such as the adrenal cortex (the outer layer of the adrenal gland). Here, and in blood vessels and possibly other sites, the expression of HSP-70 appears to be closely related to hormones released in response to stress, such as the glucocorticoids and catecholamines. Eventually, answers to the puzzle of heat shock proteins may throw light on some parts of the neuroendocrine system, whose hormones and growth factors also appear to be major factors in the aging process.”

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Aging Theory Card 5

Hormones

“In 1989, at Veterans Administration hospitals in Milwaukee and Chicago, a small group of men aged 60 and over began receiving injections three times a week that dramatically reversed some signs of aging. The injections increased their lean body (and presumably muscle) mass, reduced excess fat, and thickened skin. When the injections stopped, the men's new strength ebbed and signs of aging returned.

What the men were taking was recombinant human growth hormone (GH), a synthetic version of the hormone that is produced in the pituitary gland and plays a critical part in normal childhood growth and development. Now researchers are learning that GH, or the decline of GH, seems also to play a role in the aging process in at least some individuals.

The idea that hormones are linked to aging is not new. We have long known that some hormones decline with age. Human growth hormone levels decrease in about half of all adults with the passage of time. Production of the sex hormones estrogen and testosterone tends to fall off. Hormones with less familiar names, like melatonin and thymosin, are also not as abundant in older as in younger adults.”

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Hormones and Research on Aging

“Produced by glands, organs, and tissues, hormones are the body's chemical messengers, flowing through the blood stream and searching out cells fitted with special receptors. Each receptor, like a lock, can be opened by the specific hormone that fits it and also, to a lesser extent, by closely related hormones. Here are some of the hormones and other growth factors of special interest to gerontologists.

Estrogen. The female hormone, estrogen is used in hormone replacement therapy to relieve discomforts of menopause. Produced mainly by the ovaries, it slows the bone thinning that accompanies aging and may help prevent frailty and disability. After menopause, fat tissue is the major source of a weaker form of estrogen than that produced by the ovaries.

Growth Hormone. This product of the pituitary gland appears to play a role in body composition and muscle and bone strength. It is released through the action of another trophic factor called growth hormone releasing hormone, which is produced in the brain. It works by stimulating the production of insulin-like growth factor, which comes mainly from the liver. All three are being studied for their potential to strengthen muscle and bones and prevent frailty among older people.

Melatonin. This hormone from the pineal gland responds to light and seems to regulate various seasonal changes in the body. As it declines during aging, it may trigger changes throughout the endocrine system.

Testosterone. The male hormone, testosterone is produced in the testes and may decline with age, though less frequently or significantly than estrogen in women. Researchers are investigating its ability to strengthen muscles and prevent frailty and disability in older men when administered as testosterone therapy. They are also looking at its side effects, which may include an increased risk of certain cancers, particularly prostate cancer.

DHEA. Short for dehydroepiandrosterone, DHEA is produced in the adrenal glands. It is a weak male hormone and a precursor to some other hormones, including testosterone and estrogen. DHEA is being studied for its possible effects on selected aspects of aging, including immune system decline, and its potential to prevent certain chronic diseases, like cancer and multiple sclerosis.”

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Aging Theory Card 6

The Immune System

“When Sherechiyo Izumi contracted pneumonia and died at the age of 120, it was his immune system that failed. One of the many bacteria or viruses that cause pneumonia broke through the elaborate, natural defenses that protect humans from infection. Scientists have long known that these defenses decline with age; now, some of the underlying mechanisms are coming to light.

A multiplicity of cells, substances, and organs make up the immune system. The thymus, spleen, tonsils, bone marrow, and lymphatic system, for example, produce, store, and transport a host of cells and substances -- B-lymphocytes and T-lymphocytes, antibodies, interleukins, and interferon, to name a few. Several are of special interest to gerontologists. These include the white blood cells or lymphocytes, which fight invading bacteria and other foreign cells.

Lymphocytes fall into two major classes: B-cells and T-cells. B-cells mature in the bone marrow, and one of their functions is to secrete antibodies in response to infectious agents or antigens. T-cells develop in the thymus, which shrinks in size as people age; they are divided into cytotoxic T-cells and helper T-cells. Cytotoxic T-cells attack infected or damaged cells directly. Helper T-cells produce powerful chemicals, lymphokines, that mobilize other immune system substances and cells.

T-cells and their lymphokine products have intrigued gerontologists ever since it was learned that T-cells -- or more precisely the functioning population of T-cells -- declines with age. While the number of T-cells remains about the same, the proportion of them that proliferate and function declines. Studies have also shown that in older people, T-cells destroyed by trauma, such as burns, take longer to renew than they do in younger people.

Most research on the aging immune system now centers on these cells. One group of T-cell products, interleukins, occurs at different levels as people age. The interleukins -- there are about a dozen identified so far -- serve as messengers, relaying signals that regulate the immune response. Some, like interleukin-6, rise with age, leading to speculation that they interfere in some way with the immune response. Others, like interleukin-2, which stimulates T-cell proliferation, tend to fall with age.

Gerontologists continue to study the interleukins, not only for clues to the mechanisms of aging, but also for their potential in primary care. Findings to date suggest that tests for interleukins, though not yet available, may someday help in the detection and treatment of immune problems.

Another focus of research is the interaction of hormones and the immune system. DHEA, for example, has been shown to revive immune responses in aging animals (see Hormones and Research on Aging). Reducing estrogen levels depresses IL-2 levels. And two pituitary hormones, prolactin and growth hormone, may also be linked to the immune response. Pituitary tumor cells, implanted in aged rats, have induced the thymus to grow to its youthful size and increased the proportion of helper T-cells and other immune system cells.

While both the immune and the endocrine systems are undoubtedly involved in aging, researchers continue to search for the mechanisms to explain their effects. One approach to studying aging, caloric restriction, is expected to yield some clues.”

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Aging Theory Card 7

Caloric Restriction

“In a laboratory at the University of California at Los Angeles, thousands of mice are living to the advanced ages of 30 and 40 months or more -- far beyond their normal life spans. The fundamental reasons are not yet understood. It may have something to do with DNA repair rates, or free radical levels, or hormonal balance, or cell senescence, or all of these plus other mechanisms.

What is known is that the mice live on restricted diets? Fed 30 to 60 percent fewer calories than normal (but all the necessary nutrients), the mice survive months longer than mice on a normal feeding schedule.

The findings in this UCLA laboratory, headed by Roy Walford, are not isolated ones. In studies in other laboratories, again and again, undernutrition has increased the life spans of nearly every animal species studied -- protozoa, fruit flies, mice, rats, and other laboratory animals. Now researchers are investigating whether and how caloric restriction will affect aging in primates, human's closest relatives in the animal kingdom.

Particularly intriguing to many gerontologists are findings that animals on restricted diets have reduced rates of disease. In one of the largest studies to date, Roderick Bronson at Tufts University found that caloric restriction not only extended life span in mice, but also prevented or slowed down development of every disease and all types of tumors. These results, described as stunning by gerontologists, have raised hope that further study of caloric restriction will help uncover the mechanisms responsible for disease in old age.

However, whether or not caloric restriction would have the same effect in humans remains a major question. Studies with monkeys are underway at the National Institute on Aging, where rhesus and squirrel monkeys are growing up on a calorically restricted diet. At the University of Wisconsin, preliminary results in Richard Weindruch's laboratory show some promising early signs of improved health in aged monkeys kept on restricted diets.”

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The Next Step: Caloric Restriction in Primates

“At the NIH Animal Center in Poolesville, Maryland, about 75 rhesus and squirrel monkeys are on diets; they eat 30 percent less than they would normally but get all the necessary nutrients. Another 75 monkeys, the control group, are eating as much as they want or ad libitum. The differences between the two groups, as they reach maturity and begin to age, are expected to provide insights into how caloric restriction influences life span.

The monkeys that arrived at the Poolesville laboratory in 1987 have responded to caloric restriction as expected; their maturation, measured by factors such as skeletal development and onset of puberty, has been delayed by about a year or year and a half. This is comparable to the delays in maturation seen in calorically restricted rodents.

As the monkeys grow into young adulthood and beyond, George Ruth and his colleagues at the NIA's Gerontology Research Center in Baltimore, where the project is coordinated, will be monitoring dozens of signs of aging, ranging from immune response to activity level to anti-oxidant levels to fingernail growth. The measurements will be compared with those of the monkeys in the control group and should provide leads to some of the anti-aging mechanisms at work in caloric restriction.”

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Aging Theory Card 8

Behavioral Factors

“Salads in fast-food restaurants and low-fat labels in supermarkets signal a transformation in Americans' eating habits that is reflected in mortality rates. Deaths from heart disease have declined 45 percent in the United States since 1950, partly due to the switch to lower-fat, lower-cholesterol diets, and to other behavioral factors, like smoking cessation and exercise.

Diet and exercise, in particular, are thought to have a major impact on a constellation of changes that are common with advancing age. These include higher levels of fats or lipids in the blood, changing levels of blood sugar and insulin, a tendency toward obesity, and increased central body fat -- that which settles around the waist and abdomen. So common are these among older people that they have been given a name -- syndrome x -- and their relationship to heart and other cardiovascular diseases is the focus of many studies.

Syndrome x may be preventable through low-fat and low-cholesterol diets, but these are not the only aspects of nutrition that may influence life expectancy. Gerontologists have been scrutinizing a wide range of nutrients with an eye toward their role in aging processes. Calcium and vitamin D, for example, help reduce the thinning of bones that accompanies aging in almost everyone but particularly in older women, many of whom are at high risk for osteoporosis. Another nutrient, vitamin E, may be critical to the immune system, while beta carotene, vitamin C, and vitamin E appear to fight oxidative damage.

Startling to many experts is the finding that most older people are not getting the recommended daily allowances (RDAs) of some nutrients. The Baltimore Longitudinal Study on Aging found deficiencies among elderly people in calcium, zinc, iron, magnesium, vitamins B6, B12, D, and E, and folic acid, a finding confirmed at the USDA Human Nutrition Research Center on Aging. Nutritionists point out that precisely what the RDAs should be for older people is not clear.

Researchers are also studying exercise as a behavioral factor that may have an impact on how long we live -- or at least on how healthy we are in old age. One landmark study at Tufts has shown that exercise can strengthen muscles, improve mobility, and reduce frailty even among 90-year-olds.”

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Exercise at 90: It Works.

“Exercise is a powerful health promoter at any time of life. Even 80- and 90-year-olds can benefit, according to a study by Maria Fiatarone of the USDA Human Nutrition Center on Aging at Tufts University. Here is how Fiatarone described her findings to the House Select Committee on Aging in February 1991:

"Starting with a small group of ten 90-year-old residents of the Hebrew Rehabilitation Center for Aged in Massachusetts, we demonstrated that the muscle weakness and atrophy of aging were in fact not at all immutable. These residents increased their leg muscle strength by 174 percent and their muscle size by 9 percent after only 8 weeks of weight-lifting exercise. More importantly, as we have expanded this research to a much larger group of volunteers through the support of grants from the National Institute on Aging and others, it is clear that such training can improve walking speeds, mobility, independence in daily activities, and reduce dependence on canes, walkers, and wheelchairs in some individuals. At a cellular level, we now have preliminary evidence that this increased muscle function is accompanied by the actual growth of new muscle fibers, a finding never before demonstrated after strength training."

Rose Karsh, a participant in the study, described it from her point of view:

"When I finished the study I was able to lift 50 pounds with each leg which surprised me very much at my age. After the test was over I was able to walk around the center without any assistance, and it made me feel very proud that I could do that. It made me feel younger and gayer. I use my cane to protect myself from falling only when I walk outside. I don't have to use a walker."

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