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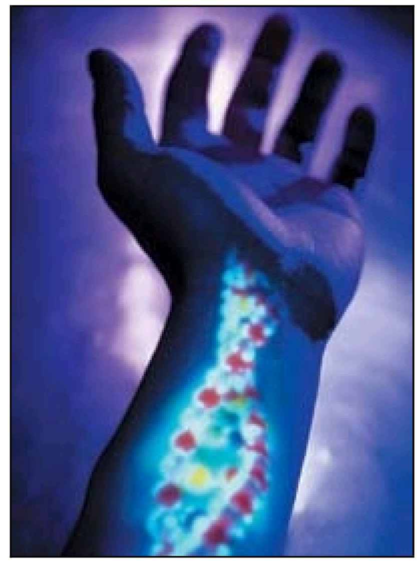
REPORT

Discovering The Genetic Controls That Dictate Life Span
Profile of Cynthia Kenyon, Ph.D.



Single-celled organisms don't ever really die of old age; they divide to produce offspring, making the dividing organism both parent and child. Barring external events that might squelch out a line of these microscopic creatures, they can renew themselves indefinitely. More complex organisms-including humans-pay a dear price for their complexity: they age and die. It seems that passing our genes on to our progeny via germ cells (sperm and egg) essentially makes the rest of the cells that comprise us obsolete. It follows that we age and die once we lose our capacity to reproduce.

By Melissa Block

Cynthia Kenyon, Ph.D. Professor of Biochemistry and Biophysics, University of California, San Francisco

The question remains, What exactly causes cells to age? What causes the loss of organ function that eventually leads to breakdown and demise, often with a period of chronic degenerative illness in between? Scientists have identified several possible mechanisms. Some are based on the concept that aging is caused by cellular wear and tear, while others focus on genetically programmed “aging clocks” that kick in at a predetermined point of an organism’s life span. Theories involving wear and tear include free radical stress, the accumulation of cellular wastes, the binding of sugars to proteins (glycation), the shortening of chromosomes with each cellular division (eventually leading to the activation of an as yet unexplained self-destruct mechanism), or the deterioration of the tiny ‘engines’ that power each cell (mitochondria). Although there is substantial evidence that all of these factors come into play during the aging process, are these factors causes of aging, or are they effects of a pre-programmed genetic code designed to limit life span?

It is becoming ever more apparent that the manipulation of specific genes may be our ticket to immortality. It has long been suspected that the DNA within the cells of complex organisms is designed to senesce and die once reproductive viability is past.[1] Genetic theories of aging imply that by changing the activity of certain genes, we might be able to alter the body’s inherent aging clock. With gene therapy, it may be possible to program our cells to circumvent or control the processes of wear and tear—or, at the very least, to slow them down.

Biochemist Cynthia Kenyon, Ph.D. has devoted her research efforts to identifying life-extending genes within the genome of a tiny worm called Caehorhabditis elegans, or C. elegans for short.[2] These efforts have revealed the existence of specific genes that, when mutated or manipulated, double the life span of these worms. These genetically modified nematodes don’t spend more time in old age; they stay young and active longer than “wild-type” (unmodified) nematodes do.

This research has caused quite a stir in anti-aging circles. It provides strong support for the notion that the aging process is under genetic control, and offers hope for a future where such genes could be manipulated to extend youthful, healthy life span. The problem, of course, is that a one-millimeter-long worm that feeds on bacteria bears only the most negligible resemblance to the complex, cognizant hominid that is man. Or does it?

An introduction to C. elegans

The similarities between nematodes and human beings are far from obvious to the naked eye, but they have inspired hundreds of scientists worldwide to investigate the biology of this diminutive worm. An effort to sequence the entire 100,000,000 bases of DNA in its genome is currently underway.

Nematodes—smooth-skinned, unsegmented worms with cylindrical bodies tapered at each end—are conceived from sperm and egg during the process of mating, just as we are. They measure only eight microns in length at birth and a millimeter in length at adulthood, but they possess a nervous system and a rudimentary brain, as well as the senses of taste, smell and touch. Nematodes are among the most primitive organisms known to exist today, and yet they are sensitive to temperature and light, exhibit behaviors, and are capable of learning. A nematode starts out as an embryo, undergoes the process of cell differentiation (the development of various cell types with differing functions), hatches from one of about 200 eggs laid by the parent, and grows to adulthood and sexual maturity within the first four days of life. They reproduce, age and die just as we do, but their life spans average two to three weeks rather than seven to eight decades.

It has been known for several years that nematodes with certain mutations in a gene known as daf-2 live longer than their normal counterparts. Dr. Kenyon's research team found that this mutation more than doubled the worms' life spans- the most significant life extension that had been reported in any organism up to that point.

In short, many of the processes modern biologists seek to understand go on within both C. elegans and Homo sapiens. Similar genes are thought to prompt development, cell differentiation and aging in both species. Because of the nematode's short life span; because its body contains only 959 distinct cells based on the code within its 17,800 genes; and because its transparent body provides for easy visualization of these cells under a microscope, the nematode provides us with an ideal organism in which to study the activity of genes with anti-aging potential. In fact, the nematode genome is thought to contain copies of about 70% of the genes in the human genome! Dr. Kenyon's award-winning research will lead to a better understanding of how those genes operate in more complex organisms such as fruit flies, rodents and—eventually—human beings.

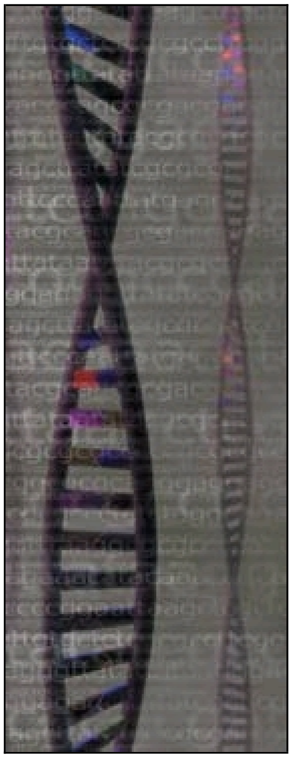
Cynthia Kenyon, Ph.D. A brief biography

Cynthia Kenyon, Ph.D. was born in Chicago, Illinois. In 1976 she graduated from the University of Georgia with a degree in chemistry and biochemistry. At the prestigious Massachusetts Institute of Technology, she earned a Ph.D. with research focused on gene regulation in E. coli bacteria. She further refined her skills with a postdoctoral fellowship at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. In 1986 she became an assistant professor at UCSF and was promoted to Professor in the Department of Biochemistry and Biophysics in 1992.

Her work with C. elegans earned her a Herbert Boyer Distinguished Professorship in 1997 and an award from the Ellison Medical Foundation in 1998. She also was awarded the King Faisal International Prize for Medicine, given by the Saudi Arabian King Faisal Foundation for excellence in medical research—for which she received a 240-carat, 200-gram gold medal and a $200,000 cash award.

The research and its implications

It has been known for several years that nematodes with certain mutations in a gene known as daf-2 live longer than their normal counterparts. In 1993, Dr. Kenyon and colleagues published a study in Nature that describes this life-extending genetic mutation.[3] Her research team found that this mutation more than doubled the worms' life spans—the most significant life extension that had been reported in any organism up to that point. They found that this mutation of daf-2 also required the activity of a second gene called daf-16. These changes in the daf-2 gene trigger changes in the "fountain of youth" gene, daf-16; the daf-16 gene then attaches to DNA within cell nuclei, controlling gene activity in a manner that leads to the formation of new proteins that guide growth and development.



The activities of the daf-2 and daf-16 genes change in normal, “wild-type” nematodes during times of food shortage or overpopulation. As a result, they enter a state of suspended animation called dauer diapause. This can only happen in prepubescent nematodes; once they have been through puberty and reached adulthood, they no longer have the ability to make this transformation. While in dauer, they don’t eat or reproduce, but can remain in this state for up to five months. Once the food shortage ends or the population thins out, the genes switch back off and dauer ends, bringing the nematode back into its normal life cycle.

In Dr. Kenyon’s 1993 study, the mutant nematodes didn’t enter dauer, but a slightly different action of the daf-2 gene—caused by a “weak mutation” of that gene—caused them to live twice as long as normal, and to remain more youthful throughout much of their extended life span. This early study showed Dr. Kenyon and her colleagues that the life-extending qualities of these genes could be activated without sending the nematode into dauer. The long-lived nematodes were active and could reproduce normally.

In other experiments, organisms with lengthened life spans have appeared to incur less wear and tear because of slowed metabolisms and decreased activity. Fruitflies with a similar longevity gene were infertile. While the mutant Dr. Kenyon’s lab examined for this study may have had a slower metabolic rate than normal nematodes, it has since been shown that mutations that affect the same body functions yield worms with normal metabolic rates. Some daf-2 mutations reduce fertility; others do not. “Gene activity effects on reproduction and aging can be uncoupled from one another,” Dr. Kenyon concludes. This means that with specific genetic manipulation, we may be able to extend life span without altering metabolism or reproductive capacity—a new and very exciting finding in life extension research.

In her research, Dr. Kenyon has sought to discover how daf-2 and daf-16 work together to alter the life span of C. elegans. Her team has published a series of papers describing the complex interplay between the daf-16 gene and the resulting cascade of other responses in the cells throughout the body.[4-6] These responses serve as secondary signals that control the growth and longevity of the individual tissues that make up the organism. Further studies[7,8] showed that the daf-2 gene’s activity is not isolated to the cell within which it resides; altered daf-2 activity in a small group of cells affects many other cells, even those without the altered gene, extending their healthy life span. This could explain how the activation of these genes within a few cells can coordinate the rate at which the entire organism ages.

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Gene expression and longevity

Dr. Kenyon's work has also focused on gene expression—the process by which genes "program" for the production of body tissues.[5,6] Genes aren't simply inert blueprints that code for the structure of our cells; their expression is variable and complex. Each organism's specific genetic code tells only a small part of the story of its physiology, as you well know if you have ever been acquainted with a set of identical twins. Although they have exactly the same genes, the environment shapes the expression of those genes into individuals that may be as different as night and day.

Genes aren't simply inert blueprints that code for the structure of our cells; their expression is variable and complex. Each organism's specific genetic code tells only a small part of the story of its physiology,

By studying the ways in which the genetic code is transformed into living cells—and how those cells then assemble themselves into the requisite arrangements for building entire organisms—Dr. Kenyon's team has gained important insights into the mechanisms of cell division, cell differentiation, cell behavior, neurotransmitter formation and cell death. Her research has examined the similarities between the gene expression of C. elegans, insects and vertebrates.[1] Such insights are valuable tools for understanding the anti-aging action of daf-2, daf-16 and similar genes in various organisms.

The roles of insulin and IGF-1

One of the most fascinating findings of Dr. Kenyon's research has to do with the effects of the hormone insulin and the growth factor IGF-1 on the aging process. Insulin's role in aging—in particular, in the acceleration of aging—is becoming more apparent as the epidemic of type II diabetes continues unabated in the American population. The chronically high insulin levels seen in people with prediabetes (insulin resistance) and type II diabetes have a potent age-accelerating effect throughout the body.

In humans and many other animals, restricting caloric intake while ensuring adequate micronutrient intake—undernutrition without malnutrition—has been shown to consistently lengthen life span and postpone the onset of aging, cancer and degenerative diseases. Caloric restriction rapidly leads to a significant drop in insulin levels, and insulin stays low as long as food is scarce. Lower insulin levels could be an important mechanism for the life extension seen with dietary restriction.

Insulin-like growth factor-1 (IGF-1) is structurally similar to insulin, and attaches to the same hormone receptor sites as insulin. (A hormone or other biochemical exerts its effects by fitting into a receptor site like a key into a lock, "turning on" certain cell functions in the process.) IGF-1 and insulin have different functions in the body, however. Normally secreted from the liver in response to growth hormone release from the pituitary gland, IGF-1 is receiving much attention today because of its youth-enhancing effects. In fact, it is responsible for most of the preservation of lean body mass, fat loss and tissue-building properties once attributed to growth hormone.

In studies published during the late 1990s, the laboratory of Gary Ruvkun at Harvard, who had long been studying the role of daf-2 in the process of dauer formation, discovered an interesting characteristic of the daf-2 gene9—one that makes its study extremely valuable for insights into human aging. Dr. Ruvkun found that daf-2 encodes a protein that closely resembles the insulin and IGF-1 receptor in the bodies of human beings. Dr. Kenyon's lab,[2,10] as well as the Ruvkun lab, showed that daf-16 genes code for a regulatory biochemical called FKHR, and in humans, insulin decreases the expression of certain genes by antagonizing FKHR activity. When insulin levels drop due to caloric restriction, FKHR levels rise, and this could also help to explain why this practice increases life span.

The newest research from the Kenyon lab

It has long been known that reproduction is intimately involved in the aging process. Although the stresses of parenting could well have something to do with this connection, there is far more to the relationship between the bearing of progeny and the onset of senescence than endless carpooling, discipline problems, household chores or rising college tuitions. Nuno Arantes-Oliveira, Javier Apfeld, and Andrew Dillin, colleagues and students of Dr. Kenyon's who perform nematode research at her laboratory at UCSF, have come one step closer to understanding how reproduction and longevity are linked to one another. The results of their study—coauthored with Dr. Kenyon—appear in the January 18, 2002 issue of the journal Science.

Dr. Arantes-Oliveira's research focuses on germ-line stem cells, primitive cells continually made in the gonads

Parallels between daf-2, daf-16, and human insulin/IGF-1 receptors are good evidence that research into these genes in C. elegans will lead us to life-extending gene therapies for humans. Dr. Kenyon's research suggests that the reduced activity of daf-2 that precedes nematodes' entry into dauer is analagous to this drop in insulin production. It could be that the drop in daf-2 activity has similar physiological effects to those of a drop in insulin levels; the human gene that triggers this change may be activated by lack of food, just as it is in nematodes. According to Dr. Kenyon, " .the signaling cascade prompted by daf-2 in certain cells occurs in a similar way in the insulin and IGF family of receptors in mammals in response to caloric restriction." In time, we may be able to use gene therapies that offer the benefits of caloric restriction without having to be in a state of semistarvation throughout our lives.

Reproduction, sensory perception and life span

Studies from Cynthia Kenyon's lab also examine the ways in which life span is influenced by signals from the reproductive system and sense organs.[8,11] Prepubescent nematodes can sense overcrowding and food scarcity, and their bodies respond by altering genetic activity, which decreases fertility and activity by sending them into dauer diapause. By gaining an understanding of the ways in which genes affect this process, researchers hope to find ways to alter those genes that will reap the benefits of genetically extended life span without the liabilities of infertility or suspended animation.

In a nematode study published in Nature in 1999,[11] Dr. Kenyon and a research associate destroyed the cells that give rise to germ cells (sperm and eggs). They found that worms without the ability to make germ cells lived significantly longer. The study's authors conclude that signals from the reproductive organs affect the activity of the daf-16 genes (without affecting daf-2), as well as another gene called daf-12. The daf-12 gene encodes another hormone receptor, suggesting that the germ cells regulate a hormone that affects life span. This study provides evidence that the animal's body coordinates its reproductive function with its rate of aging, so that it can reproduce while still youthful.
Another study, published a few months later, showed that nematodes with defects in certain sensory neurons had impaired sensory perception.[8] Interestingly, those nematodes had longer life spans—further evidence that environmental cues have much to do with the genetic regulation of life span.

Future directions

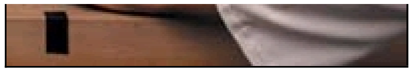
With continuing research efforts, Dr. Kenyon, her colleagues and the many other scientists delving into the mysteries of anti-aging genes hope to someday discover how to adjust the aging clock in humans. If a drug can be developed to trigger or suppress the activity of appropriate genes, we could see the kind of life extension previously seen only in calorically restricted laboratory animals. The human equivalent of such a life span increase could add an additional 20 to 60 healthy, vital years to human life.

Dr. Kenyon has also started a company called Elixir, based in Boston, that will attempt to use the information we and others are learning about the genes that control aging to develop ways of extending youthfulness and improving the quality of old age.

throughout adult development that eventually differentiate into either sperm or egg. (These stem cells are not as versatile as embryonic stem cells, which can be used to grow any type of tissue.) With specific genetic manipulations, the researchers were able to in essence remove these germ-line stem cells without disturbing the somatic gonad cells—the cells that make up the rest of the reproductive organs. The result: a life extension of 60%, whether this change occurred in youth or adulthood. Longevity could be increased even in adults who were already actively reproducing; this suggests that the aging process is plastic throughout life, not dictated by unchangeable factors set in place before birth.

Other studies have shown that the elimination of the entire reproductive system, including both germ-line cells and somatic gonad cells, does not increase life span. Previous research has shown that somatic gonad cells have a life-extending effect, while germ-line stem cells have a life-shortening effect. These two systems balance one another out, but when the latter is removed, the life-extending effects of the somatic cells prevail.

Dr. Arantes-Oliveira and colleagues believe that germ-line stem cells send a hormonal message that reduces life span. The ablation (removal) of germ-line cells affected the activity of daf-12, a gene that regulates a life span-affecting steroid hormone. The results of the study also suggest that germ-line cells may act to decrease life span by downregulating the activity of the daf-16 gene. Worms that had their germ-line cells ablated showed increased resistance against oxidation, heat and radiation. Hormonal cues sent out by the germ-line cells could act to decrease life span by lowering resistance to these stresses. According to Dr. Kenyon, the study shows that "these proliferating stem cells are master control cells, sitting at the top of paths that affect both reproduction and aging. . . We're now searching for the missing pieces. We're looking for other proteins that may be involved in this surprising level of control over life span. . . we particularly want to know more about this steroid hormone. What is it? Do humans have it?"



What are the implications of this research for humans who wish to live longer lives? It's further proof of the price higher animals pay for their complexity: because we reproduce, we senesce and die. Once we've created our progeny, nature sees us as obsolete. As we move towards a more comprehensive understanding of the biochemical and genetic factors that make this a reality, we can look forward to a day when those factors can be controlled.

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