Worm Genes Imply a Master Clock

Newly discovered genes in the nematode may offer insight into aging, by suggesting that bodily processes are paced by a genetic clock. A combination of mutations can increase the worm's life-span fivefold

What's the secret to long life? For the nematode *Caenorhabditis elegans*, it's slow, easy living, in which all life's events occur in a leisurely rhythm, according to work described on page 1010 of this issue. The new research, by Siegfried Hekimi and Bernard Lakowski of McGill University in Montreal, identifies four genes that, when mutated, can make these worms use energy more efficiently, feed and swim at a slower pace—and live many times their normal life-span. Some of the experimental nematodes lived for almost 2 months, far longer than their expected 9 days.

Researchers on aging already knew about one kind of life-prolonging mutation in the nematode, in genes that can shunt the developing larva into a dormant state. But the new mutations seem to work differently: They somehow bog down an internal clock, causing the worm to slack off physically and perhaps metabolically. In Hekimi's view, this suggests that life follows the beat of a genetic master clock. "It shows that there is such a thing as a central biological clock which puts into synchrony everything that has a temporal component," he says.

Other experts on aging aren't ready to accept that sweeping interpretation, emphasizing that these genes may simply be one of many genetic components to aging, and that other genes, as well as environmental factors, can influence how long organisms live. But they applaud the new results. The ability to lengthen the life of the worm fivefold is "absolutely amazing," marvels Judith Campisi, a molecular biologist at the Lawrence Berkeley National Laboratory in Berkeley, California. "That's phenomenal."

And the new work dovetails nicely with other recent research on the genetics of aging, including last month's report of the discovery of the gene responsible for Werner's syndrome, a disease that accelerates certain aging processes (*Science*, 12 April, pp. 193 and 258). "What is exciting is that the two genes together suggest we may be getting a handle on aging," Campisi says.

The clock genes aren't the first that have turned out to affect nematode life-span. The *daf* group of genes regulates whether the maturing larva sidesteps into a dormant state known as a dauer stage, an event spurred by food shortages or crowding; some of the *daf* genes, if activated, can also prolong the life of an adult worm. That effect requires the presence of an intact copy of one crucial gene, *daf-16*.

LAKOWSKI AND HEKIMI

Round-the-clock. The team *(top)* worked long hours on the clock gene in nematodes, such as in this young worm *(above)* and an old one *(right)*.

But Hekimi caught a glimpse of a different life-extending mechanism when he discovered the first clock gene, *clk-1*, last year. Mutations in this gene caused individual cells to divide more slowly, and the animal as a whole spent more time in each phase of its life cycle, living about 50% longer than usual. In addition, mature worms ate and defecated less frequently, and wiggled their bodies more slowly as they swam. Otherwise, the mutants looked and behaved normally. They metabolized food the same way their normal counterparts did, but they used the energy from that food more efficiently, probably spending less energy per unit time, Hekimi says.

Now Hekimi and Lakowski describe two more clock genes, *clk-2* and *clk-3*. By producing nematodes with combinations of mutations, they evaluated how these three genes interact with each other and with other genes—and they saw much more dramatic changes in life-span. Nematodes with mutations in two of the clock genes lived three and four times longer than normal. Worms combining a clock gene mutation with a mutation in *daf-2* lived more than five times longer than normal—the largest increase in mean life-span ever seen in any organism. So it seems that slowing life down also extends it. "These genes seem to set the rate of metabolism and the rate at which things happen. Every kind of periodic or temporal process is slowed down," says Cynthia Kenyon, a geneticist and developmental biologist from the University of California, San Francisco. Clock genes may set this internal pacemaker by regulating genes involved in metabolism, Hekimi explains, but he can't yet say exactly what clk proteins do.

Investigators are also marveling over the ability of the clock genes to put their stamp on an organism's life-span very early in life. One gene shows a maternal effect: Even if a young worm's *clk-1* gene is a mutant, a single normal *clk-1* gene in the mother can restrict its offspring to a normal life-span. This implies that the mother's clk-1 protein, which is passed on in the egg, somehow controls or substitutes for the progeny's *clk-1* gene, explains Leonard Guarente, a yeast geneticist at the Massachusetts Institute of Technology in Cambridge, Massachusetts. Whatever the mechanism, the mother's clock genes "are doing something in the gametes that's determining life-span," Guarente says. "That's an unbelievable finding."

Hekimi hopes that the new work will help resolve the debate about what aging really is. The idea that "rate of living" is important to life-span ties into a theory that disintegration and death—aging's ultimate conclusion—result from the accumulation of damage to DNA and to cells by highly reactive oxidative byproducts of metabolic processes. With life in slow motion, those processes may produce fewer destructive byproducts, and damage may accumulate more slowly or may be repaired more effectively, Hekimi suggests.

But other aging experts don't buy the "rate of living" theory or even that a master clock capable of slowing down life exists. If there is such a timer, they emphasize, it will be but one component of aging. "These experiments say that the *clk* genes are a regulator, but not *the* regulator, of aging," Campisi says.

For one thing, she and Kenyon say, other, as-yet-unidentified genetic clocks are likely to be meting out life-span. "We're just at the very earliest stages of [finding] these genes," Kenyon notes. And aging is likely to have other kinds of regulators—such as the recently discovered gene for Werner's syndrome, which causes premature aging when it's mutated. Unlike the clock genes, which affect nondividing, postmitotic cells like those of nerves and muscles, the Werner's syndrome gene influences aging in cells still capable of dividing, so-called mitotic tissue such as skin, kidney, or liver, Campisi explains. And this gene seems to act not by slowing a clock but by affecting how cells read or copy their DNA.

There is no one mechanism of aging, says Huber Warner of the National Institute on Aging in Bethesda, Maryland. "There's both genetic and environmental factors," he points out. And although harried humans may be tempted to apply these findings to their own lives, no one yet knows whether these genes even exist in humans, or what the proteins they code for really do.

But Hekimi's team is making progress—they have discovered a potentially equivalent gene in yeast. And they are exploring whether there's any connection between the *clk* genes and the fact that restricting food intake can extend life in animals from fruit flies to mammals. Hekimi and others would like to clone the *clk* and *daf* genes and study the proteins themselves, but that's a step no one has yet taken. "I'm running around like a chicken with its head cut off, trying to get all this done," Hekimi laments. Slow, easy living may be the key to long life, but for genetic clock researchers, the pace of life has just gotten faster.

–Elizabeth Pennisi

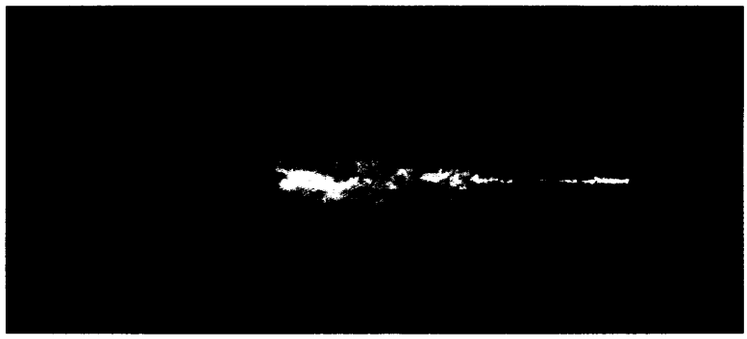
ASTROPHYSICS

A Glow From the First Galaxies?

A joint French-Dutch team may have uncovered a faint reddish glow from the cosmos's first generation of galaxies. The putative galaxies themselves are too faint and far off to be seen, but the glow of far infrared radiation emitted by shrouds of dust surrounding these first galaxies may have turned up in data collected by NASA's Cosmic Background Explorer (COBE) satellite.

COBE's original claim to fame was its detection, 6 years ago, of the detailed spectrum of the cosmic microwave background, the afterglow of the big bang itself. But finding the infrared signal of the primeval galaxies that formed millions of years later would be a comparable feat, because it requires stripping away foreground sources of infrared radiation to reveal the faint relict signal. The difficulties are such that team leader Jean-Loup Puget of the Space Astrophysics Institute in Orsay describes the detection, reported in the 1 April issue of *Astronomy and Astrophysics*, as "tentative." And COBE scientists chasing the same signal are circumspect: "Maybe there is something there," says John Mather, COBE's project scientist at NASA's Goddard Space Flight Center in Greenbelt, Maryland. "We certainly don't want to say there's none there; we just think it's not a proof."

The detection of infrared light from the earliest galaxies could help explain a puzzle: the amounts of heavy elements—which can only be created in the nuclear furnaces of stars—found in the present-day universe. To some cosmologists, current levels of these heavy elements imply an early generation of stars and galaxies, too old and distant to be visible directly. These "first-epoch" galaxies would likely be rich in gas and dust, which would absorb the starlight and re-emit it at longer wavelengths. The expansion of the universe would displace the signal even farther into the infrared region of the spectrum, and the result, today, would be a faint, far-infrared glow—the cosmic far-infrared background (CFIRB).



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Foreground signal. A radio map of neutral hydrogen in our galaxy helped researchers isolate a possible cosmic background glow.

To search for it, Puget and his colleagues began with recently released data from two of COBE's infrared instruments. They then subtracted foreground signals, one of which comes from dust between the planets and another from dust in our galaxy. Says Puget, "The main difficulty in this game is to take out the galactic contribution."

He and his colleagues have a new tool for doing so: an improved hydrogen map of our galaxy made by Puget's collaborators, Dap Hartmann and Butler Burton from the Leiden Observatory in the Netherlands. The survey, made with the Dwingeloo 25-meter radiotelescope, "improves substantially over what has been available," says Burton. And as the distribution of dust generally follows that of hydrogen, the researchers can correlate the hydrogen map with the far-infrared signal as measured by COBE, then extrapolate the correlation down to the zero hydrogen level to eliminate the infrared contribution from the galaxy.

What remains, claims Puget, is a far-infrared signal extending over a wavelength range of 200 to 1000 micrometers, with a gentle peak at 300 micrometers. The signal is even across the sky and is quite strong, consistent with emission from early galaxies, according to some models. But Puget concedes that there is "a bit of controversy between us and the COBE team" over whether the signal he and his colleages have isolated is a true cosmic far-infrared background.

The point of contention is the Franco-Dutch group's extrapolation from the hydrogen map. "Simply running the line down to zero is fraught with uncertainty," says COBE team member Richard Shafer. COBE's own analysis, made using a different hydrogen map and less sweeping assumptions, will appear in a trio of papers, the first of which has been accepted by the *Astrophysical Journal*. The U.S. researchers believe that features such as a "galactic halo"—a halo of dust surrounding the Milky Way—could in principle be responsible for a residual signal, and need to be carefully analyzed.

Puget and his colleagues, however, support their claims with a clutch of astrophysical arguments and invoke Occam's razor, maintaining that a CFIRB is the "least contrived" explanation of the signal. "I would be tempted to agree with Puget that it is probably extragalactic," says theorist Alberto Franceschini of the University of Padova, Italy, noting that the residual signal is even in all directions and is close to the level predicted by some models.

But the message from NASA's Mather is to expect the unexpected. "I don't believe in the predictive power of Occam's razor," he asserts. "As near as I can tell, the astrophysical situation is that things are usually complicated, not simple, and it is unnatural to assume simplicity."

–Andrew Watson

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