LONGEVITY

Growing Old Together

Simple evolutionary arguments don't demand that organisms share mechanisms of aging. But new work is strengthening the case that common processes control the life-spans of biology's favorite model systems

At the Retirement Home for Aging Model Organisms, each creature might have rocked on the front porch complaining about its own species' particular way of growing old. Now a spate of new papers suggests that these organisms in fact break down in similar ways as they pass their primes. And it's seeming more likely that mammals, too, will pull up a chair and swap stories about similar failing molecular pathways.

In the past decade, researchers have discovered an array of genes that control aging, but it was questionable whether one organism's methods for dipping into the fountain of youth would apply to any other. Yet reports on pages 104 and 107 show that a signaling pathway that tunes the worm life-span also operates in flies. A third article, published online today by *Science* (www.sciencexpress.org), reports that a gene related to a member of this pathway likewise influences aging in yeast. Other recent work suggests that an aging gene discovered several years ago in yeast also controls life-span in worms. And researchers speculate that mammals share similar aging pathways.

"It's all coming together," says molecular geneticist Cynthia Kenyon of the University of California, San Francisco (UCSF). "This aging system that we know about in the worm is out there in other animals, regulating their aging. Maybe not in the same exact form, but it's there. It's unbelievable, simply unbelievable."

This congruence is surprising because natural selection acts on genes that influence reproductive success, so those that accelerate or decelerate aging might be expected to lie beyond the reach of evolution's mighty arm. As molecular geneticist Gordon Lithgow of the University of Manchester in the United Kingdom points out, "If aging is a collection of nonadaptive deleterious events, why on Earth should they be conserved across a wide variety of species?"

Aging gracefully without reproducing

No Hollywood star has grown old under as much scrutiny as the roundworm *Caenorhabditis elegans*. Extensive studies have revealed a detailed picture of a molecular signaling pathway that controls the worm's longevity. At the heart of the pathway lies the *daf-2* gene, which encodes a member of the insulin family of cell surface receptors. Upon binding an insulin-related hormone, daf-2 receptors trigger the activation and repression of a suite of other genes. Certain mutations in *daf-2* allow worms to wriggle into ripe old ages that greatly exceed those of their normal counterparts. Other genes in the pathway also affect longevity, and signals from both the reproductive and sensory systems feed into it as well. For example, genetically pinning a clothespin to a worm's nose by disrupting olfactory signaling appears to extend life via the *daf-2* pathway.

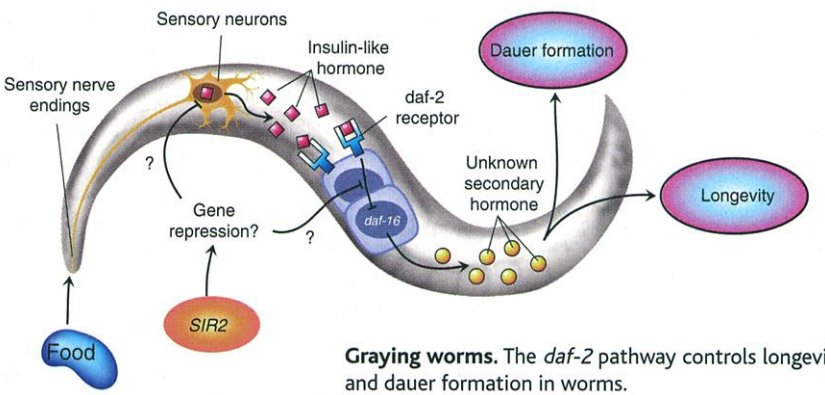
Now, two teams report that a related insulin-like pathway shapes life-span in flies as well. Female *Drosophila melanogaster* that carry only defective copies of the *daf-2* equivalent (*InR*) buzz around long after normal flies keel over, according to a group led by Marc Tatar, an evolutionary geneticist at Brown University in Providence, Rhode Island. Similarly, animals with inactive versions of another member of the pathway called *chico* (see diagram, p. 43) flit into extreme dotage, report geneticists Linda Partridge and David Gems of University College London and colleagues. In both cases, adding back an operational version of the appropriate gene returns life-span to almost normal. Together, these results suggest that functional *InR* and *chico* genes accelerate aging. The work is "tremendously exciting," says John Tower, a molecular biologist at the University of Southern California (USC) in Los Angeles. "To see [the aging pathway] conserved in two such different species makes you hypothesize that the pathway may be more general."

How these mutations confer longevity is a puzzle, however. Other work has shown that stalling or blocking reproduction in flies enhances longevity. Such findings bolster conventional wisdom about how animals allocate limited resources: If they make lots of babies, they burn through the energy that would otherwise preserve their own bodies. The newly described *chico* mutant females are almost sterile, so the Partridge and Gems team tested whether another mutation that prevents *Drosophila* from making eggs would also lengthen life to the same extent.

They found that sterility apparently isn't the only factor that sets back the clock in *chico* mutants: *chico* flies survived longer than the other sterile and long-lived mutant, called *ovo*. Furthermore, flies that carry one good and one bad copy of *chico* outlive *ovo* flies, even though these heterozygotes are more fertile than *ovo* mutants. The commonly observed trade-off between reproductive capacity and longevity might arise not simply because of energy investments, suggests Gems, but because a single system normally controls both processes. He cautions that the new results do not rule out a direct connection between fertility and life-span: The flies might be making the critical energy investment in reproductive activities before the mutation halts egg production.

InR mutant flies, which are also sterile, provided another way to explore the relation between aging and reproduction—or at least fertility hormones. Normally, flies put reproduction on hold during the winter by tapering off levels of juvenile hormone (JH). It turns out that the long-lived *InR* mutants produce abnormally small amounts of this hormone, suggesting that low JH levels may mediate the mutants' life-span extension. To test this, the researchers exposed flies to a chemical that mimics JH.

The results indicate that JH might indeed be driving *InR* mutants' longevity, at least partially. The chemical didn't alter the life-spans of wild-type flies much, but it pushed mortality in *InR* flies back toward normal. This work "makes a leap from the genetic pathways to the hormonal signals that may be affecting life-span," says Lithgow, adding that the finding "begs the question of what



Graying worms. The *daf-2* pathway controls longevity and dauer formation in worms.

ILLUSTRATION: CAMERON SLAYDEN

endocrine signals in mammals might be involved in determining longevity."

Handling stress with maturity

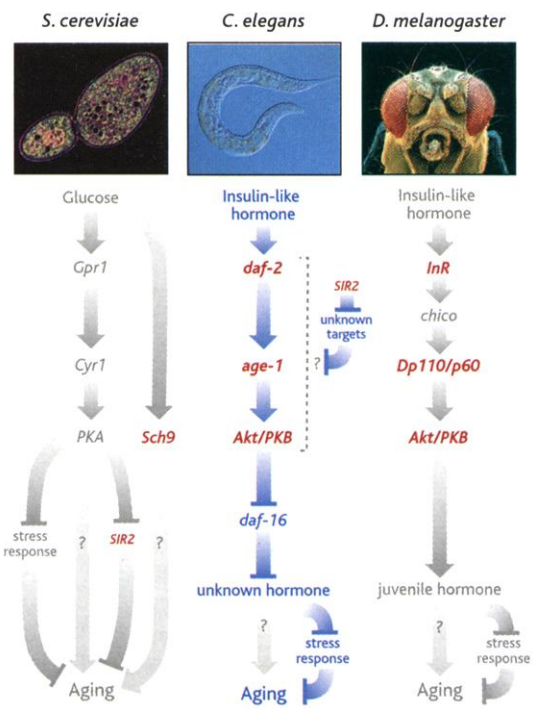
Both fly papers examine another possible explanation for the staying power of *chico* and *InR* flies: resistance to stresses such as heat and oxidative damage. Long-lived mice, worms, and flies tolerate these and other physical and chemical insults better than do normal organisms. Furthermore, treatments that defend against damage from free radicals, such as overproduction of the enzyme superoxide dismutase or exposure to chemicals that perform a similar detoxifying reaction, confer long life on flies and worms. The researchers therefore wanted to know whether the mutants displayed unusual hardiness when subjected to harsh conditions. The results were inconclusive, but neither team conducted exhaustive tests. "These data don't move that argument either way," says Lithgow. "There's a lot of supportive evidence that there's a relationship between stress and aging."

Indeed, the work on yeast reported today advances the claim that stress resistance lengthens life. Valter Longo, a molecular geneticist at USC, and colleagues battered a population of yeast mutants with heat or paraquat, a chemical that creates reactive oxygen molecules. Among the survivors, they found two strains that endured both treatments. These mutants also lived longer than wild-type yeast and mutants that tolerated only heat or paraquat, but not both. One of the mutants carries a defect in *Sch9*, which resembles *Akt1* and *Akt2*, genes that act in the *C. elegans* daf-2 pathway. When the researchers engineered a deletion of *Sch9*, they found that the resulting strain survived three times longer than did wild-type cells.

Both *Sch9* and the other yeast gene that emerged from both the heat and paraquat screens, adenylate cyclase (*Cyr1*), are know to participate in pathways that decrease stress resistance. Indeed, the two mutant strains tolerate not only heat and paraquat, but also hydrogen peroxide. And Longo's group found that genes that protect against heat shock increase survival in *Cyr1* mutants. He suggests that resistance to multiple stresses promotes extended longevity.

Other researchers previously implicated the adenylate cyclase pathway in yeast staying power. Several years ago, Leonard Guarente of the Massachusetts Institute of Technology and colleagues established that overproduction of the yeast protein Sir2 increases a different measure of longevity, the number of times a mother cell produces a daughter cell. Last September, his team showed that *SIR2* allows yeast to live longer via the adenylate cyclase pathway (*Science*, 22 September 2000, p. 2126). And Guarente recently extended the relevance of his work with *SIR2* by implicating a homologous gene in the process of worm aging. Overproducing the worm relative of Sir2 increases average life-span by up to 50%, he reported in the 8 March issue of *Nature*. Furthermore, he gathered genetic evidence that *Sir2* operates in the *daf-2* pathway.

Guarente suggests that *SIR2* and its kin mediate life-span by the same mechanism in many creatures: They remove an acetyl chemical group from DNA-binding proteins, allowing them to halt gene expression. But the targeted genes perform a variety of physiological roles. "Deacetylation of some protein is important for longevity, but how that plays out in different organisms is likely to be very, very different," Guarente says. His team found that nutrient deprivation spurs Sir2 to extend life-span, and this ability to respond surroundings, he says, "allows an organism to hang around longer when food is scarce. When things get better, you're still there and your neighbor's not."



Copycats. Similar genes (red) control aging in yeast, worms, and flies. Arrows indicate gene activation (not necessarily direct); blocks indicate repression.

This link between environmental conditions and aging pathways also provides an explanation for how "aging" and "antiaging" genes might have evolved. In worms, the *daf-2* pathway controls life-span, fertility, and entry into a semidormant state that allows prepubescent worms to wait out rough times. Crowding and lack of food, for example, trigger this "dauer" state; the trade-off is that dauer worms can't reproduce. The life-span genes "all seem to be allowing these animals to survive periods of food deprivation and harsh conditions," says UCSF's Kenyon. "Now we're learning that by tinkering with this system, it's possible to change life-span in a healthy way. You don't have to be a dauer to do it."

Hungry but wizened

The connection between limited food and longevity is reminiscent of the one well-established treatment that stalls aging in mammals: calorie restriction. Calorie-restricted mammals have low levels of both insulin and insulin-like growth factor–1 (IGF-1). Several receptors respond to such hormones in mammals, including separate insulin and IGF-1 receptors, both of which resemble the single daf-2 receptor that underlies the aging pathway in *C. elegans*.

"You can make a very strong case that there is a link between IGF signaling and aging" in mammals, says Gems. Some of the best evidence comes from previous research on three strains of long-lived mice. They carry mutations in different genes that affect growth hormone signaling, and all have low levels of IGF-1 in the blood, as well as alterations in the amounts of other hormones. Like many long-lived fly mutants, these mice "are small, have reduced reproductive function, mutations in what looks like a similar pathway, and more of a life-span effect on females than males," says Andrzej Bartke, a mammalian endocrinologist at Southern Illinois University in Carbondale. "To what extent the [fly and mouse] genes have corresponding functions, it's hard to know. But these papers are very exciting because they add an enormous amount of evidence that the parallelism does indeed exist."

The parallels among flies, worms, and yeast are falling into place, but connecting these pathways with mammalian aging will take more work. Other pathways are out of whack in the mouse mutants, warns William Sonntag, an endocrinologist at Wake Forest University School of Medicine in Winston-Salem, North Carolina, so it's too early to draw solid connections between IGF-1 and aging pathways in *C. elegans* and *Drosophila*. But he is cautiously optimistic. "The fly and nematode results make us more enthusiastic that similar mechanisms are working in vertebrates and mammals," he says. "If it transfers [from worms] to flies, there's the possibility that it will transfer to mammals."

–EVELYN STRAUSS

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