Worm Longevity Gene Cloned

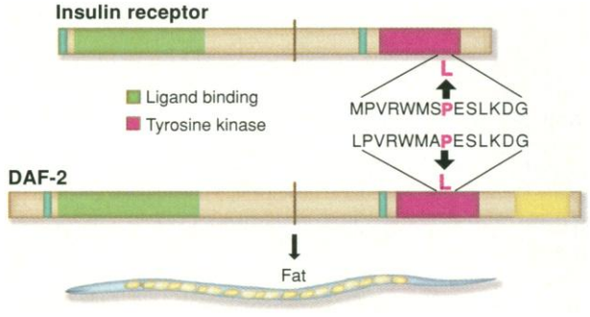
A gene that helps control the life-span of the nematode *C. elegans* encodes the worm version of the insulin receptor, thereby providing a possible link between aging and glucose metabolism

While our canine companions age as much in 1 year as we do in 7, the clock runs even more rapidly for the lowly worm known as *Caenorhabditis elegans*. The tiny nematodes of this species age the equivalent of 5 human years for every day they spend grubbing in the dirt searching for tasty bacteria, usually dying when they are 14 days old. The worms do, however, have a way to put aging on hold—one that humans might envy: In times of stress, such as when overpopulation leads to overcrowding and food scarcity, they can store fat, stop eating, and enter the so-called "dauer" phase (from the German for durable), a state of suspended animation that can last for 2 months or more. In human terms, that's like having yourself cryogenically preserved until the year 2297. Now, a Boston-based research team has new results that help explain just how nematodes extend their lives—and suggest a tantalizing connection to aging in mammals.

In this week's *Science*, geneticist Gary Ruvkun and his colleagues at Massachusetts General Hospital (MGH), Harvard Medical School in Boston report that they have cloned and sequenced a gene that, when damaged, can block or enhance the ability of C. *elegans* to make the switch to the dauer stage (see page 942). The gene, called *daf-2* (for dauer-formation defect 2), is one of a bushel of genes harvested over the last decade that help the worm enter suspended animation. But *daf-2*'s newly decoded gene sequence is particularly revealing. The protein it encodes appears to be the worm equivalent of the human insulin receptor, the molecule that "listens" for the hormone insulin, which is secreted in response to a rise in blood sugar, and passes its metabolism-enhancing signal to our cells' interiors. The similarity implies that the very system the worm uses to monitor and alter its metabolism has become part of the switch that shifts its metabolism into "suspend" mode, drastically lengthening its life when times are bad.

Simply finding an analog to the human insulin receptor in C. *elegans* is a surprise, says Jim Thomas, a geneticist at the University of Washington in Seattle who also studies dauer initiation. He notes that scientists "weren't anticipating that the fundamental genetic circuitry that regulates glucose metabolism in mammals would be evolutionarily that ancient"—apparently dating to a time before nematodes and mammals diverged, perhaps some 700 million to 800 million years ago.

But beyond providing yet another example of evolution's parsimonious ways, the finding raises a tantalizing possibility: that changes in glucose metabolism could be the key to slowing the aging process in higher organisms, including humans. If some of the same genetic circuitry triggered in the worms by the DAF-2 signal accounts for the life-span extension seen in rats and mice under conditions of caloric restriction, "that would be a phenomenal discovery," says Don Riddle, a geneticist at the University of Missouri in Columbia, who studies dauer initiation. It might spur the design of drugs that could stretch human life-spans by tricking cells into entering a dauerlike stage, even when they aren't being starved.



SOURCE: G. RUVKUN

Parallel paths. Changing a proline (P) to a leucine (L) In the human insulin receptor leads to diabetes and obesity, while the same mutation in *daf-2* leads to increased fat deposition in the worm.

When Riddle decided to study the dauer initiation of C. *elegans* in 1974, researchers already knew that worms enter the dauer phase when they detect pheromones secreted by neighboring worms—a sign of excess population density and increased competition for food. Riddle wanted to find out how the biochemical alarms set off when chemosensory neurons in a worm's cuticle detect these pheromones lead to such specific tissue changes as increased fat deposition around the intestines and a thickened cuticle. In screens for mutant worms that either can't become dauers or enter the dauer stage inappropriately, Riddle, Thomas, Ruvkun, and other researchers turned up nearly three dozen genes, including *daf-2*. Their proteins seem to make up at least two parallel "signal transduction pathways," biochemical bucket brigades that supply genes with information about conditions inside and outside the organism.

In 1992, molecular geneticists Cynthia Kenyon of the University of California, San Francisco (UCSF), and Pamela Larson in Riddle's lab provided a clue to what *daf-2*'s pathway does. They found that worms with minor mutations in the gene live two to three times as long as normal, but without becoming dauers. Those findings uncoupled life-span extensions from the other changes that occur in dauers, says Kenyon, suggesting that the *daf-2* pathway can regulate longevity without input from the other pathway—the alarm system triggered by the pheromones.

Last year, Ruvkun's group found more intriguing clues about the connection between *daf* genes and the longevity of C. *elegans*. The MGH team cloned another gene, *daf-23*, and found that it encodes a so-called PI3 kinase. This familiar type of membrane-bound protein transmits signals from receptors into the cell by activating so-called "second messenger" molecules, which pass on signals that ultimately reach the nucleus and alter gene activity. PI3 kinases are among the many molecules in mammalian cells known to be altered when insulin binds to its receptor, suggesting that *daf-23*'s arm of the dauer pathway regulates metabolism.

The team knew that *daf-23* mutations have effects much like those in *daf-2*, so Ruvkun and lab members Koutarou Kimura, Heidi Tissenbaum, and Yanxia Liu reasoned that the proteins encoded by the two genes might be partners in the same arm of the dauer pathway. But when they set out to clone *daf-2*, bad luck slowed their hunt: The gene lay in the 10% of worms' DNA that has not been sequenced by the C. *elegans* genome project. But their persistence in tracking *daf-2* paid off. A comparison of the finished gene sequence with the databases showed that the DAF-2 protein shares 35% of its amino acid sequence with the human insulin receptor and 34% with the insulin-like growth factor-1 receptor—enough to indicate that the three share a common evolutionary origin, and, presumably, similar functions. Moreover, the researchers found that DAF-2 regulates metabolism as its mammalian cousin, the insulin receptor, does.

Putting their findings together into a single scenario for the *daf-2*/*daf-23* pathway, Ruvkun's group proposes that during times of plenty, *C. elegans* maintains high levels of an insulin-like hormone, which binds to DAF-2. This, in turn, may trigger DAF-23 to activate the second messenger, passing an "okay to burn fuel" signal to the cell interior. But when the worms grow so numerous that they threaten to overtax their food supply, two things happen: Increased pheromone concentrations trip individual worms' chemosensory alarms, and internal insulin levels decrease, a sign of plummeting glucose availability. The two signals together push the worms into the dauer stage.

Mice fed meager diets may go through parallel physiological calculations, suggests S. Michal Jazwinski, a geneticist studying aging at Louisiana State University Medical Center in New Orleans. The caloric restriction pushes the mice into a high-efficiency state, in which normal 2-year life-spans increase by up to 40%. "They metabolize as much glucose on a per-gram basis as other animals, but they can utilize that glucose more efficiently," Jazwinski explains. As a result, they show fewer of the changes, such as oxidative tissue damage, thought to lead to aging. If human cells could be fooled into making a dauerlike transition to efficient energy use, Jazwinski speculates, it might eventually be possible to soften the ravages of aging.

The existence of a food-sensitive, longevity-inducing mechanism in species as distantly related as nematodes and rodents suggests that nature has long been experimenting with such inhibitors of aging. "You could imagine that in a primitive metazoan, a way evolved for the animal to make it through bad times, and that core regulatory ability still exists in different organisms but is expressed in different ways," says UCSF's Kenyon.

Ruvkun speculates that the high incidence of diabetes among humans may be an indirect legacy of this adaptation. Like the defects seen in the long-lived *daf-2* worms, minor variations in the genes encoding insulin, its receptor, or other components of its signaling pathways might be advantageous during times of famine, thus gaining a selective advantage. Such variations, however, also underlie some forms of diabetes.

Indeed, even if the long-lived worms don't show the way to vastly extending the human life-span, they offer researchers a new model system in which to study insulin signaling. That, Riddle, Ruvkun, and other researchers point out, may improve biologists' chances of designing treatments for diabetes, the seventh leading cause of death in the United States. "Not everything we find will be directly applicable," says Jazwinski, "but now that we're generating findings more and more quickly, the odds are in our favor."

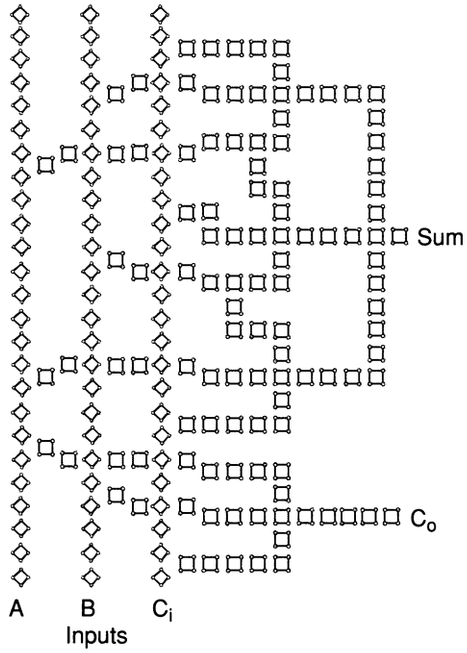
–Wade Roush

TECHNOLOGY

Quantum Cells Make a Bid To Outshrink Transistors

Electrical engineers are heading straight for a bruising encounter with the laws of physics as they continue to shrink transistors. Even the most gung-ho circuit builders know that heat overload and quantum effects, such as the elusive behavior of electrons on very small scales, will eventually stop them from packing more and more transistors onto a single computer chip. But 6 years ago, a pair of electrical engineers, Craig Lent and Wolfgang Porod at the University of Notre Dame in Indiana proposed a scheme for dodging those limits—even exploiting them.

They realized that when transistor sizes bottom out, the quantum fuzziness of very small scales might actually be the key to shrinking electronics still further. They proposed that dominolike arrays of "quantum dots," in which electrons would quantum-mechanically "tunnel" from dot to dot, might one day outshrink transistors. The notion met with incredulity in the electrical engineering world, where more conventional schemes relying on quantum dots have yet to demonstrate their practicality (*Science*, 17 January, p. 303). A paper on page 928 of this issue shows, however, that Lent and Porod's quantum-dot dominoes—called quantum-dot cellular automata (QCA)—really do work, at least one at a time.



SOURCE: C. LENT AND P. D. TOUGAW

Domino theory. The interactions between many quantum-dot cells, each with four dots, create this adder, designed by Craig Lent and P. Douglas Tougaw.

The paper, by Alexei Orlov and several colleagues at Notre Dame—including Lent—describes the first functioning model of a single, four-dot QCA cell. "We showed that this little thing goes click clack," says Lent. Spanning 8 microns, several times the size of today's smallest transistors, and working only when cooled all the way to 15 millikelvin to keep thermal noise from rattling electrons out of their dots, the cell "is just the first baby step" for the technology, says co-author Gary Bernstein.

Some researchers are hanging on to their earlier skepticism, saying that the QCA approach is conceptually flawed and won't work when it is extended to an entire system of cells. But the group's working QCA has impressed others. "This is a key demonstration that the concept could work," says Pierre Petroff, a materials scientist at the University of California, Santa Barbara (UCSB). The remaining hurdles—though daunting—are largely technical, says Terry Fountain, in the department of physics and astronomy at University College London. "The Lent-Porod approach does constitute a new and promising possibility to shrink computer architectures," Fountain says, which could, in principle, reduce circuit areas by factors of as much as 50,000 compared to the smallest feasible transistors.

Existing chips are etched with thousands or millions of transistors, in which electrical currents are switched on and off with electric fields—or, equivalently, voltage biases—in semiconducting materials based on silicon. Conduction channels, or "wires," link the transistors and other components of a chip to create the physical basis of binary logic—the electronic 1s and 0s that are further manipulated in computations. But within the next decade or two, as the size of the smallest circuit features drops from today's 1/3 of a micron to less than 1/10 of a micron, the physical limits facing conventional electronics will assert themselves.

For one thing, the proliferating interconnections will start to wipe out the gains due to smaller sizes. For another, the heat generated by electrical resistance will be harder to dissipate. And finally there is the wavelike, quantum-mechanical nature of particles on tiny scales, a fuzziness that lets electrons tunnel and escape through the walls set up to channel them—the narrower the walls, the easier the tunneling.