FARM REPORT

Beyond DNA

Longevity passed on through non-genetic means.

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Illustration: Stuart Briers

By **Kristin Sainani**

Slimy, squirmy and generally icky, worms may not be the most pleasant research subjects. But, when it comes to unraveling the secrets of long life, they may just be a scientist's greatest allies.

For two decades, the tiny roundworm *C. elegans* has been the go-to organism for discovering longevity genes. When mutated, these genes extend the worm's lifespan—usually just two to three weeks—to as long as nine months. (That's like extending a human life to 750 years.) Since many of the genes have counterparts in people, they have given scientists numerous clues into how and why we age.

Now, a team of Stanford scientists has added a surprising twist to the story. Associate professor of genetics Anne Brunet and her colleagues discovered that the offspring of some genetically long-lived worms enjoy prolonged lives even when they don't inherit the life-extending mutation. The finding could have widespread implications for understanding how environmental exposures or behaviors—which rarely alter an organism's DNA sequence—can nevertheless affect health and lifespan for generations.

The worms inherit a memory of longevity through epigenetic changes, that is, alterations made on top of the genes. (The prefix epi- comes from the Greek meaning over or above.) Chemical tags reversibly attach to DNA or to histones, the proteins that help compact DNA into chromosomes, without altering the underlying genetic code. Rather, these epigenetic changes affect gene accessibility and expression. For example, adding methyl groups to specific locations on histones causes DNA to unwind, turning genes on; whereas adding these groups to other locations causes DNA to coil more tightly, turning genes off.

Until recently, scientists believed that epigenetic marks were wiped clean between generations. But Brunet's study is one of a growing number that challenge this dogma. Her team is the first to show that longevity can be inherited via an epigenetic mechanism. "This opens the speculative possibility that what we do during our life—whether we smoke, what we eat—will impact the lifespan of future generations even if they are no longer exposed to these stimuli," Brunet says.

In 2010, Eric Greer, PhD '09, then a postdoc student in Brunet's lab, asked to pursue a line of questioning that Brunet says was a "bit heretical." In previous work, Greer had discovered that tampering with a particular methyl mark—by mutating one of the proteins responsible for affixing it to histones—increased lifespan in *C. elegans* by 20 to 30 percent. Greer wondered if the epigenetic changes and accompanying longevity could be transmitted to future generations without transmitting the instigating mutation.

Greer's theory had some precedence in the literature. Several studies had demonstrated epigenetic inheritance for simpler traits. For example, in one experiment, yellow mice given a special diet during pregnancy had brown children and grandchildren due to epigenetic changes in the gene for coat color. But the idea that more complex traits like aging could undergo epigenetic inheritance remained a subject of intense debate. "At the beginning, I thought it would never work," Brunet says. "This is the mark of really exceptional students: They have ideas and they persist in them even when their own advisers are thinking it's not going to work."

To test his theory, Greer crossed the mutant worms with normal worms to derive genetically normal progeny. Astoundingly, even though the progeny did not carry the initial mutation, they still had an extended lifespan. What's more, their children and grandchildren also benefitted. The long lifespan disappeared abruptly in the fourth generation.

"It was really quite beautiful. The finding was very clear and consistent," comments Cynthia Kenyon, a pioneer in the genetics of aging who directs the Hillblom Center for the Biology of Aging at UCSF. "There's some imprint that's left behind by events that happen in one generation that can be carried forth for several more generations; and then there's a switch back to normal."

Multiple variations of the experiment yielded the same results, so it's unlikely that the findings were due to an extraneous mutation in the strain or another artifact. "An extraordinary claim requires extraordinary proof, so we had to test it rigorously," Brunet says. The results were published in the journal *Nature* last fall.

"It's really just remarkable," says Kenyon. "I think this is one of the most important papers in decades in the aging field."

Exactly how the epigenetic signal is transmitted across generations remains unclear. At first, Brunet's team assumed that the mutant parents passed the aberrant pattern of methyl marks directly to their progeny. However, they found that global levels of this mark, which were reduced in the parents, appeared normal in the progeny.

Greer, now a postdoctoral fellow at Harvard Medical School, speculates that perhaps the mark remains altered at only a few hotspots in the genome that are important in aging. Alternatively, the changes in the parents' chromosomes may set off a chain of events; and one of these downstream effects may be inherited. "Eggs have a certain amount of their mother's proteins and RNA, which are necessary for the initial stages of development," he says. "So it's possible that the progeny of these long-lived worms are inheriting some sort of information in the form of protein or RNA."

Brunet's group hopes to replicate the phenomenon in higher animals, including African killifish and mice. Chances are good that "it's not just a worm thing," says Kenyon. "Of all the genes that have been discovered to affect aging in the worms, almost all of them have been found to affect aging in other organisms." Already, others have shown that the gene that Greer mutated in worms also increases lifespan when mutated in fruit flies. "This suggests that the gene has a conserved effect on longevity. And, if that's true, then it may also have a conserved effect on transgenerational longevity," says Greer.

Whether epigenetic inheritance occurs in humans remains controversial and difficult to prove. But some epidemiologic research hints at it. In one series of studies, researchers explored multigenerational data from an isolated community in Northern Sweden that experienced alternating periods of plenty and famine at the end of the 19th and throughout the 20th century. Men who were exposed to periods of overabundant food before puberty (a key stage for sperm development) had grandsons who were at increased risk of diabetes, suggesting an epigenetic effect.

"It really makes you stop and think," Greer says. "If I eat this burger, it might not only be affecting my health, but it could potentially affect the health of my children and grandchildren."

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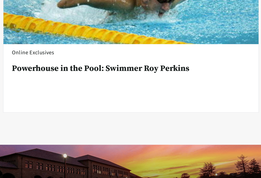

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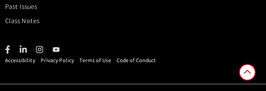

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