

Live Long and Prosper

Mix amyloid plaques with longevity and you get mice that not only live longer, but healthier too.



Andrew Dillin has found a way to manipulate the IGF pathway to sequester misfolded proteins.

Lou Mora

ANDREW DILLIN WANTS TO INCREASE THE HUMAN HEALTH SPAN — NOT just years, but healthy years. He believes the secret to preventing many age-related neurotoxic diseases—including Alzheimer’s, Parkinson’s, and Lou Gehrig’s diseases—lies in the body’s ability to recognize and sequester improperly folded proteins. ¶ Dillin, an HHMI investigator at the Salk Institute for Biological Studies, has been building a strong

case for his misfolded-protein theory. A few years ago, he showed that there are mechanisms in immature worms that can inactivate misfolded, toxic proteins; as the animals age, however, that surveillance system degrades until the aggregation of those proteins leads to disease. Now, he and his colleagues have linked that finding to mice engineered to exhibit Alzheimer’s disease. [Prions are a different set of proteins that misfold with different results—see “A Silver Lining,” page 22.]

Amyloid beta, or A β , is a misfolded protein that accumulates in the brains of Alzheimer’s patients and creates dense plaques that are a hallmark of the disease. When Dillin genetically reprograms mice to have a longer lifespan, they seem to retain the youthful ability to isolate, compartmentalize, and pack away A β proteins. The result: plaques that appear similar to those of Alzheimer’s but are denser and seemingly benign. Somehow, the surveillance mechanism identifies and secludes the dangerous proteins in a way that older brains cannot.

He began to take a hard look at aging during his postdoc at the University of California, San Francisco. From 1999 to 2002, he studied the genetics of aging in the lab of Cynthia Kenyon, who in 1993 discovered that changing a single gene could double a roundworm’s lifespan. Changing the gene, called *daf-2*, downregulated the insulin/insulin growth factor (IGF) pathway, which is found in organisms from the tiny worm to the largest mammals.

The IGF pathway is one of three genetic pathways known to affect aging. Dillin had a hand in discovering the other two. One, involved in mitochondrial signaling, he discovered in 2002 during his time in Kenyon’s lab. “If you reduce mitochondrial function you can increase lifespan,” he says. “If you go

down too far, it kills the animal, but at a certain level you get a positive response.” In his own lab, Dillin discovered the genetic determinant responsible for longevity induced by caloric restriction—another long-known but little-understood cause of increased lifespan—and found that a different signaling pathway, acting on the roundworm gene *pha-4* (*FoxA* in mammals), was responsible.

Dillin contends these three distinct pathways have at least one thing in common: “We think that all these pathways, when they are downregulated, trick the system to turn on the protein surveillance machinery much more highly, to really take care of the proteome,” he says.

Using Kenyon’s discovery of the IGF pathway as his springboard, Dillin has

“This is the first study to show that you’ve not only extended an animal’s lifespan but also actually improved its quality of life.”

ANDREW DILLIN

begun investigating whether downregulating the IGF pathway can keep an animal healthy as it lives longer. A postdoc in his lab, Ehud Cohen, combined a worm model of Alzheimer’s—in which A β proteins accumulate in the roundworm’s body wall—with the long-lived, IGF-downregulated worms. The onset of toxicity was delayed in the worms. “I thought the protected worms would actually have fewer plaques than the unprotected worms. That’s what any neurologist would tell you,” Dillin says. “But they actually had more.”

The longer-lived worms accumulated plaques, but the plaques seemed far less toxic than those in the regular IGF worms. “It was a really striking result, because it was

so clear that it wasn’t just time—there was something inherent about remaining youthful,” Dillin says.

When they moved the Alzheimer’s research to mice, Dillin and Cohen, now at the Hebrew University Medical School in Jerusalem, found even more striking results. In research published in *Cell* on December 11, 2009, they created an Alzheimer’s mouse model with downregulated IGF signaling and compared those animals with mice engineered to have Alzheimer’s with a normal lifespan. Just like the worms, mice with downregulated IGF still had A β aggregating in their brains—with as many plaques as their Alzheimer’s addled counterparts—but they were almost completely asymptomatic.

The results confounded the group for the better part of a year. But they eventually found that the longer-lived mice had plaques that were far denser and in a conformation that likely eliminated much of the misfolded proteins’ toxicity. Rather than

destructive, the plaques in these mice were actually protective, amassing the dangerous protein in such a way as to inactivate it. Something about muting the IGF pathway, Dillin believes, allows for continued protein surveillance and protection from mechanisms that have gone awry.

“This is the first study to show that you’ve not only extended an animal’s lifespan but also actually improved its quality of life,” Dillin says. The transgenic mice were living longer, and they were eluding a disease they had been genetically programmed to develop. Dillin is investigating the mechanisms involved and is looking at other neural conditions as well, including Parkinson’s and Lou Gehrig’s diseases. ■ —LAUREN GRAVITZ