

Research Roundup

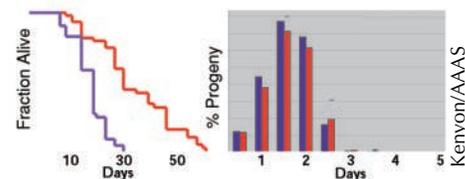
Viva the worm

Like yin and yang, good things usually come at a cost. If you live longer, then you give up reproductive fitness in return. The merits of this model—termed antagonistic pleiotropy—have been argued by evolutionary biologists for half a century. Some believe that the effort of reproduction is necessarily linked to deterioration characteristic of aging. But now Andrew Dillin (Salk Institute for Biological Studies, La Jolla, CA), Douglas Crawford, and Cynthia Kenyon (University of California, San Francisco, CA) have challenged the idea by uncoupling reproduction and aging.

They focused their studies on worms, in which the insulin pathway controls both reproduction and aging. Mutations in the DAF-2 insulin-like receptor prolong the lifespan of a worm, but reduce its fertility. The new data

indicate that with good timing, this need not be the case. The group used RNA interference to reduce *daf-2* levels, thereby disrupting insulin signaling, at discrete developmental stages. Disruption of DAF-2 during adulthood extended lifespan without affecting reproduction. The time of onset and duration of reproduction, on the other hand, was set by DAF-2 signaling during development, so later disruption had no effect.

There are some arguments for conservation of the system in other species. Mice with low levels of the insulin-related IGF-1 live longer and, says Dillin, “the insulin pathway in worms is almost identical to [the pathway in] humans.” But the elusive fountain of youth is not exactly within reach. The relationship between insulin signaling and aging in humans has not been



Loss of DAF-2 (red) in adulthood increases lifespan (left), but does not affect when or how many progeny are made (right).

established, and interfering with all aspects of insulin signaling in humans would induce diabetes. Thus, researchers would first have to find an aging-specific component in humans. The consequences of shutting down such a component also remain unknown. Fortunately, *daf-2* worms do not seem to suffer from a general metabolic slowdown; otherwise, an antiaging drug might turn out to be a big snooze. ■

Reference: Dillin, A., et al. 2002. *Science*. 398:830–834.

Polyamino acids take amyloid form

The folding of a polypeptide is a tug-of-war with bonds within the main chain fighting against interactions between the side chains, according to new results from Marcus Fändrich (IMB, Jena, Germany) and Christopher Dobson (University of Cambridge, Cambridge, UK). The winner determines whether a polypeptide forms a well-behaved globular structure or the dangerous amyloid fibrils that are associated with diseases such as Alzheimer's or Parkinson's.

Protein folding depends on specific side-chain interactions, but the new results show that amyloid formation does not. The authors examined polyamino acids (PAAs), peptide repeats of one amino acid that cannot fold into globular structures. Repeats of lysine, glutamine, and other amino acids were, however, able to form fibers with the distinctive cross- β structure of amyloids. “Proteins are defined by the sequence of their side chains,” says Fändrich. “PAAs don't have sequence patterns, but still give rise to amyloids. This means [that amyloid] structure isn't defined by the side chains and

their interactions, but rather by the main chain.” It may also explain why proline insertions, which alter the main chain, perturb amyloid formation.

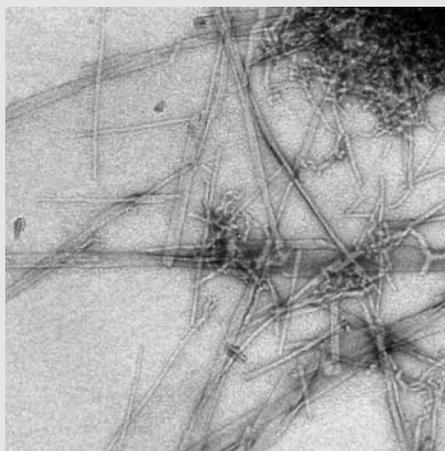
Depending on the environment, some PAA side chains were

more resistant to amyloid formation than others, however. Charged side chains resisted amyloid formation, probably because they are difficult to align within the densely packed β sheets. Indeed, the most common repeat associated with amyloid diseases is glutamine, an uncharged amino acid.

But glutamine is not the only amyloid-forming side chain. Recently, alanine and leucine expansions were also noted in diseases or associated with nuclear fibers. Fändrich is not surprised. “People said it was the [glutamine] side chains—that they could interact by hydrogen bonds,” he says. “Our data say polylysine and polythreonine work just as well.

I imagine this is a more general phenomenon, and we are just realizing how important it is.” ■

Reference: Fändrich, M., et al. 2002. *EMBO J*. 21:5682–5690.



Although lacking a specific side-chain pattern, polythreonine forms amyloid-like fibers.

Dobson/EMBO