HIGHLIGHTS

AGEING

The fly that won't die

Methuselah, according to the Book of Genesis, lived for a remarkable 969 years. By comparison, a lifespan of 70 days isn't much to write home about, unless you're a fruitfly, that is — in which case it's nearly twice as long you'd expect to live. Rogina and colleagues recently noticed that some of their mutagenized flies were doing just that — living for double the average of a normal fly. But these researchers did more than just give their mutant a catchy name — *I'm not dead yet* (*Indy*) — they identified a single gene that when disrupted doubles lifespan and encodes a protein that is directly involved in energy metabolism. Altering energy metabolism can mimic a well-known cause of longevity in many species — restricting calorie intake.

The five independent *P*-element insertions that doubled the average lifespan of flies were at a single locus, from which Rogina *et al*. cloned a gene with homology to two mammalian dicarboxylate cotransporters. These membrane proteins function in the uptake and recycling of Krebs cycle intermediates. When two *P*-elements that disrupted the first intron of this gene were excised in two separate fly lines, *Indy* flies reverted to a normal lifespan. Furthermore, unlike other long-living mutant flies, their longevity was not due to delayed or altered fertility, and *Indy* flies showed no developmental delays, as seen in some long-lived *C. elegans* mutants.

Further clues as to how the *Indy* mutations might cause longevity come from the gene's expression at sites associated with fat and glycogen storage and energy metabolism. INDY's homology to dicarboxylate cotransporters indicates that it functions directly in intermediary metabolism — an important finding as other longevity-inducing genes have been found to have indirect effects on metabolism. The authors suggest that a mild reduction in *Indy* expression might create a metabolic state similar to that induced by longevity-promoting calorie restriction. Too great a disturbance of this process, however, is not beneficial to the fly — lifespan extension is most dramatic in *Indy* heterozygotes, and flies that carry an *Indy* mutation over an *Indy*-deleted chromosome die earlier than normal. The *Indy* gene provides the first direct genetic link between ageing and metabolism and a way into unravelling why reduced calorie intake extends lifespan. Research into *Indy* may even lead to life-extending drugs, but the prospect of another Methuselah is still some way off.

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References and links

ORIGINAL RESEARCH PAPER Rogina, B. *et al*. Extended life span conferred by cotransporter gene mutations in *Drosophila*. *Science* **290**, 2137–2140 (2000)
FURTHER READING Guarente, L. & Kenyon, C. Genetic pathways that regulate ageing in model organisms. *Nature* **408**, 255–262 (2000)
WEB SITE Stephen Helfand's lab

Courtesy of Blanka Rogina.