AGEING

A midlife crisis for sirtuins

> sirtuins might primarily affect physiological homeostasis and stress responses

Sirtuins are NAD^+-dependent protein deacetylases that are believed to promote longevity in several organisms. Although controversial, the connection between sirtuins and extended lifespan has dramatically boosted research into these proteins over the past 10 years; but now this link is being challenged again.

Guarente and colleagues originally found in 1999 that increased expression of the protein silent information regulator 2 (Sir2) extended lifespan in budding yeast. They subsequently reported in *Nature* in 2001 that extra copies of the Sir2-related gene from *Caenorhabditis elegans* (*sir-2.1*) extended worm lifespan by up to 50%. Two approaches led to this conclusion. First, the authors obtained *C. elegans* strains with duplications of several different chromosomal regions and found that a duplication of chromosome IV that contained *sir-2.1* extended worm lifespan, whereas a very similar duplication that lacked the region carrying the *sir-2.1* locus did not. This suggested that *sir-2.1* was responsible for the phenotype observed.

In a second approach, the authors injected worms with a genomic fragment containing *sir-2.1* to derive stable transgenic lines, and found that each line which had several extra copies of *sir-2.1* showed a long lifespan. This work laid important foundations for other studies of sirtuins in ageing, although mixed reports of their roles have been the cause of some debate in the field.

The findings above are now being challenged by the work of Gems and colleagues, who claim that the increased lifespan phenotype that had been previously observed is attributable to the organism's genetic background. To test this, the authors outcrossed *C. elegans* transgenic lines containing extra copies of *sir-2.1* to a wild-type line. They found that although the protein levels of SIR-2.1 were not affected, outcrossing did abrogate effects on longevity. Furthermore, they found that longevity was linked to another mutation, which affects sensory neurons; consistent with this, sensory neuron defects are known to extend lifespan. Gems and colleagues also report similar findings in *Drosophila melanogaster*: overexpression of *Sir2*, which was previously reported to increase *D. melanogaster* lifespan relative to that of wild-type controls, had no effect on longevity when compared with appropriate transgenic controls. Together, this suggests that SIR2 might not be affecting longevity after all.

Guarente and colleagues, however, stand by their original results: they now report that although *sir-2.1* does not have the dramatic effect on lifespan that they had originally found, it does affect it to a lesser extent, increasing *C. elegans* lifespan up to ~14%. They also show that, in accordance with the results from Gems and colleagues, the effect on longevity in their original strains was enhanced by a mutation in a second gene, which conferred sensory neuron defects.

These reports highlight how studies of genetic effects on lifespan should carefully take into account genetic backgrounds and the potential mutagenic effects of transgene insertions. As Cantó and Auwerx comment in an accompanying article (Lombard *et al.*), such analyses should be complemented by biochemical studies that reveal the extent to which genetic manipulations result in altered protein activity. As for sirtuins, future work will continue to elucidate their role in ageing. Importantly, mammalian sirtuins have been implicated in the suppression of age-associated diseases. As argued by Lombard and Pletcher, this suggests that sirtuins might primarily affect physiological homeostasis and stress responses, rather than ageing per se. They have in fact been shown to suppress metabolic dysfunctions and the development of certain types of cancer, so there is no doubt much more to come from sirtuins.

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FURTHER READING Lombard, D. B. *et al.* Ageing: longevity hits a roadblock. *Nature* **477**, 410–411 (2011)

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