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Journal Club

AGEING

CRACKING GENETIC CODES OF LONGEVITY

Archimedes once said, "Give me a lever long enough and a fulcrum, and I shall move the world." For geneticists, give them a phenotype discernible and inheritable, and they shall find the gene. Unravelling the link between genes and phenotypes has been driving our understanding of diverse biological processes. Longevity is not an exception. Like many other phenotypes, it is, at least in part, genetically controlled. The discovery of genes regulating longevity not only advances our fundamental knowledge on the ageing process, but also provides valuable handles for improving health in later life.

The first longevity-regulatory genes were discovered in *Caenorhabditis elegans*. These multicellular animals have a short lifespan coupled with the ease of genetic manipulation, making them well suited for isolating mutations that increase lifespan. The first mutagenesis screen for pro-longevity mutants employed temperature-sensitive mutants that cannot reproduce at the restrictive temperature, which enabled the quantitative measurement of lifespan on a population of individuals over their lifetime. This screen and following genetic studies identified the *age-1* mutation that increases both mean and maximal lifespans (Klass, 1983; Friedman et al. 1988). In another study that analysed temperature-sensitive mutants that form developmental arrested dauer larvae at the restrictive temperature, *daf-2* mutations that double the lifespans of adult animals were discovered (Kenyon et al. 1993). Although both *age-1* and *daf-2* mutants generate less progeny than wild-type animals, blocking reproduction per se did not extend lifespans, indicating that the pro-longevity phenotypes observed in those mutants were not due to reduced fecundity. Of note, the pro-longevity phenotype of *daf-2* mutants is dependent on another factor, as *daf-16;daf-2* double mutants have normal lifespan. Strikingly, *age-1*, *daf-2* and *daf-16* function in the same insulin/IGF-1 signalling pathway. The longevity-regulatory effect of this signalling pathway has been later confirmed in other organisms including humans. These early studies in *C. elegans* and the power of genetics did lay a cornerstone for a new era of research, which has been attracting scientists like me to enter the field of ageing biology and decipher the molecular codes of longevity.

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ORIGINAL ARTICLES Klass, M. R. A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. *Mech. Ageing Dev.* **22**, 279–286 (1983) | Friedman, D. B. et al. A mutation in the age-1 gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. *Genetics* **118**, 75–86 (1988) | Kenyon, C. et al. *C. elegans* mutant that lives twice as long as wild type. *Nature* **336**, 461–464 (1993)