Mechanisms and Evolution of Aging

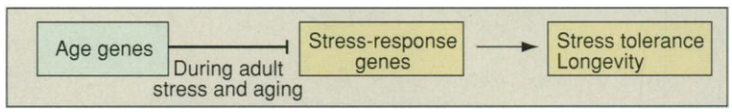
Gordon J. Lithgow and Thomas B. L. Kirkwood

Single-gene mutations that extend the life-span of the worm *Caenorhabditis elegans* dramatically demonstrate the genetic basis of aging and may eventually lead to the elucidation of aging mechanisms. At the same time, evolution theory provides a powerful insight into the genetic basis of aging, and recent experiments are allowing these ideas to be tested and refined.

One of the clearest messages to emerge from evolution theory is that aging is not likely to be regulated in the same programmed way as are early life processes such as development (*1*). The reason is simple. In the natural world, organisms die from a wide array of extrinsic as well as intrinsic causes, and in most species, few individuals live long enough to show obvious signs of senescence. Natural selection cannot plausibly explain the evolution of a temporal control system or "aging clock" whose primary function is to bring about senescence and death in only a handful of survivors, especially when this action is detrimental to the individuals in which it occurs.

Nevertheless, it is abundantly clear that genes do influence aging and longevity (*2*). What kinds of genes are these likely to be? Some of the strongest candidates are genes that regulate the processes of somatic maintenance and repair, such as the stress-response systems. Maintenance is beneficial and necessary up to a point, but most maintenance systems have hidden costs, for example, an energy requirement. The disposable soma theory of aging (*3*) points out that it is actually disadvantageous to increase maintenance beyond a level sufficient to keep the organism in good shape through its natural life expectancy in the wild, because the extra costs will eat into resources that in terms of natural selection are better used to boost other functions that will enhance fitness.

With its short 20-day life-span and accommodating genetics, the microscopic *C. elegans* worm is fast becoming an important system for genetic studies on aging. Are the life-span extension mutants of *C. elegans* consistent with the evolutionary theories of aging? The first "Age" mutation to be described, *age-1*(*hx546*), increases mean life-span by 65% and maximum life-span by 110% (*4*). Under normal laboratory conditions, strains carrying *age-1*(*hx546*) appear very similar to wild-type strains in their length of embryogenesis, postembryonic developmental time, and fertility period, with some slight reduction in reproductive output (*4, 5*). How can a single-gene mutation have such a dramatic effect on the rate of aging? One plausible model is that *age-1* is a coordinate regulator of a range of stress-response genes that shift cellular physiology toward maintenance. This model (see figure) is based on the finding that *age-1* mutant strains are better equipped than their wild-type counterparts to overcome the effects of extrinsic stress (*5–9*). First, *age-1*(*hx546*) confers resistance to hydrogen peroxide (H_2O_2) and paraquat (*6, 7*). Both of these agents cause oxidative stress by promoting the generation of highly reactive hydroxyl radicals. The mutant also accumulates fewer deletions of the mitochondrial genome, an age-related phenomenon thought to be the result of damage by radicals (*10*). The idea that oxidative stress resistance is due to a regulatory alteration comes from the observation that *age-1* mutants have elevated activities of the antioxidant enzymes Cu,Zn–superoxide dismutase and catalase, which together detoxify H_2O_2 and paraquat (*6, 7*).



Stress tolerance: The key to a long life?

The *age-1* mutant was also found to have increased intrinsic thermotolerance. When young worms are subjected to lethal heat shocks, the *age-1* mutants are 40% more resistant than are their wild-type counterparts (*5*). This finding, together with the fact that short, nonlethal heat shocks induce both thermotolerance and extended life-span, leads to the suggestion that heat shock proteins may slow aging processes (*8*). Finally, *age-1* mutant worms are resistant to ultraviolet (UV) radiation, a phenotype that has proved an excellent predictor of life-span (*9*).

Critical support for the idea that stress resistance is causally related to extended life-span comes from the analysis of other Age mutants (*11–14*). Mutations in the genes *daf-2*, *daf-23*, *daf-28*, and *spe-26* extend life-span and also confer a set of stress resistance phenotypes. All the Age mutations tested so far are resistant to oxidative stress, thermal stress, and UV radiation—with the degree of resistance often proportional to the extension in life-span. It would be parsimonious to conclude that these mutations extend life-span by a common mechanism. Classical genetic analysis of these mutations lends support to this notion. The life-span phenotypes of *daf-2*, *daf-23*, *spe-26*, and *age-1* all depend on the wild-type function of another gene, *daf-16* (*9, 11, 13*). The *daf* genes are well known to nematode geneticists because they encode components of a signal transduction pathway critical during development. It now appears that this pathway influences the maintenance of the adult worm.

An apparent challenge to the evolutionary arguments against an aging clock is the discovery of a new class of *age* genes defined by the *clk* mutants (for "abnormal function of biological clocks"). The *clk* mutants display a range of phenotypes—including slow development, a slow cell cycle, slow and irregular behavioral rhythms, and extended life-span (*14*). The mutants seem to have lost temporal control, but even *clk-1* confers resistance to UV light, so these mutations may eventually fall into line with the other Age mutations (*9*).

It is too soon to know whether the Age mutations, and genetic analysis in general, will validate the carefully prepared evolutionary theory of aging. However, we can be encouraged by the emerging story, which places an emphasis on the actions of stress-response genes in prolonging life-span rather than on the action of clock-type genes in truncating it.

The authors are in the Biological Gerontology Group, University of Manchester, 3.239 Stopford Building, Oxford Road, Manchester, UK, M13 9PT. E-mail: gordon.lithgow@man.ac.uk

References

1. T. B. L. Kirkwood and T. Cremer, *Hum. Genet.* **60**, 101 (1982).
2. C. E. Finch, *Longevity, Senescence, and the Genome* (Univ. of Chicago Press, Chicago, 1990).
3. T. B. L. Kirkwood and C. Franceschi, *Ann. N.Y. Acad. Sci.* **663**, 412 (1992).
4. D. B. Friedman and T. E. Johnson, *Genetics* **118**, 75 (1988).
5. G. J. Lithgow, T. M. White, D. A. Hinerfeld, T. E. Johnson, *J. Gerontol. Biol. Sci.* **49**, B270 (1994).
6. P. L. Larsen, *Proc. Natl. Acad. Sci. U.S.A.* **90**, 8905 (1993).
7. J. R. Vanfleteren, *Biochem. J.* **292**, 605 (1993).
8. G. J. Lithgow, T. M. White, S. Melov, T. E. Johnson, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 7540 (1995).
9. S. Murakami and T. E. Johnson, *Genetics*, in press.
10. S. Melov, G. J. Lithgow, D. R. Fischer, P. M. Tedesco, T. E. Johnson, *Nucleic Acids Res.* **23**, 1419 (1995).
11. C. Kenyon, J. Chang, E. Gensch, A. Rudner, R. Tabtiang, *Nature* **366**, 461 (1993).
12. W. A. Van Voorhies, *ibid.* **360**, 456 (1992).
13. P. L. Larsen, P. S. Albert, D. L. Riddle, *Genetics* **139**, 1567 (1995).
14. A. Wong, P. Boutis, S. Hekimi, *ibid.*, p. 1247.