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Book Review

The Molecular Genetics of Aging

Results and Problems in Cell Differentiation, Vol. 29; Siegfried Hekimi (Ed.); Springer, Berlin, 2000, ISBN 3-540-66663-X

Tithonus would be among those who disagree with the editor's claim that "many people would consider it desirable if human life span could be extended". To live forever sounds appealing, particularly if your lover is Eos, the goddess of dawn, but neglecting to have arranged with Zeus for eternal youth as well as immortality proved a blunder. In spite of ambrosial food and celestial housing, Tithonus aged inevitably to immobility. When he could only feebly croak he was mercifully turned into a grasshopper. Surely that is not the fate envisioned by the authors of this excellent collection of essays on the molecular genetics of aging, but the myth makes clear the difference between lifespan and aging, a distinction addressed by several authors here.

The study of aging and of lifespan is being transformed by the isolation of many single gene mutations that increase lifespan in yeast, worms, flies and mice. This collection of articles describes the analysis of these mutations and the development of additional tools for their study. Mutations in many, if not most, genes can affect lifespan. How then do you select those most relevant to the aging process? The authors here use two strategies. One is to identify or select mutations that increase rather than decrease lifespan, reasoning that this is less likely to identify mutations that just make organisms sick. The second is to select mutations altering processes thought to be involved in aging, such as oxidative damage, and see if they alter lifespan. Characterization of both kinds of mutations is showing a common theme across organisms: many of the mutations that increase lifespan also increase stress responses, particularly to oxidative stress, and they alter metabolism.

There remains much to be done, however, to bridge the large gap between identified molecular alterations in mutants and their effect on the organism's lifespan. Much of this gap is caused by the complexity of gene interactions during development, which causes all developmental mutations to have multiple phenotypes. Thus it is difficult to relate any single molecular or cellular defect, whether in a signaling pathway or a mitochondrial enzyme, to a holistic organismal phenotype like lifespan. In addition, the observed phenotype is not a property of the gene but a property of the particular alleles being studied. In several of the best studied genes that can mutate to increase longevity, e.g. *daf*-2 in *C. elegans*, alleles vary greatly in phenotype in a manner not explained simply from their molecular defects. Much of our understanding of other developmental genes has come from comparing the phenotypes of different alleles, but interpretation is dependent on knowing whether mutations are null, partial loss-of-function or gain-of-function. A

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disconcerting number of the genes described in these chapters are defined by single alleles, whose affects on the gene aren't known.

An even more fundamental problem interpreting mutations that increase lifespan is caused by varying interpretations of what is meant by "the function of a gene". To an experimental geneticist, the function of a gene is to do whatever is missing when the gene is knocked out. To an evolutionary biologist, however, the biological function of a gene is do that what has been acted on by natural selection to maintain and modify the gene. This evolutionary definition of function is much harder to establish, but I suspect that it is not the function identified by the experimental geneticist more often than we admit. This problem arises most acutely if we ask, are there really any genes whose function have been selected to increase lifespan? Medawar and others have argued against this for more than half a century, because it is hard to envision how natural selection can act on gene function beyond the reproductive period of an organism, unless the post-reproductive organism cares directly for its young. Thus whatever determines post-reproductive lifespan must result from genetic drift or natural selection for other pleiotropic phenotypes. Thus the terms such as 'aging genes,' 'gerontogenes," 'lifespan assurance genes,' and 'genetic pathways for lifespan,' though appealing, are biologically misleading.

On the other hand, there are clearly mutations that do increase lifespan. If natural selection did not act on the mutated genes to influence lifespan, what biological function were they selected for, and how is it that they have a pleiotropic effect on lifespan? Surely, understanding what these mutations are doing and explaining how they lead to increased lifespan will be central to our understanding of the aging process. This book provides an excellent description of how this genetic analysis is progressing, and it conveys a sense of the excitement felt by these investigators as they identify and analyze new lifespan mutants. The book would have benefited if the authors could have commented on each others chapters, which could also have reduced the multiple descriptions of the model organisms, particularly *C. elegans.*

The fascinating opening chapter by Perls et al., examines evidence for the genetic determination of maximum human lifespan based of families of centenarians. Since centenarians are the fastest growing age group this analysis is particularly timely. This chapter makes clear the distinction between mean and maximum lifespan and addresses the indirect selective pressures that might lead to genetic determination of maximum lifespan. Families with clusters of centenarians provide clear evidence for a genetic component of extreme longevity. The authors also discuss evidence that there is a correlation between delayed menopause and extreme longevity. They support the argument that this could be a causal connection if the genes that regulate the timing of menopause were closely linked (or the same) as genes that regulate how fast we age. Together with the argument that menopause is adaptive to ensure parenting by reducing the risk of death associated with late childbirth, they argue that it is selection for delayed reproductive senescence that could lead to inheritance of extreme longevity. A corollary of this argument is that since modern obstetrics reduces the mortality risk during childbirth (at least in some parts of the world), there is no longer selection that would lead to further increases in maximum human lifespan.

For *C. elegans*, Lithgow also uses evolutionary arguments to explain why the worm's life in the inhospitable soil environment has led to selection for effective stress responses

early in life to ensure reproduction. He then goes on to review evidence that mutations that increase life span also lead to increased generalized stress responses, to oxidative stress as well as to thermal and UV stress. He is cautious about drawing the conclusion that it is just the increased stress response which leads to increased longevity, but he clearly recognizes the way that natural selection for increased stress response could lead, secondarily, to increased worm lifespan.

Three additional chapters describe further correlation between aging and metabolic activity, oxidative stress and other stress. Jazwinski argues that the life span in yeast, defined as the number of cell divisions an individual cell completes, is controlled by the coordination of metabolic activity and resistance to stress. He proposes a model where this coordination is provided by the RAS family of small GTPases. These act to maintain homeostatis of both metabolic activity and stress responses, with metabolic activity as the primary determinant of lifespan. Since RAS GTPases are central to regulation of many biological processes, this is a case where it is not clear on what selective pressure is acting. The effect on lifespan is likely to be secondary to more immediate needs of the cells.

The role of oxidative stress in aging in worms is described by Ishii and Hartman, and a critical overview of the status of this widely held explanation for aging is proved by Sohal et al. *C. elegans* mutants selected to be more sensitive to oxidative damage do die early, particularly when exposed to high oxygen levels. In addition they accumulate biochemical markers of aging, increased protein carbonyls and increased fluorescent materials, more rapidly. One of these is a mutation in the cytochrome b560 component of mitochondrial succinate-ubiquinone reductase. Recently, it has been shown that the lifespan of this mutant was increased by treatment with antioxidants further supporting the role of oxidative damage in reducing lifespan (Melov et al., 2000).

As in studies on yeast, Sohal et al. discuss the relation between metabolic rate, oxidative stress and antioxidation defenses. They emphasize the importance of distinguishing chronological age from physiological age, particularly in poikilotherms. The lifespan of both worms and flies can be increased more than most of the long-lived mutants simply by growing the animals at lower temperature. This presumably reflects reduced metabolic rate and shows the importance of taking into account the metabolic potential in aging studies. The authors argue that mutations or conditions that increase resistance to stress and elevate antioxidative defenses also induce a hypometabolic state and all three together contribute to reducing oxidative damage, which results in an increased lifespan. In a section on hazards of life-span analysis in Drosophila they describe difficulties interpreting transgenic experiments (including their own) which overexpress antioxidant proteins such as SOD or catalase. Difficulties can arise from variation in genetic background, variable expression of transgenes, and biochemical and physiological compensation by induction or suppression of natural antioxidants. For decisive experiments to be done to establish the causal relationships between oxidative stress and aging, it will be essential to both increase and decrease oxidative damage while determining as many parameters as possible. Ideally, one needs to vary the levels of oxidative damage genetically or environmentally and determine lifespan while measuring oxygen consumption, oxidative damage to proteins, lipids and DNA, levels of antioxidants and levels of other stress response proteins. This has yet to be accomplished cleanly in any organism.

Hekimi provides a detailed review of aging and lifespan mutations in *C. elegans*. This

includes studies on mutations in the pathways that control an inducible dormancy, and on the effects of caloric restriction induced using mutations that do not feed properly. By combining these he tries to determine if they are acting in sequential or parallel pathways. This is difficult to do with mutations affecting different cells, but he finds that it is possible that reduced metabolic rate could be the most proximal cause of slow aging, although the metabolic rate has not been measured directly in many of these experiments. Much of the discussion focuses on the clock mutations isolated in his own laboratory. These mutations slow practically all developmental processes including aging, and they extend lifespan substantially. He concludes from this that *clk*-1 affects a regulatory process that is somehow involved in setting the rate at which the organism lives its life, and he provides a regulatory model to explain how the various mutations contribute to lifespan control. Since the publication of this book, mutations in the *clk*-1 gene have been shown to alter coenzyme Q biosynthesis, an affect concealed initially by coenzyme Q provided to the worms by the bacteria on which they feed (Jonassen et al. 2001). Thus in *clk*-1 mutants there is a simple defect in a fundamental biochemical process needed for energy generation. This is an example of alternative meanings of gene function. Surely, it makes little sense to describe the *clk* genes as part of a regulatory process setting the rate of living if they simply alter a basic step in energy metabolism.

A new approach to aging in *C. elegans* is described by Herndon and Driscoll. Much has been learned about pathways of programmed and necrotic cell death in *C. elegans* and mutants are available altering many of the steps. Herndon and Driscoll use these mutants to ask whether programmed cell death or necrotic cell death contribute to overall lifespan. They find no evidence that mutants altering programmed cell death alter lifespan, although not all classes have been tested. Intriguingly, mutants that suppress necrotic cell death do shown increased lifespan. The relation between these mutants and others that influence lifespan will be of considerable interest.

Two chapters demonstrate the genetic engineering of organisms to provide specific markers for aging research. Helfand and Rogina have used enhancer trap screens to obtain Drosophila lines with β-galactosidase gene insertions that provide precise reporters for gene expression. They shown that regulation of some genes is not altered at all during aging, showing that there is not an overall loss of gene regulation. Of more importance, they identify genes whose expression is altered during aging which could serve as markers for aging studies. In the mouse, Dollé describes an ingenious β-galactosidase plasmid system for monitoring mutation accumulation and shows that it responds to mutations known to alter genome stability.

In chapters on mammals, Bartke describes the relation of endocrine control to delayed aging in dwarf mice and Van Zant given an excellent review of stem cells in the study of aging. This is a topic of growing significance as more and more stem cells are being isolated and induced to grow into a wider variety of tissues than had been previously suspected.

This excellent collection of chapters does not yet provide the solution to Tihonus's dilemma. The mechanisms of aging have not yet been established, although they are hinted at by consistent examples of resistance to stress and oxidative damage. One can't come away from reading this volume, however, without believing that molecular genetics will indeed lead to understanding the mechanisms of aging in model organisms at

least. If these mechanisms are conserved, as so much of our genomes are conserved, this will surely help us understand and slow the deleterious effects of aging. Will this then make humans immortal? Without the intervention of Zeus to aid our overpopulated planet, let us hope not.

References

Jonassen, T., Larsen, P.L., Clarke, C.E., 2001. A dietary source of coenzyme Q is essential for growth of long-lived *Caenorhabditis elegans clk*-1 mutants. Proc. Natl. Acad. Sci. USA 98, 421–426.

Melov, S., Ravenscroft, J., Malik, S., Gill, M.S., Walker, D.W., Clayton, P.E., Wallce, D.C., Malfroy, B., Doctrow, S.R., Lithgow, G.J., 2000. Extension of life-span with superoxide dismutase/catalase mimetics. Science 289, 1567–1569.

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