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Perspective

Comparative Biology of Aging

Steven N. Austad

Department of Cellular and Structural Biology, Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center, San Antonio.

Virtually, all research on basic mechanisms of aging has used species that are short lived and thus demonstrably unsuccessful at combating basic aging processes. A novel comparative approach would use a diversity of populations and species, focusing on those with particularly long, healthy lives, seeking the causative mechanisms that distinguish them from shorter lived relatives. Species of interest from this perspective include the naked mole rat, a mouse-size rodent that lives up to 30 years in the laboratory, and the little brown bat, which lives up to 34 years in the wild. Comparisons among dogs of different sizes, which differ by more than 50% in health span might also prove rewarding, as might novel species chosen because of their similarity to humans in certain key traits. Primates, because of their sophisticated cognitive ability, are a group of special value, and small, short-lived primates like the common marmoset might prove especially beneficial. Cell repositories and tissue banks from key species, as well as genomic and analytic tools optimized for comparative studies, would make valuable contributions to a new comparative approach to basic aging research.

BIOCHEMIST Leslie Orgel famously stated that "evolution is cleverer than you are," by which he meant that natural selection is likely to discover solutions to complex problems that might elude a directly focused investigation of such problems. Support for this claim is inherent in the increasing use of algorithms based on natural selection to solve problems in diverse fields such as computer programming, drug design, and industrial scheduling. The fundamental premise of comparative aging studies is that nature has designed mechanisms of exceptional resistance to basic aging processes, and that by identifying and investigating such resistance, we might discover senescence-retarding mechanisms that differ from, and are superior to, those elucidated by the study of short-lived species such as worms, flies, and mice.

Selection of species for comparative investigation should be based on several criteria. First, key species should be exceptionally long lived for their body size, with added interest in those species that are known to survive exceptionally long in the wild. Extreme survival in the wild indicates preservation of high-level physical function and not just avoidance of death from intrinsic processes. Two mammal species of this nature would be (a) the naked mole rat (*Heterocephalus glaber*), a mouse-size subterranean rodent that lives at least 17 years in the wild and almost twice that in captivity, avoids many age-related changes that plague other species, and is remarkably resistant to developing tumors (1), and (b) the little brown bat (*Myotis lucifugus*), a common, well-studied bat of North America, which despite weighing roughly one third as much as a mouse lives up to at least 34 years in the wild, and for which the entire genome has been sequenced to 2× coverage and is currently in the last stages of full 7× coverage sequencing (http://www.broad.mit.edu/science/projects/mammals-models/brown-bat/brown-bat). These are only two examples. Long life, defined by species that live at least twice as long as expected for their body size, has evolved repeatedly in mammals. In principle, studies could use multiple species spread out among the many branches of the mammalian evolutionary tree. This would also allow researchers to address whether there are many, few, or just one route to the evolution of slow aging.

Second, the most informative species might also be those in which closely related species (or even other members of the same species) senesce at a substantially different rate. Pairwise comparisons among a broad series of such long- and short-lived species might be particularly useful in identifying new processes and pathways modulating the rate of senescence. For example, the evening bat (*Nycticeius humeralis*) is closely related to the long-lived little brown bat, and field studies indicate that it lives no longer than 6 years in the wild (2). Some species, a particularly well-defined example is the domestic dog, display substantial genetic variation for aging rate within the species, with some dog breeds remaining healthy and surviving more than 50% longer than others (3) (see also article by Miller [4]). Two particular strengths of dogs as model organisms are that the canine genome, including its variants, is being rapidly fleshed out (coverage includes ~99% of the euchromatic genome and 2.5 million single nucleotide polymorphisms [SNPs]) and assessment of health span as well as a diversity of chronic, age-related diseases is

better described for dogs than for any other nonhuman organism (5,6). Another potential example is the horse, in which small breeds also appear to age more slowly than large breeds (3). A disadvantage of horses relative to dogs is their longer life, greater cost, and less well-characterized clinical health profile. A third type of particularly informative model would be one in which dramatic variation within the species can result from environmental intervention. A striking example of such a species is the honeybee (*Apis mellifera*), which depending upon the composition of the larval diet, can produce workers that live a few months or queens that live up to a few years (7). Some ant species have an even more dramatic (~500-fold) difference between worker and queen longevity (8), although the same genomic resources are not available for ants as for bees (9).

Third, there might also be species of investigatory interest because of certain similarities they bear to humans. For instance, cognitive abilities of worms, flies, and mice are rudimentary compared with humans. Thus, studies of age-related cognitive decline must necessarily be relatively crude with respect to human capabilities. Modeling something like executive function (planning and organization of activities), for instance, remains a problem with invertebrate models and even mice. Nonhuman primates, however, allow investigation of these subtle types of cognitive decline (10). Although virtually all nonhuman primate studies on aging to date have used rhesus monkeys, smaller, more tractable, and shorter lived primate models are available. The common marmoset (*Callithrix jacchus*) is a rat-size New World primate that has the cognitive capacity to perform touch-screen computer learning tests (11), yet lives only about 7 years on average and 16 years at a maximum (12). Thus, animals pass from vigorous young adulthood to senescence within only about a 5-year span, facilitating longitudinal studies of aging in a reasonable time period. Another advantage of common marmosets for aging research is that they typically bear dizygotic twins, allowing for control of maternal effects if that is important in one's experimental design. A full 7× coverage of their whole genome is currently in the final stage of sequencing, including the development of SNPs (http://www.hgsc.bcm.tmc.edu/projects/marmoset/).

Understanding of reproductive senescence might also be fertile ground for comparative investigation. For instance, we currently have little insight into the molecular sources of variation in the rate of decline of spermatogenesis or oogenesis. Furthermore, we do not understand the nature and variability of rate of decline in offspring quality with age. Although there has been some controversy over the so-called Lansing Effect, which states that older parents will bear shorter lived offspring (13), there is no controversy that older parents are more likely to have children with serious genetic anomalies compared with younger parents. Yet the mechanistic reasons underlying the complex differences between the sexes are only vaguely understood (14). A comparative approach might yield new insight on these issues.

One area of research that might warrant considerable development is the comparative biology of stem cells. Even short-lived species that are largely postmitotic such as fruit flies have stem cells for renewal of specific tissues (15). Longer lived organisms with many renewing tissues have stem cells that survive and replicate for considerably longer, and some apparently "nonaging" organisms may owe their longevity to the performance of their stem cells (16,17). The comparative analysis of cellular processes, the proteome, and gene expression patterns may reveal a considerable amount about how nature has designed stem cells to survive only a short period versus for decades.

In addition to the identification of informative new species and populations for mechanistic studies of aging, new resources and tools for comparative biology will also be important. Although captive colonies of a large array of species are not a tenable goal, tissue and cell resources from a substantial range of informative species may be. Low passage number, nontransformed fibroblasts from an array of roughly 200 samples from about 50 primate species are currently available for purchase from the Coriell Institute for Medical Research. This institute also maintains cell cultures from about 20 nonprimate species of interest to biogerontologists. Fibroblasts from other mammal species of gerontological interest such as naked mole rats and various bat and squirrel species are also maintained in several laboratories of individual investigators across the United States and abroad. A collaboration to obtain, store, and encourage investigator's use of both cell and tissue samples from diverse species of special interest has recently been established between the National Institute on Aging-supported Nathan Shock Centers of Excellence in the Biology of Aging at the University of Michigan and the University of Texas Health Science Center San Antonio. Additional information about these resources may be obtained by contacting me directly.

One type of cellular resource that may be particularly useful to comparative biologists is a bank of induced pluripotent stem (iPS) cells from diverse species (see also article by Sharpless and Schatten, [18]). Because these cells can be created from fibroblasts and can then be differentiated into multiple cell types (19), such a bank might alleviate many of the difficulties of getting fresh tissue samples from species not commonly kept in laboratory or zoo settings. Moreover, it appears as if the reprogramming of differentiated cells into iPS cells can be accomplished with genes from another mammal species, as the critical mouse transcription factors have been successfully used to make human IPS cells (20).

Other resources useful for cellular and molecular investigations of aging would include genomic, transcriptomic, proteomic, and metabolomic data for a range of informative species. Of these, the resource likely to be most immediately available for comparative research is genomics data. There are currently more than 90 vertebrate species with whole genome sequences finished, in

process, or in the advanced planning stages as listed by the International Sequencing Consortium (http://www.intlgenome.org/viewDatabase.cfm), and with the astonishing rate of increase in sequencing power, this list will no doubt grow rapidly. Other "--omics" resources will develop more slowly, but some thought should be given to the systematic and rational collection of these data for species of exceptional interest to investigators in the comparative biology of aging.

Analytic tools for the massive welter of comparative data soon to be available also require development. It is now apparent that issues involving such potential confounding variables as phylogeny and body size must be accounted for in comparative longevity analyses, but tools for implementing these analyses have only recently become widely known in the field (21). These analytic tools could be further developed, but new tools, particularly for exploratory analyses, also require development.

An interesting initial endeavor aimed at developing such a resource would be the Human Ageing Genomic Resources Web site (http://genomics.senescence.info), a project directed by João Pedro de Magalhães of the University of Liverpool. A fairly comprehensive and searchable compilation of information on genes that have been associated with aging in traditional model species plus humans.

This Web site is also the most reliable and thoroughly curated source of information on the longevity of vertebrate species. In addition to its function as a data source, the Web site also provides links to public gene and protein databases and a range of computational tools for data-mining sequences, generating phylogenetic profiles, assessing protein–protein interactions, and other analyses.

The comparative biology of aging is complex. Done thoroughly, it will require collaboration between many types of investigators who do not commonly interact with one another, such as evolutionary biologists, cell biologists, zoologists, demographers, physiologists, experts in functional genomics and systems biology, and no doubt other subdisciplines which I have neglected. However, the payoff for such an effort may well prove invaluable for moving forward aging research in productive, potentially unexpected directions.

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Correspondence

Address correspondence to Steven N. Austad, PhD, Department of Cellular and Structural Biology, Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center San Antonio, San Antonio, TX, 78245-3207. E-mail: austad@uthscsa.edu

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