Journal of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 2, 161–163
doi:10.1093/gerona/gln067

Advance Access publication on February 18, 2009

Special Issue: Biology of Aging Summit

Perspective

Can We Develop Genetically Tractable Models to Assess Healthspan (Rather Than Life Span) in Animal Models?

Marc Tatar

Division of Biology and Medicine, Brown University, Providence, Rhode Island.

Understanding healthspan is arguably the most relevant clinical, social, and economic feature of aging research. The model systems of worm, fly, and mouse are potentially powerful tools to achieve this aim. These models provide two unique approaches. The first is based on genetic screening for gain or loss of function mutations that ameliorate senescence. Genetic factors discovered by this process permit us to recognize causal and regulatory mechanisms of aging. A related screen looks for compounds that slow aging or act upon proteins that were initially identified from genetic analysis. The second research strategy uses manipulations of targeted genetic factors to test causal explanations for aging. These studies include transgenic organisms and genetic epistasis analysis. Overall, genetically driven research with model organisms is largely responsible for the breakthrough of aging biology in the past 15 years. Aging in these contexts, however, has been measured almost exclusively from cohort survival statistics such as life expectancy and age-specific mortality. This is for a good reason. Manipulated factors that extend life span are thought to unambiguously slow senescence and thus to reflect underlying causes of the aging process. But this approach is also common for a practical reason—healthspan is a poorly defined commodity in humans, let alone for genetic animal model systems. It was the consensus of the working session that making healthspan an operational metric would be an innovation needed for the genetic power of model systems to address this aspect of human aging.

Key Word: Functional senescence—Healthspan—*Drosophila*—*C. elegans.*

THE problem of defining healthspan is not new. This issue was also recognized as a central challenge at the National Academies Keck Futures Initiative: The Future of Human Healthspan: Demography, Evolution, Medicine, and Bioengineering (1). This group agreed that "healthspan should be defined as the length of time an individual is able to maintain good health, but would not be equated with lifespan. Health was defined as the ability for a system to maintain or return to homeostasis in response to challenges" (p. 3). George Martin of our session paraphrased this by noting that health is a continuum with degrees of robustness measured as ability to respond to homeostatic challenge. There are several notions represented in these statements that need to be sorted if we are to make healthspan an operational metric for experimental analysis.

First, "length of time an individual is able to maintain good health" implies that we treat healthspan as an event time variable: at some time (age), an individual passes from a state of good health to unhealthy. What is "good health" and how do we determine when an individual no longer possesses this property? The Keck report suggests that good health is the ability for "a system" to maintain homeostasis when challenged. The report does not discuss at what level of system we should look at but implies that it must be below that of the integrated whole subject because healthspan is not equal to life span (the challenge cannot be assessed at the level of the integrated subject because in this case we would judge success as alive and failure as dead, life span–defining events). Healthspan must thus be a segmented property where we examine alone or as sets the function of physiological systems. This fractionation contributes to the ambiguity of the healthspan concept because there is no consensus on how many or which systems are necessary and sufficient. Furthermore, the number of systems that are "unhealthy" can vary among people—health in this one way is a continuum. But now, without also defining a threshold, there is no dichotomous distinction to make for a subject to exist in the healthy or unhealthy state. It becomes a matter of degree and thus complicates how we measure the "length of time" between good health and otherwise. If health is a continuous property, we require an explicit discussion of the threshold criteria to delineate healthspan as an event time.

Aside from these issues of dimensionality, the test of homeostasis upon challenge is a useful feature to make health an operational measure. Good health is recognized by the ability to retain or return to normal levels when a subject is manipulated in a way to perturb a targeted system. Importantly, "normal" can be set at the level expressed by the subject just before it was exposed to the stress. This avoids two

potential problems that otherwise arise if we measure health as a deviation in performance between age classes. First, homeostasis is self-referenced and thus cannot be confounded by demographic selection acting upon heterogeneity within a cohort. Of course, age comparisons made by longitudinal analysis are also normalized within the individual, but longitudinal designs are often impractical for model animals, especially invertebrates. The second issue involves how we interpret age-dependent changes in the function of systems. We assume that a change in some parameter with age indicates degeneration. But changes may actually reflect adaptation with age. For instance, does the elevated proinflammatory status of aged humans represent a loss of immune regulation or a well-functioning defense response to chronic infection? Does increased stem cell proliferation in the mammalian gut represent loss of cell cycle control or an appropriate reaction to meet increased need for cell replacement in the tissue? By testing subjects with a challenge, we assess the capacity to retain function, whether it is what is left of the system's performance after degeneration or an adaptation.

The concept of homeostasis also comes with limitations. The baseline parameter of many physiological systems declines endogenously with age. Homeostasis does not recognize the retention of youthful performance as a measure of healthfulness. Furthermore, the rates of such declines can vary among individuals and even among systems within individuals. Using homeostasis as the criteria for health overlooks how the age-specific baseline of the system changes relative to each subject's younger performance. If healthspan includes notions of how long a subject can function in an independent, nonpathological state, defining health only by the capacity for homeostasis will omit intuitively important features of what it means to age successfully.

The unresolved operational meaning for human healthspan is an obstacle for model systems. To conduct screens or genetic analysis, we need to identify precise phenotypes with clear analogy to traits of human healthspan. Although we do not yet know what this looks like, researchers with animal models have turned to the analysis of functional aging.

In the first strategy, the performance of organism-specific traits are measured as a function of age, either longitudinally or as sampled from an aging cohort. In *Drosophila*, these traits include the capacity to climb, to fly, or to display negative geotaxis (2). As these are complex traits dependent on many systems, they may usefully reflect fly healthspan. But translating these traits to humans is abstract. As noted, human healthspan is operationally vague. Beyond this, traits such as invertebrate motion or geotaxis involve many unspecified physiological and anatomical systems. We cannot yet identify where degeneration is taking place to affect the observed change in performance. Without the ability to map sites of pathology from animal model to human we cannot fully exploit the power of the genetic systems to identify mechanisms underlying healthspan.

The second approach likewise measures age-dependent performance but focuses explicitly on anthropomorphic traits. This strategy is common with the mouse where we can assess features such as echocardiograms, grip strength, and glucose tolerance and then examine the responsible tissues in a way that is translatable to humans. The mouse, however, is limited by its genetics. It is not practical for a mutant screen, although recent progress for transgene and candidate mutant analysis is impressive. Invertebrate models provide the best platform for genetic screening. To date, these animals provide limited access to anthropomorphic traits of functional aging, although there are some promising cases. *Drosophila*, for instance, have increased sleep fragmentation with age, as seen in humans (3,4). Importantly, the homeostasis of the sleep system can be measured in flies as in humans. In both species, the capacity for sleep rebound after deprivation is reduced in old subjects. Aging of the myocardium has also been modeled in *Drosophila*, both with and without pacing as a challenge (5,6). The relevance of the fly as a model for healthy aging is also clear in this study where genetic manipulations that extend longevity postponed the age-dependent degeneration of heart performance. Likewise, sarcopenia is readily studied in aging *Caenorhabditis elegans* where investigators can follow locomotion while muscle structure is visualized through the adult cuticle (7). Mutants that extend life span were also shown to postpone sarcopenia in the worm, and to correlate with the rate of lipofuscin accumulation and the stability of proteins. Age-dependent change of innate immune function is attracting attention in both the worm and the fly. The homology of these models to the human system is notable because mutational screens in the fly originally discovered the signal transduction pathway for mammalian nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) . Several studies report increased baseline expression of the NFkB-like targeted genes for antimicrobial peptides in aged flies, and it is possible to analyze the homeostasis of the fly immune pathway upon virulent and nonvirulent challenge (8–11).

Systems that may comprise components of human healthspan are thus already represented in standard animal systems. The highest homology involves traits with anthropomorphic features. Given that healthspan in humans is still imperfectly defined, a productive strategy for worm, fly, and mouse is to expand and refine the repertoire of functional aging traits designed to reflect specific human attributes. Importantly, improved healthspan can be suggested from animal models when genetic manipulations slow or postpone the change in age-dependent performance (12). In this way, we can still dissect the mechanisms associated with slow loss of function without having to specify the time an individual remains in good health.

To further this goal, we recommend a workshop with geriatricians, experts in functional aging of human systems, and animal model specialists. The objective would be to

identify priorities and strategies to "reverse translate" critical aspects of human functional aging into appropriate, analogous animal phenotypes. How, for instance, could osteoporosis be studied in mouse, fly, or even worm? Although loss of bone integrity cannot be directly modeled in invertebrates, these animals may still express molecular aspects of the osteoporosis process and thereby display as yet unrecognized degenerative traits with anthropomorphic value. Key to this endeavor would be to have the animal models reflect consensus on what comprises the important features of human functional aging. The collection of these traits might then represent what it means to have success along the continuum of health with age, that is, a lengthy healthspan. By identifying potential counterparts in the genetic animal systems, we can set a research agenda for future experimental genetic analysis of human healthspan and healthy aging.

Acknowledgments

The authors thank all the participants in this very lively discussion that occurred within the context of the Biology of Aging Summit in September 2008.

Correspondence

Address correspondence to Marc Tatar, PhD, Division of Biology and Medicine, Box G-W, Brown University, Providence, RI 02912. Email: marc_tatar@Brown.edu

References

1. The National Academies Keck Futures Initiative: The Future of Human Healthspan: Demography, Evolution, Medicine, and Bioengineering, Task Group Summaries. Arnold and Mabel Beckma Center, Irvine, CA, and The National Academies of Science 2008.
2. Grotewiel MS, Martin I, Bhandari P, Cook-Wiens E. Functional senescence in *Drosophila melanogaster*. *Ageing Res Rev.* 2005; 4:372–397.
3. Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. Correlates of sleep and waking in *Drosophila melanogaster*. *Science.* 2000;287: 1834–1837.
4. Shaw PJ, Tononi G, Greenspan RJ, Robinson DF. Stress response genes protect against lethal effects of sleep deprivation in Drosophila. *Nature.* 2002;417:287–291.
5. Ocorr K, Reeves NL, Wessells RJ, et al. KCNQ potassium channel mutations cause cardiac arrhythmias in Drosophila that mimic the effects of aging. *Proc Natl Acad Sci U S A.* 2007;104: 3943–3948.
6. Wessells RJ, Fitzgerald E, Cypser JR, Tatar M, Bodmer R. Insulin regulation of heart function in aging fruit flies. *Nat Genet.* 2004; 36:1275–1281.
7. Herndon LA, Schmeissner PJ, Dudaronek JM, et al. Stochastic and genetic factors influence tissue-specific decline in ageing *C. elegans*. *Nature.* 2002;419:808–814.
8. Zerofsky M, Harel E, Silverman N, Tatar M. Aging of the innate immune response in *Drosophila melanogaster*. *Aging Cell.* 2005; 4:103–108.
9. Ren C, Webster P, Finkel SE, Tower J. Increased internal and external bacterial load during Drosophila aging without life-span trade-off. *Cell Metab.* 2007;6:144–152.
10. Ramsden S, Cheung YY, Seroude L. Functional analysis of the Drosophila immune response during aging. *Aging Cell.* 2008; 7:225–236.
11. Libert S, Chao Y, Chu X, Pletcher SD. Trade-offs between longevity and pathogen resistance in *Drosophila melanogaster* are mediated by NFkappaB signaling. *Aging Cell.* 2006;5:533–543.
12. Martin I, Gargano JW, Grotewiel MS. A proposed set of descriptors for functional senescence data. *Aging Cell.* 2005;4:161–164.

Received December 9, 2008
Accepted December 9, 2008
Decision Editor: Huber R. Warner, PhD