Evolutionary Nutrigenomics

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Chapter 11
Evolutionary Nutrigenomics

Michael R. Rose, Anthony D. Long, Laurence D. Mueller, Cristina L. Rizza, Kennedy C. Matsagas, Lee F. Greer, and Bryant Villeponteau

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11.1 Introduction: Aging Arises from a Failure of Adaptation, Not Cumulative Damage

The common assumption among gerontologists is that aging is a process of inexorably accumulating damage or disharmony. This assumption has held sway since Aristotle, the chief source of variation in the articulation of this assumption being the historically prevalent fashions in biological thought, from the four Greek elements of air, fire, water, and earth to contemporaneous notions about oxidation, free radicals, and the like (Rose 2007). The falsity of this assumption is revealed by three obdurate biological facts:

(i) there are organisms like fissile sea anemones and Hydra which show no detectable aging;
(ii) species are sustained by unbroken cell lineages that are hundreds of millions of years old, whether those lineages engage in sex or not; and

M.R. Rose (✉)
Genescient, LLC, Irvine, CA, USA
e-mail: mrose@genescient.com

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(iii) in some laboratory cohorts of sufficient size, actuarial aging comes to a halt at late adult ages (Rose 2008).

None of these now well-established features of aging are compatible with the view that aging is simply and solely a result of inexorably accumulating damage, disharmony, or the like.

Instead, aging is due to sustained declines in Hamilton's Forces of Natural Selection (Hamilton 1966; Charlesworth 1980; Rose 1991; Rose et al. 2007). Natural selection is what produces adaptation, the term "adaptation" referring to attributes useful for survival and reproduction. As the power of natural selection declines, a decline that Hamilton's Forces quantify explicitly and from first principles, adaptation is expected to decline. This is how evolutionary biologists explain aging.

Cases in which aging does not occur at all, such as strictly and symmetrically fissile species or evolving germ lines, are instances where Hamilton's Forces do not decline at any point. Notably, it has recently been shown that the apparent cessation of aging late in adult life is also explicable in terms of Hamilton's Forces (Mueller and Rose 1996; Rose et al. 2002; Rauser et al. 2006). That is, there is a direct correspondence between situations in which aging is not observed and circumstances in which Hamilton's Forces do not decline. This is one of many types of empirical evidence that support the Hamiltonian explanation of aging (Rose 1991; Rose et al. 2007). Significantly for Popperian scientists, there are no well-attested refutations of the Hamiltonian theory of aging. This is a significant advantage of the Hamiltonian theory of aging for evolutionary geneticists, physicists, and other scientists who practice "strong inference" (vid. Platt 1964).

Naturally enough, evolutionary biologists have been able to readily and substantially postpone aging by manipulating Hamilton's Forces (Rose and Charlesworth 1980; Luckinbill et al. 1984; Rose 1991), a track record that is unmatched by attempts to manipulate aging based on non-evolutionary gerontological theories. This is not surprising, because most mainstream gerontological theories are variants of Aristotle's original error about aging. Our conclusion is that the Hamiltonian gerontology provides the best scientific foundation for properly thought-out attempts to substantially intervene in the process of aging (Rose 1991, 2008).

11.2 Making SENSE: Strategies for Engineering Negligible Senescence Evolutionarily

In this article, we principally address this question of how to use Hamilton's Forces to ameliorate human aging. This is a question that we have long pursued (e.g. Rose 1984, 2005, 2008), generally without making any material headway. There was a singular reason for this past failure: evolutionary biologists had not been given the resources to pursue any of their proposals as to how we might ameliorate aging in

humans, despite their notable successes both at explaining aging scientifically and at slowing aging in laboratory populations. We will not comment here on why this regrettable situation was allowed to subsist, and turn instead to recent developments that have proven surprisingly positive.

We have recently summarized alternative strategies for engineering negligible senescence based on the scientific foundations supplied by evolutionary biology ("SENSE"), rather than the typical foundations supplied by current fashions in cell and molecular gerontology (Rose 2008). These SENSE strategies are based on using Hamilton's Forces to produce model organisms with slowed aging and then reverse-engineering the biology of those organisms to discover interventions that can be used to ameliorate human aging.

The chief issue within Hamiltonian gerontology has been the best type of organism to use in this project. In the 1980s, it was supposed that only a mammalian species would yield Hamiltonian results that could be reliably reverse-engineered (e.g. Rose 1984), because of the close evolutionary relationship among mammalian species and the then-considerable difficulty of discerning genetic commonalities between humans and less-related species, such as insects and nematodes. But with the advent of powerful genomic technologies circa the year 2000, it became apparent that it might be possible to use fruit flies that had been forced to evolve slower aging using Hamiltonian methods (Rose et al. 2004), the so-called "Methuselah Flies," as an alternative to mice, so long as "SENSE Methuselah Mice" were not available (Rose 2008). Thus the most immediate prospect for SENSE is the use of Hamiltonian, or SENSE, Methuselah Flies as a source of genomic information with which to develop useful ways to ameliorate human aging. It is this prospect which is our chief concern here.

11.3 Using Double-Screen Genomics to Identify Targets for Intervention

With the whole-genome sequencing of both humans and fruit flies circa 2000, as well as the concomitant advent of whole-genome tools for measuring gene expression, there is now an "information superhighway" connecting fruit flies and humans. It is now trivial to identify corresponding genes ("orthologs") between these species. Furthermore, it is easy to compare genetic and gene-expression differences between Methuselah Flies produced using Hamiltonian methods with their matched controls.

In 2006, Genescient LLC took advantage of these technologies to compare whole-genome gene-expression patterns in Methuselah Flies with their matched controls. We found about 1,000 genes showing statistically significant differences in expression. These genes are thus presumptive candidates for the genetic changes that underlie the substantially ameliorated aging achieved using Hamiltonian methods in fruit flies. Even more exciting for the purpose of reverse-engineering interventions, in 2007 we found that more than 700 of these genes had matching "orthologous" loci in the human genome.

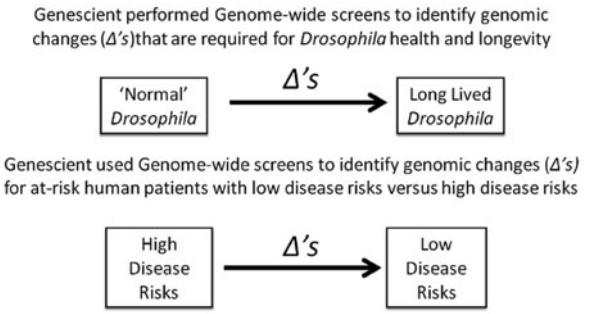

Fig. 11.1 Genescient identified human aging genes. Compared low and high risk patients with chronic diseases to wild-type and long-lived flies to obtain orthologs related to aging

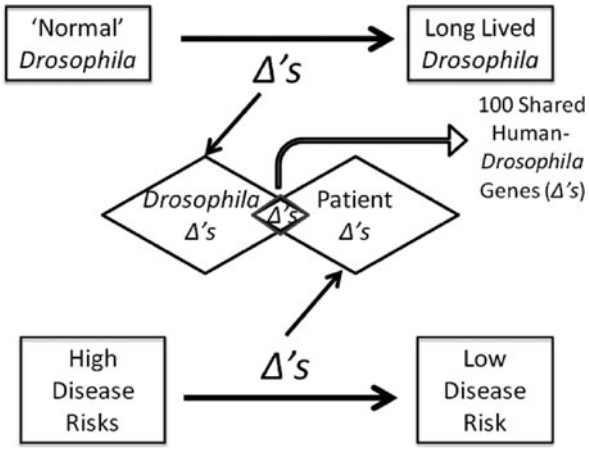

Fig. 11.2 Genetic overlap identifies shared aging pathways. Overlap of Drosophila longevity genes and human disease genes generating greater health risks

The second phase of our work was to use extant human genome-wide association studies (GWAS) to ascertain whether any of these orthologous loci were statistically associated with reduced risks of aging-associated disease. So far, we have more than 100 human genes showing such statistical associations with risks of contracting such diseases. These genes thus became Genescient's targets for intervention.

Figures 11.1 and 11.2 give a crude graphical outline of the two basic genomic screens that we have performed, searching for genomic changes that are associated with increased lifespan in Drosophila as well as better chronic disease outcomes in human subjects.

11.4 Pharmaceutical Versus Nutritional Intervention Strategies

So long as one supposes that aging is due to just a few "master regulatory" genes (e.g. Guarente and Kenyon 2000) or a handful of fully delimited types of accumulating damage (e.g. de Grey and Rae 2007), then it is reasonable to suppose

that massively effective "anti-aging" pharmaceuticals might be discovered. In other words, so long as aging is NOT conceived in Hamiltonian terms, then anti-aging pharmaceuticals should be possible, despite the failure of all attempts to produce any such agents throughout the lengthy history of the many attempts to do exactly that.

But on the Hamiltonian view of aging, and given Genescient's own genomic results described above, it is only to be expected that aging involves a failure of natural selection across hundreds of genes, with many physiological mechanisms of aging produced by these failures of adaptation. The prospects for developing FDA-approvable pharmaceuticals for such a "Many-Headed Monster" as aging (cf. Rose and Long 2002) are extremely doubtful, if not hopeless. But does this mean that there are no prospects for ameliorating human aging? We don't think so.

Understanding how natural selection creates adaptations is the key to understanding Genescient's evolutionary nutrigenomic strategy. There are a few cases (such as those involving short-term selection for resistance to antibiotics, heavy metals, or pesticides) where natural selection produces adaptations based on single genetic changes. But when the genetic basis of typical adaptations is studied, adaptations such as body size or resistance to cancer, it is commonly found that many genes underlie these adaptations. Thus it is no surprise to evolutionary geneticists that the genetic basis of the several-fold extension of Methuselah Fly lifespans involves hundreds of genes. To re-shape aging, we will need to make appropriate adjustments involving many biochemical pathways.

At this point, a reader of the gerontological literature might point to the "longevity mutants" that have been such an obsession in recent gerontological research (reviewed in Guarente and Kenyon 2000, as well as Arking 2006). Such "longevity" mutations have been known for more than fifty years (e.g. Maynard Smith 1958). When they are studied with greater and greater care for their side-effects, which has not always been standard practice within the gerontological research community, they are characteristically found to show debilitating effects on fitness, reproduction, and related functions (Van Voorhies et al. 2006). The pathways that are "knocked-out" by these "longevity mutants" typically produce extended lifespan in a manner that is achieved at great physiological cost, such as sterility, dwarfism, or metabolic hibernation. Such side-effects make these "longevity genes" unlikely targets for the extension of "human healthspan," although they might be useful targets for preserving the lives of hospitalized patients under extreme medical conditions, in which reproductive incapacitation or impaired cognition might not be issues.

To return to the Hamiltonian perspective, the technological problem is evidently one of re-tuning hundreds of genetically-defined mechanisms of aging. This problem is readily solved by natural selection, as the Hamiltonian Methuselah Flies directly demonstrate. Furthermore, we know from detailed studies of individual loci in these flies that these manifold re-tunings do not involve "knocking-out" or otherwise destroying normal genetic mechanisms (Rose et al. 2004; Teotonio et al. 2009). Instead, as Genescient's own genomic findings show in great detail, the evolutionary changes that lead to greatly slowed aging involve relatively subtle changes in gene

frequency and gene expression, in most cases. Such subtle changes are not effects that pharmaceuticals notably emulate.

Instead, the best strategy for emulating the effects of natural selection in extending lifespan several-fold is nutritional supplementation. This does NOT mean ingesting large quantities of hundreds of supplements that one or another molecular biologist supposes might be beneficial based on results obtained using in vitro cell cultures. Indeed, the wholesale failure of such research to produce extended human healthspans suggests the greatest caution in using guidelines derived from such work.

The Hamiltonian perspective suggests instead using nutritional supplements in the same manner as evolution uses genetic variants of small effect. Genetic changes that do not have massively disruptive effects, unlike the "longevity mutants," are likely to alter a number of physiological mechanisms a small amount. Similarly, nutritional supplements that do not have drastic effects are likely to have moderate effects on a number of physiological mechanisms. This does NOT, however, mean that these effects are on the whole benign. Just that they are moderate.

In Hamiltonian experiments in which we evolve postponed aging in model animal species, natural selection "screens" such moderate, often diffuse, genetic effects, favoring those variants that have benign effects accumulated over the entire spectrum of physiological functions. Likewise, we have to screen candidate "nutrigenomic agents" for their benefits, just as natural selection would. Just because a nutritional supplement seems like it should be beneficial based on our genomic findings is no guarantee that it will in fact be useful in the amelioration of human aging.

11.5 Genescient Uses Two Key Accelerators to Identify Evolutionary Nutrigenomic Agents

Genescient's evolutionary nutrigenomic approach is based on emulating natural selection, using nutritional supplements in lieu of genetic variation, with two major "accelerators," as follows:

Accelerator 1: We choose candidate substances based on biochemical associations between the effects of candidate substances and the pathways that Genescient has identified genomically. Mutation supplies "blind variation" for natural selection to act on. While we are very far from supposing that contemporary biochemistry is infallible, the physiological mechanisms and gene products disclosed by Genescient's Hamiltonian genomics provide valuable clues that can be combined with the published literature and small-molecule databases to direct us toward some nutritional supplement choices over others. Thus, our first accelerator lets us *do even better than natural selection*, by using our proprietary genomic insights combined with extant biochemical information.

Accelerator 2: We first test our candidate nutrigenomic agents using fruit fly healthspan assays, followed by human functional tests. Since we operate within the Hamiltonian paradigm, we are not interested in substances that might increase longevity at great functional cost. Instead, we are interested in supplements that will

enhance longevity, fertility, cognitive function, physical performance, *et cetera*, all at the same time. This means that we seek substances that can be shown to have both long-term and short-term benefits.

In principle, all our developmental research could be performed on human subjects. But to seek measurable benefits for human healthspan, when we expect such benefits to be of small magnitude for any single supplement, is commercially hopeless. We would never get access to the funding required to test dozens, not to say eventually hundreds, of candidate nutritional supplements over large test groups of human subjects over decades, prior to marketing the compounded nutrigenomic agents as commercial products.

This is where the evolutionary foundations of our nutrigenomic strategy pay particularly large dividends. All the genetic mechanisms targeted by our nutrigenomic candidate substances have been implicated in *both* fruit flies and humans. If we have an excellent nutritional supplement based appropriately on genes that are associated with healthspan in both fruit flies and humans, it should benefit both fruit flies *and* human subjects. We can readily screen for lifelong benefits in fruit flies. Genescient scientists have decades of expertise in accurately and efficiently characterizing longevity, mortality rates, fecundity, male mating success, and related lifelong indicators of healthspan in fruit flies. We can also readily screen for useful, short-term, functional benefits in humans, because there is no other organism for which we have better metrics for short-term function. Naturally enough, we start with fruit fly tests, passing candidate nutrigenomic agents on to human testing only once we have cleared them for lifelong benefits in fruit flies. Figure 11.3 summarizes this R&D strategy.

11.6 Genescient Progress Report

It might be useful to summarize Genescient's progress to date in broad terms. [We are in the process of writing up and submitting detailed "data papers" for publication in the scientific literature.] That way the reader will have a more concrete idea

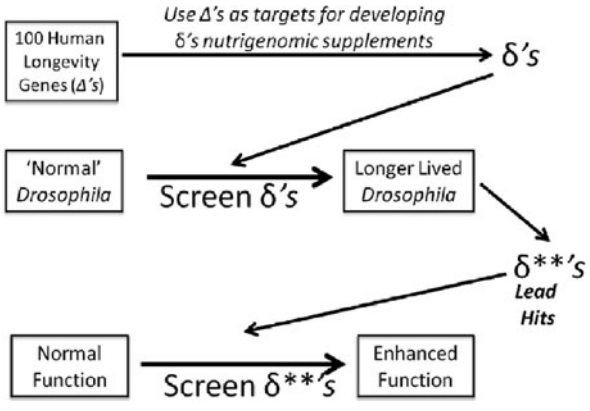

Fig. 11.3 Shared aging genes are used to develop nutrigenomic treatments. Substances (δ's) are identified that act on human disease pathways and then are tested in fly aging assays. Lead hits that extend fly healthspan are screened in humans for enhanced function

of what Genescient has accomplished, by way of materially embodying its R&D strategy.

1. We have already performed an extensive genomic inventory of the gene-expression changes that underlie the several-fold extension of lifespan in Hamiltonian Methuselah Flies. We have found about 1,000 genes for which there are statistically significant and consistent changes in gene expression that result from selection for increased adaptation at later ages, including survival to, and function at, much later ages than is normal for laboratory fruit flies.
2. We have used GWAS databases to identify more than 100 genetic loci that are associated with *both* increased fly lifespan *and* decreased risk of chronic human diseases, such as cardiovascular and metabolic disorders.
3. We have used the key loci identified in step 2 to choose nutritional supplements that we regard as candidates for nutrigenomic agents that might give enhanced healthspan in both humans and fruit flies.
4. One significant result from this initial screen is that high doses were often less effective than low or moderate doses. Therefore, more of a longevity compound is not necessarily better.

We are now performing trials to test for the effects of combinations of nutrigenomic agents that have passed through our R&D program. We also plan human trials to test for short-term functional effects of our candidate nutrigenomic agents. Following the completion of these tests, we would like to produce nutrigenomic products for sale in the marketplace.

11.7 Conclusions: Prospects for Evolutionary Nutrigenomics

Genescient's evolutionary nutrigenomic R&D strategy is expandable in many directions, and on a very large scale. Here are several ways we can build on what we have accomplished to this point.

1. The genomic work we have done to this point with the Hamiltonian Methuselah Flies is just a start. New genomic technologies are being released rapidly, from tiling arrays to large-scale rapid re-sequencing. The use of any and all of these technologies will reveal still more detail concerning the genomic foundations of the Hamiltonian prolongation of healthspan.
2. Likewise, human population genomics is a rapidly burgeoning field. As more human genomic data become available, we will find still more genes that are key for aging in both fruit flies and humans.
3. Given enough resources, we can select on mice using Hamiltonian strategies, as originally proposed 25 years ago. Such mice would provide still more genomic information concerning the genetic controls on human aging.

4. Small-molecule databases are rapidly improving, thanks to the application of high-throughput methods for detecting interactions between individual gene-products and candidate small molecules. These databases will furnish more candidates for testing as potential nutrigenomic agents.
5. We look forward to the development of better, and more widely-accepted, protocols for testing human functions, whether cognitive, athletic, or metabolic.

There is nothing easy or magical about the Hamiltonian approach to the amelioration of human aging. But it may well be the best strategy for radical extension of human healthspan that is both scientifically well-founded and experimentally supported. We regard the alternatives as more challenging, however widely accepted within conventional gerontology or geriatrics. As we have said before (Rose 2008), the difficulty of materially extending useful healthspan helps reveal which of the contending scientific and technological approaches to aging are well-founded, and which are not.

References

Arking R (2006) The Biology of Aging: Observations and Principles, 3rd edn. Oxford University Press, New York

Charlesworth B (1980) Evolution in Age-Structured Populations. Cambridge University Press, London

De Grey A, Rae M (2007) Ending Aging, The Rejuvenation Breakthroughs that could Reverse Human Aging in our Lifetime. Methuselah Foundation

Guarente L, Kenyon C (2000) Genetic pathways that regulate ageing in model organisms. Nature 408:255–262

Hamilton WD (1966) The moulding of senescence by natural selection. J Theoret Biol 12:12–45

Luckinbill LS, Arking R, Clare MJ, Cirocco WC (1984) Selection for delayed senescence in *Drosophila melanogaster*. Evolution 38:996–1003

Maynard Smith J (1958) The effects of temperature and of egg-laying on the longevity of *Drosophila subobscura*. J Exp Biol 35:832–842

Mueller LD, Rose MR (1996) Evolutionary theory predicts late-life mortality plateaus. Proc Natl Acad Sci USA 93:15249–15253

Platt JR (1964) Strong inference. Science 146:347–353

Rauser CL, Mueller LD, Rose MR (2006) The evolution of late life. Aging Res Rev 5:14–32

Rose MR (1984) The evolutionary route to Methuselah. New Scientist 103:15–18

Rose MR (1991) Evolutionary Biology of Aging. Oxford University Press, New York

Rose MR (2005) The Long Tomorrow, How Evolutionary Biology can help us Postpone Aging. Oxford University Press, New York

Rose MR (2007) End of the line. Quart Rev Biol 82:395–400

Rose MR (2008) Making SENSE: strategies for engineering negligible senescence evolutionarily. Rejuvenation Res 11:527–534

Rose M, Charlesworth B (1980) A test of evolutionary theories of senescence. Nature 287: 141–142

Rose MR, Long AD (2002) Ageing: The many-headed monster. Curr Biol 12:R311–R312

Rose MR, Drapeau MD, Yazdi PG, Shah KH, Moise DB, Thakar RR, Rauser CL, Mueller LD (2002) Evolution of late-life mortality in *Drosophila melanogaster*. Evolution 56:1982–1991

Rose MR, Passananti HB, Matos M (eds) (2004) Methuselah Flies, A Case Study in the Evolution of Aging. World Scientific, Singapore

Rose MR, Rauser CL, Benford G, Matos M, Mueller LD (2007) Hamilton's forces of natural selection after forty years. Evolution 61:1265–1276
Teotonio H, Chelo IM, Bradic M, Rose MR, Long AD (2009) Experimental evolution reveals natural selection on standing genetic variation. Nat Genet doi:10.1038/ng.289
Van Voorhies W, Curtsinger JW, Rose MR (2006) Do longevity mutants always show trade-offs? Exp Gerontol 41:1055–1058