Aging in Mouse and Human Systems

A Comparative Study

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ABSTRACT: This article discusses the significance of mouse models as a basis for elucidating the aging process in humans. We identify certain parallels between mouse and human systems and review the theoretical and empirical support for the claim that the large divergence in the rate of aging between the two species resides in differences in the stability of their metabolic networks. We will show that these differences in metabolic stability have their origin in the different ecological constraints the species experience during their evolutionary history. We exploit these ideas to compare the effect of caloric restriction on murine and human systems. The studies predict that the large increases in mean life span and maximum life-span potential observed in laboratory rodents subject to caloric restriction will not obtain in human populations. We predict that, in view of the different metabolic stability of the two systems, caloric restriction will have no effect on the maximum life-span potential of humans, and a relatively minor effect on the mean life span of nonobese populations. This article thus points to certain intrinsic limitations in the use of mouse models in elucidating the aging process in humans. We furthermore contend the view that these limitations can be mitigated by considering the metabolic stability of the two species.

KEYWORDS: aging; metabolic stability; entropy; caloric restriction

INTRODUCTION

Maximal life-span potential is defined as the maximum observed life span of a species. This value is usually obtained with animals living under favorable conditions where the factors that induce extrinsic mortality are considerably reduced. There is about a 50-fold range of maximum life-span potential for the mammalian species. Mice and humans with a maximum life-span potential of

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4 years and 120 years, respectively, are at two extremes of the longevity continuum. In spite of these large differences in life span, mouse models constitute one of the primary systems in studies of human longevity. The prevalence of mouse models in the analysis of age-related diseases and the rate of aging in humans has a biological rationale.

Mouse and human cells are endowed with a similar molecular apparatus that regulates differentiation and death. The cells are also similar in the molecular mechanisms by which they execute basic cellular processes. Mice and humans also share organs and systemic physiology and show a certain consistency in disease pathogenesis. Comparative studies of cancer pathogenesis, for example, show that mouse tumors have histological features similar to those of comparable human tumors and that the frequency of cancer is similar in spite of the large differences in life span. In addition, mice acquire mutations in an equivalent spectrum of protooncogenes and tumor suppressor genes.[1]

The problem this article addresses is: Are these similarities in cellular processes and disease pathogenesis sufficiently robust that experimental findings from mouse models can be extrapolated to study aging in human systems?

Aging, in its broadest sense, is the progressive and irreversible loss of function accompanied by increasing mortality with advancing age.[2] The rate of senescence can be defined as the rate at which the various physiological processes decline. In order to evaluate the significance of mouse models in the analysis of aging, the question that needs to be addressed is: Is the aging process in mouse and human systems defined by equivalent rates of senescence, and concomitantly, homologous molecular mechanisms?

This problem was initially discussed in Demetrius,[3] where we argued that mice and humans, in spite of certain similarities in system physiology and age-associated disease pathogenesis, will be defined by distinct differences in their rates of senescence. Consequently, the mechanisms underlying the aging process in the two systems will be similar.

This article will further develop this argument by delineating the physiological and demographic basis for the claim that mice and human systems will be defined by critical differences in their aging processes. We propose a molecular mechanism and provide an evolutionary rationale for these species-specific differences in the rates of aging: The models we propose point to certain intrinsic limitations in the use of mouse models to study human longevity.

This review is organized around two concepts: (i) metabolic stability, a molecular property which pertains to the regulatory network that defines the metabolic pathway in cells, and (ii) evolutionary entropy, a population property that describes the demographic network that defines a population of replicating organisms.

The concept of metabolic stability was originally introduced in an analytic theory of longevity to provide a molecular mechanism for the large variation in life span observed between species.[4]

Metabolic stability, roughly speaking, describes the capacity of the metabolic network to maintain steady-state values of redox couples in response to random perturbations in the rates of enzymatic processes. The significance of this concept in studies of aging resides in the metabolic stability-longevity principle. This asserts that metabolic stability is the prime determinant of the rate of aging and is positively correlated with the maximal life-span potential of a species. Accordingly, strongly stable networks will be defined by slow rates of aging, whereas weakly stable networks will be defined by rapid rates of aging.[3,4]

The concept of evolutionary entropy was introduced to provide an evolutionary rationale for the large differences in species life span.[4] Evolutionary entropy, a function of the age-specific fecundity and mortality of individuals in a population, predicts the outcome of competition between a rare mutant and the wild type.[5] This life-history parameter characterizes demographic stability, which is the ability of the population to maintain steady-state values of population size in the face of random perturbations in age-specific birth and death rates.[6] Evolutionary entropy is the cornerstone of a class of dynamical models—directionality theory—which studies changes in the genotypic and phenotypic composition of populations under mutation and selection.

This article is organized as follows. We first contrast mouse and human systems in terms of their physiology, disease pathogenesis, and life history. We exploit this contrast to show that mouse and human systems will be defined by decisive differences in their rates of aging. The molecular mechanisms underlying these differences and their evolutionary basis are then delineated. These developments are then exploited to analyze the effect of interventions such as caloric restriction on the mean and maximum life span in mammalian species. Finally, we contrast the new theory of aging described in this article with earlier studies of the senescent process: the metabolic rate–oxidative stress theory proposed by Harman[7] and the evolutionary theory of senescence advanced by Medawar,[8] Williams,[9] and Hamilton.[10]

COMPARATIVE BIOLOGY: MICE VERSUS HUMANS

Mice share genes, organ systems, and systemic physiology with humans. The species, however, differ significantly in terms of physiological properties, disease pathogenesis, and life-history attributes. We will briefly summarize the nature and extent of these differences and discuss their implications in understanding the divergences in the rate of aging in the two species.

1. *Physiological properties*: Mice and human systems are known to show significant differences in the production rate of reactive oxygen species (ROS)—a term used to describe molecular species, such as superoxide radical, hydrogen peroxide, and hydroxyl-free radical. ROS are involved

as specific signaling molecules under physiological conditions and also act as an essential host defense mechanism against infection.[11–13] Decreased levels of ROS may therefore interfere with the physiological role of oxidants in cellular signaling and host defense. Increased levels of ROS, however, can lead to random damage to proteins, lipids, and DNA. The existence of both positive and deleterious effects of ROS suggests that regulating overall levels of ROS will be a critical factor in aging, and that the capacity to maintain ROS within certain prescribed bounds will be an important element in determining longevity.[4] This capacity will to a large extent depend on factors such as (*a*) proton conductance (*b*) metabolic efficiency, and (*c*) the proton motive force, parameters that are involved in ROS production. These parameters depend, among other features, on the phospholipid composition of the biomembrane—a property that is known to differ between mice and human species.[14] We can therefore conclude that mice and humans, in spite of similarities in the basic molecular processes, will be described by differences in their capacity to maintain stable concentrations of ROS. Consequently, these organisms will be characterized by significant disparities in their rate of aging.

2. *Pathogenesis*: In addition to the differences in the physiological properties of the two species, there exist striking dissimilarities in disease pathogenesis, assessed, for example, in terms of cancer incidence and susceptibility.[15,16] Although the dynamics of tumor progression from benign to malignant state is similar in both rodent and human cancers, there exist significant differences in both the nature of the cancer and the susceptibility of individuals to the disease. In mice, mesenchymal and hematopoietic malignancies prevail and the incidence of invasive cancer increases exponentially with age. In humans, the nature of the cancer and its invasive dynamics are highly age-dependent. Sarcomas and lymphomas are the prevalent malignancies in children, and the incidence of cancer increases linearly with age. Among adults, epithelial carcinomas predominate. Invasive cancer increases exponentially with age from age 40 to 80 years. Beyond the age of 80 years, the incidence of cancer becomes independent of age.[17,18] These differences in the rate of pathogenesis of the two species indicate that the senescence process in mice and humans is driven by qualitatively different mechanisms.
3. *Life history*: The term *life history* refers to a population-level property. It describes the age-specific fecundity and mortality of the individuals in a population. Enormous variability in life history traits exist between species. The variability in life history can be described in terms of the following demographic variables: age of sexual maturity, size of progeny sets, and reproductive span. These parameters show a large range of variation between species. Within the mammalian lineage, the range of

TABLE 1. Life-history variation in mammals

Demographic property	Mammals' range of variation	Mice	Humans
Age of sexual maturity	9 days–13 years	35–50 months	13 years
Litter size	1–16	4–8	1
Reproductive span	1 year–35 years	2 years	35 years

variation and the corresponding values for mice and humans are shown in TABLE 1.[19]

Analysis of demographic models shows that this life-history variability can be characterized in terms of the parameter, evolutionary entropy, a function of age-specific fecundity and mortality distribution. Entropy characterizes the variability in the age at which individuals reproduce and die. The demographic parameter is an information-theoretic measure that describes the uncertainty in the age of the mother of a randomly chosen newborn. High-entropy systems distribute their reproductive activity throughout different stages of their life cycle. These populations are defined by late age of sexual maturity, small litter size, and broad reproductive span. Low-entropy systems concentrate their reproduction at a single stage in their life cycle. These populations are defined by early age of sexual maturity, small litter size, and narrow reproductive span.

The significance of evolutionary entropy in studies of aging resides in the fact that entropy is positively correlated with maximum life-span potential, the life span of an organism in a protected environment.[4]

Mice (a low-entropy species), and humans (a high-entropy species) occupy different poles of the entropy continuum. This property, together with the positive correlation between entropy and maximum life span, provides further support for the proposition that mice and humans, in spite of similarities at the genetic, molecular, and cellular levels, will be sharply divergent in their rates of aging.

METABOLIC STABILITY: A MOLECULAR MECHANISM OF AGING

The large divergences in physiological properties, disease pathogenesis, and life-history properties entail that mice and human systems, in spite of congruencies at the molecular and cellular level, will be defined by significant differences in their rate of aging.

The question of interest now becomes: What is the molecular mechanism that underlies these divergences in the rate of senescence? Can this variability be explained in terms of processes at the cellular level? These issues, as shown in Ref. 3, can be addressed in terms of the concept of metabolic stability, a measure of the robustness of the regulatory networks that are involved in cell metabolism.[4]

Metabolic Networks, Metabolic Stability, and Life Span

The term *metabolic stability* refers to the capacity of the metabolic network to control and maintain an adequate redox balance in the face of random perturbations in the reaction rates of the underlying enzymatic processes. This concept is the fundamental notion in the new theory of longevity proposed in Ref. 4. According to this theory, the senescence-related loss of function at the organismic level is due to the dysregulation of the steady-state values of redox couples. The model contends that deviations from redox balance are an intrinsic property of all metabolic processes. These deviations derive from the chance perturbations in enzymatic reaction rates that characterize all metabolic systems where the concentration of reacting species is extremely low. We postulate that the effect of these random perturbations will accumulate over time and lead ultimately to the impairment of cellular signaling, the dysregulation of ontogenetic events, and cell death. Accordingly, senescence is the result of spontaneous changes in the metabolic condition of the cell during normal development.

In the context of this model, cell death is the result of a complete dysregulation of the regulatory networks—a state of metabolic instability. The time that elapses before this condition is attained will depend on the ability of the system to maintain cellular homeostasis in the face of random perturbations in the enzymatic reaction rates. The ability to maintain the homeostatic condition and thus decelerate the aging process can be enhanced by factors such as DNA repair. However, maximal life-span potential will be positively correlated with metabolic stability. The spontaneous nature of the process, which induces cellular dysregulation, entails that metabolic stability is not simply correlated with life span, but is a critical determinant of longevity.

These observations can be qualitatively annotated in terms of what we call the metabolic stability–longevity principle: The metabolic stability of an organism, which is its capacity to maintain steady-state concentration of redox couples in the face of random perturbations in the enzymatic reaction rates, is the prime determinant of organismic longevity.[4]

Two important implications follow immediately from this principle:

I. The metabolic stability of an organism will be a decreasing function of age.
II. The metabolic stability of an organism will be positively correlated with maximum life-span potential.

Studies consistent with (I) are the empirical investigations using *C. elegans*, which show that ATP/AMP ratio, a metabolic marker of stability, decreases with age and that organisms with a larger ATP:AMP ratio live longer.[20] Analyses consistent with (II) are comparative studies of fibroblast cells from several mammalian species, showing the relation between species life span and cell stress resistance.[21] These investigations show that the ability of cells to tolerate

oxidative stress, a physiological marker of metabolic stability, is positively correlated with life span.

ENTROPY: THE EVOLUTIONARY RATIONALE

The metabolic stability–longevity principle provides a basis for predicting the metabolic stability of the cellular network of a species from its life span. Long-lived species, such as humans, will be described by highly stable networks—metabolic systems that have a strong capacity for homeostatic regulation. Short-lived species, such as mice, will be characterized by weakly stable networks—systems with a weak capacity to maintain their homeostatic condition.

The problem we now address is: Can these species-specific differences in metabolic stability be explained in evolutionary terms? In other words, are the highly and weakly stable networks of humans and mice, respectively, the result of the process of mutation and natural selection? This problem can be resolved by appealing to directionality theory, a class of evolutionary models based on the concept of entropy as the measure of Darwinian fitness.[22]

Directionality Theory and the Evolution of Life History

Directionality theory distinguishes between species in terms of the nature and intensity of fluctuations in population numbers. The term *equilibrium species* describes species that spend the major part of their evolutionary history in the stationary growth phase or with a population size that fluctuates around some constant value. These species are subject to ecological conditions that provide limited but constant resources. Humans are a canonical example of an equilibrium species. Humans have clearly increased in size as they moved from the hunter-gathering state, to the agricultural phase, and then to industrialized populations: However, population growth rate during the hunter-gathering phase, a period that represent 99% of human history, ranged between 0.007 and 0.0015 per thousand per year. The large increases in growth rate (0.36 per 1,000) at the establishment of agriculture 10,000 years ago, and the explosion in growth rate (0.56 per 1,000) since 1750, have occurred during periods that represent 1% of human evolutionary history.[23]

The term *opportunistic species* refers to populations that are subject to large and irregular fluctuations in population size. These species are typically subject to conditions where the resources are ample but intermittently available. Wild mice are a typical example of the opportunistic state. Population size in these species reflects resource conditions that are highly variable, and hence large irregular fluctuations in numbers will be common.

Directionality theory revolves around the proposition that Darwinian fitness, the demographic property that determines the outcome of competition between

a mutant allele and the resident type, is characterized by the robustness or the demographic stability of the population. This notion of stability refers to the rate at which a population returns to its original size after a random perturbation in its age-specific birth and death rate. Strongly stable or *robust* systems are populations described by a rapid rate of return to their steady-state condition. These populations have a strong capacity for the homeostatic regulation of their numbers. Weakly stable or *flexible* systems are populations characterized by a slow rate of return to their steady state. Such systems have a correspondingly weak capacity to maintain their size in the face of chance perturbations in the individual birth and death rates. Directionality theory exploits certain analytic properties of the entropy function to predict that (*a*) among equilibrium species, mutations that increase demographic stability will have a selective advantage, as they increase the capacity of the population to efficiently exploit the limited but constant resources that define their environmental condition; but (*b*) in opportunistic species, mutations that decrease demographic stability will now have a selective advantage as they enhance the ability of the population to exploit the large variation in resource availability that defines their environmental state. The theory postulates that the dynamics of the evolutionary process of mutation and natural selection will induce changes in the life-history characteristics of the species over time, as mutant alleles replace ancestral types in response to the prevailing selective constraints. The major predictions of the theory are as follows:

A. Evolution in equilibrium species will be described by an increase in entropy. These species will be characterized by the following life-history properties: late age of sexual maturity, small progeny sets, broad reproductive span, and long life span.
B. Evolution in opportunistic species will be described by a decrease in entropy. These species will be defined by: early age of sexual maturity, large progeny sets, narrow reproductive span, and short life span.

Metabolic Stability and Directionality Theory

The evolutionary dynamics of metabolic stability can be predicted from directionality theory. The basis for the prediction resides in the tight coupling between processes at the cellular, individual, and population levels of biological organization. The dynamics of the metabolic network determine the life-history features of the population. Changes in the topology and kinetics of the network will result in changes in the individual birth and death rates. Variations that increase the robustness of the network will have a corresponding effect on the robustness or stability of the population. Consequently, changes in metabolic stability and evolutionary entropy will be positively correlated. This correlation implies that the directionality principles for evolutionary entropy

TABLE 2. Physiological and demographic properties for equilibrium and opportunistic species

Physiological and demographic properties	Equilibrium species	Opportunistic species
Metabolic stability	Strong	Weak
Demographic stability	Large	Small
Rate of senescence	Slow	Fast
Maximum life-span potential	Large	Short

can be invoked to predict evolutionary changes in metabolic stability. Accordingly, equilibrium species will be described by metabolic networks that are highly resilient with respect to random perturbations in the enzymatic reaction rates, whereas opportunistic species will be defined by metabolic networks that are highly sensitive to random fluctuations in the reaction rates.

The relationship between the physiological and demographic attributes of equilibrium species (humans) and opportunistic species (mice) are summarized in TABLE 2.

This analysis based on directionality theory provides an evolutionary rationale for the empirical observation that humans, a typical equilibrium species, consist of cells that are highly stress-resistant, whereas mice, a typical opportunistic species, are composed of cells whose metabolic dynamics are highly sensitive to random perturbations. The large differences in stability of the metabolic network in humans and mice have their origin in the different ecological constraints that these species have endured.

DIETARY RESTRICTION: EQUILIBRIUM AND OPPORTUNISTIC SPECIES

Dietary restriction (DR), the extension of life span by reduced nutrient intake without malnutrition, is often invoked as the canonical method for interventions that modulate life span. The life-span extension effects of DR go back to the pioneering experiment on rats by McCay *et al.*[24] Since the time of these experiments, some form of food restriction has been shown to increase life span in a variety of organisms, including yeast, nematodes, fruit flies, and mice.[25] The mechanisms that are responsible for increased longevity, however, have not been fully elucidated. Dietary restriction, however, has been shown to increase the efficiency of a number of key enzymes in intermediary metabolism.[26] We have appealed to this empirical fact and invoked the metabolic longevity principle to suggest a mechanism for the action of DR on life span.[4] The models predict that DR extends life span by increasing the stability of the metabolic networks.

Support for this mode of action of DR derives from studies of a genome-wide microarray expression analysis of genes in the liver.[27] The liver is the central

organ for the regulation of glucose homeostasis. Accordingly, it has a major effect on metabolic regulation during aging. A common effect of aging in liver is the induced expression of a number of stress-response genes—a condition that reduces the homeostatic capability of the organ. The experimental design reported in Cac *et al.*[27] showed that DR opposed the age-related induction of stress-response genes and inflammatory genes. This can be considered as an enhancement of homeostatic regulation, and hence an increase in the stability of the metabolic network.

The proposition that dietary restriction acts by increasing metabolic stability, and the observation that equilibrium and opportunistic species differ significantly in terms of this property, entails that the response to DR will be contingent on the equilibrium or opportunistic status of the species.

Equilibrium species have evolved to increase metabolic stability because this property enhances the capacity to adapt to the limited resource conditions these species have endured during their evolutionary history. These species will therefore be defined by a metabolic stability close to its maximal value. This implies that any further increase in metabolic stability that DR may induce will be relatively small.

Opportunistic species, by contrast, have evolved to decrease metabolic stability as this condition facilitates their capacity to adapt to the highly variable resource conditions that characterize the environmental constraints these species experience. Opportunistic species will be characterized by weak metabolic stability. Consequently, DR, when imposed on opportunistic species, will result in decisive increases in metabolic stability.

A central tenet in this new theory of longevity is that metabolic stability and longevity are positively correlated. In view of this correlation we can infer that in equilibrium species DR will have no significant effect on maximum life-span potential. DR will, however, have an effect on mean life span. The effect will be induced by the reduction in the incidence of age-related diseases, which include neoplasia, cardiovascular disease, and diabetes. These effects, however, will be relatively small since they will not involve any changes in the rate of aging.

We can furthermore infer that in the case of opportunistic species, the effect of DR on both the maximum life-span potential and the mean life span may be significant. This derives from the fact that opportunistic species are defined by weak metabolic stability. DR may induce appreciable increases in this property, thereby decelerating the rate of aging.

DR in Humans and Mice

Humans are the canonical equilibrium species. *Homo sapiens* has been subject to ecological constraints that ensure a stationary or very slow population growth throughout most of its evolutionary history. Humans will therefore evolve a life-history schedule defined by high entropy. This prediction

is consistent with the following life-history characteristics of humans: late sexual maturity, small litter size, and a long maximum life-span potential (~120 years). The high-entropy condition implies that humans will be characterized by metabolic networks whose stability is close to the maximal condition.

DR increases longevity by increasing the metabolic stability of the regulatory networks. We can therefore infer that, in the case of humans, a species close to the condition of maximal metabolic stability, DR will have negligible effect on stability, and hence no effect on maximum life span. However, DR may have an effect on mean life span. Mean life span is simply a measure of our ability to minimize premature death. DR can influence mean life span by simply reducing the incidence of diseases such as diabetes, atherosclerosis, and hypertension. These changes, however, will result in an increase in life span of only about 3–5 years—a moderate effect. Since DR will have a negligible effect on metabolic stability, it will exert no effect on the rate of aging and hence induce no changes in the human senescence process.

Mice are classical examples of opportunistic species. These organisms have been subject to ecological constraints defined by large variations in resource abundance. These species will therefore evolve a life history defined by high entropy. This situation is consistent with the following life-history characteristics of mice: early sexual maturity, large litter size, and a short maximum life span potential of ~4 years. The low-entropy condition entails that mice will be characterized by metabolic networks whose stability is close to the minimal condition. Since DR increases longevity by increasing metabolic stability, we can infer that in the case of mice, DR, by causing significant increases in metabolic stability, will influence the rate of aging and thereby induce changes in both the maximum and the mean life span. The studies described on laboratory mice and reported by McKay *et al.*[24] are consistent with this prediction.

DR in Rhesus Monkeys

We should point out at this juncture the ongoing longitudinal studies of caloric restriction on life span in rhesus monkeys.[28] These studies indicate lower incidence of disease risk and less incidence of age-related diseases in DR monkeys compared to controls: Rhesus monkeys share 92% gene homology with humans. Many biological similarities in the profile of aging also exist between the two species. These similarities have suggested to many researchers that DR in humans may result in increases in mean and maximum life span comparable to the increases that may subsequently be observed in rhesus monkeys. We contend, however, that although rhesus monkeys and humans are equilibrium species and should therefore show comparable aging patterns, the effect of DR on mean and maximum life span in the two species will be quantitatively quite distinct. The reasons for this are as follows: Rhesus monkeys and humans, although both equilibrium species, are described

by significant differences in life-history patterns. In rhesus monkeys, sexual maturity occurs at 3 to 5 years of age, mean life span is 25 years, and estimated maximum life span is 40 years. Hence rhesus monkeys will have an inferior evolutionary entropy, and consequently weaker metabolic stability than humans. Our analysis thus predicts that DR will induce changes in longevity in rhesus monkeys. These changes however, will be less pronounced than those recorded in mice—an opportunistic species—but significantly more pronounced than any changes that may occur in humans.

THE ORIGIN AND EVOLUTION OF LONGEVITY: A COMPARISON OF MODELS

Our comparative study of mice and human systems has been based on a new analytic theory of longevity that proposes a molecular mechanism for senescence, and postulates an evolutionary rationale for the species-specific differences in rates of aging.

The studies of the molecular mechanism are based on the metabolic stability concept. Our analysis has been organized around the stability–longevity principle, which asserts that metabolic stability is the prime determinant of life span.

The studies that were aimed at explaining species differences in the rate of senescence were based on directionality theory. The analysis in this case is now organized around an entropic principle. This contends that entropy predicts the outcome of competition between the mutant type and the ancestral population. Competitive success, however, is mediated by the demographic characteristics of the population. In equilibrium species, mutants with higher entropy will be selectively advantageous, whereas in opportunistic species, mutants with lower entropy will prevail.

Entropy characterizes the demographic stability or robustness of the population. Hence the entropic principle can be reformulated to assert that high demographic stability or strong robustness determines competitive success in equilibrium species, whereas weak demographic stability or flexibility confers a selective advantage in opportunistic species.

The theory we have outlined in comparing the aging process in mice and humans provides answers to two fundamental questions:

1. Why do organisms undergo progressive and irreversible physiological decline after the reproductive phase of life ceases?
2. Why do life span and the rate of aging vary between species?

Problems pertaining to how and why we age have attracted the attention of several generations of biologists. Hence, it is of some interest to view the theory described in this article with earlier efforts that have been proposed to

understand the molecular mechanism and evolutionary rationale of the senescence process.

Rate of Living and Oxidative Stress

Early efforts to delineate how we age have their origin in the phenomenological models of Pearl,[29] expressed in terms of the rate-of-living theory, and the molecular mechanism proposed by Harman,[8] in terms of free radicals. The rate-of-living theory was inspired by the following empirical observation: Lifetime energy expenditure does not vary significantly between species.[30] Pearl invoked this empirical study, based on a small group of nonprimate mammals, to propose a general tenet: species life span should be inversely correlated with mass-specific metabolic rate.

Harman[8] provided a molecular basis for the rate-of-living theory. He postulated that free radicals, endogenously generated during normal oxygen consumption in mitochondria, will cause permanent damage to DNA and lipids. The accumulation of this damage is manifested as aging.

The rate-of-living tenet and the free radical model, however, are not necessarily equivalent, since metabolic rate and ROS production rate are not always positively correlated. Both theories, however, are similar in that they postulate that production rate of biomolecules is the prime determinant of the rate of aging.

Empirical observations do not conform to either of these two theories. As regards the rate-of-living theory, considerable variation in life span, exists that cannot be explained by variation in metabolic rate. For example, birds live much longer than mammals although they have similar metabolic rate.[31] As regards the free radical theory, certain inconsistencies have also been recognized: There exists a 7-fold difference between the life span of pigeons and rats; however, ROS production by rat mitochondria is only slightly greater than that of pigeon mitochondria.[14] Bird–mammal comparisons lead to similar anomalies. As noted in Herrero and Barja[32] there is a 7-fold difference in life span between parakeet and mouse; however, the ratio of H_2O_2 production to respiration in heart mitochondria was the same in the both species.

These inconsistencies thus question the validity of the oxidative stress theory as a model for the origin of aging. The difficulties raised by the notion that production rate of metabolic species is a determinant of aging becomes quite evident in the context of the free radical theory. This theory postulates that the production rate of ROS is the prime determinant of the rate of aging. However, ROS has two kinds of effects on metabolic activity.[12,13] First, these small diffusible molecular species can interact with DNA and RNA to impair function. The molecules are also known to act as second messengers in signal transduction. Hence *increased* production may impair metabolism,

thus leading to cell death, and concomitantly, *decreased* production may compromise signal transduction and disrupt cell regulation.[12] These observations argue against the production rate of ROS as being the primary determinant of longevity, and suggest that the ability to maintain ROS within certain range of values may be more critical.

Darwinian Fitness and the Malthusian Parameter

The efforts to understand why we age have their source in the models of Medawar,[9] Hamilton,[11] and Williams.[10] The approaches of these authors differ significantly in methodology and analytical rigor. The models proposed, however, do share a common conceptual framework; namely the notion that the population growth rate or the Malthusian parameter characterizes Darwinian fitness.

The claim that fitness is determined by the rate of increase of population numbers goes back to Fisher[33] and has been the driving force in most studies of population genetics and ecology. Empirical and theoretical studies, however, do not support the Malthusian parameter as the measure of Darwinian fitness. Data from studies of invasion in a wide variety of organisms, both vertebrates and invertebrates, indicate that the population growth rate is not the main determinant of invasion success. These investigations show that the probability of the establishment of an invader is highly correlated with the amplitude of population fluctuations.[34] Analytical studies of invasion dynamics based on diffusion processes show that the rate at which a population returns to its original size after a random perturbation, a property measured by evolutionary entropy, predicts invasion success. These studies also show that the rate at which population numbers increase in size is a predictor of invasion success only in the case of populations of effectively infinite size.[35]

Production Rate and Dynamic Stability

The oxidative stress theory and the Malthusian theory of senescence may be called *production rate* theories. Both postulate that the rate at which certain metabolic and demographic processes operate is the driving mechanism that underlies the ability of these processes to adapt to the environmental conditions which modulate the dynamics of evolution. The metabolic stability theory of aging and the entropic model may be called *stability* theories. They contend that the rate at which certain metabolic and demographic processes return to their steady-state condition after a random perturbation is the central mechanism that determines the ability of these processes to respond to environmental and evolutionary constraints.

Empirical observations and analytical studies have pointed to the inconsistencies in production rate theories as a paradigm for the understanding of

adaptation in the biological processes that underlie senescence. The explanatory and predictive power of models based on stability concepts underscores the range and scope of metabolic stability-entropic factors in understanding the mechanism and evolutionary rationale of senescence. This contrast between production rate and stability theories points to the significance of homeostatic regulation as the primary mechanism for explaining diversity and adaptation in biological systems.

CONCLUSIONS

Mouse models of senescence in human populations have become a central element in many types of biomedical research. The significance of this system derives from its experimental accessibility and the fact that mice share organ systems, systemic physiology, and genes with humans.

We have addressed the question: To what extent can one extrapolate from experimental observations on mouse models to predict the dynamics of the senescent process in humans? The argument developed in this article shows that any effort to exploit murine systems to elucidate human aging or the human disease process must take into account the vast differences in the metabolic stability of the cells that compose the two species. These differences in metabolic stability derive from the contrasting evolutionary history of the species and the environmental constraints they have experienced. An understanding of this history, and its signature at the cellular level, robustness of the metabolic network, are thus crucial in elucidating human aging and human disease pathogenesis from mouse models.

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