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OPINION

What is lifespan regulation and why does it exist?

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Abstract The development of a unified conceptual framework for the field of biogerontology has been impeded by confusing and misleading terminology. Thus, distinctions and definitions are provided for key terms (and their concepts) used in the paper: senescence, lifespan, potential lifespan, essential lifespan, and lifespan regulation. An organismal perspective is then used to examine the relationships between reproduction, lifespan regulation and senescence. The principal conclusions drawn from this examination are: (1) the inevitability of death makes physiological investments in reproduction a higher priority than somatic maintenance, (2) the race between reproduction and death creates a probabilistic window of time (essential lifespan) within which reproduction must occur, (3) the integrated network of genetic processes responsible for achieving essential lifespan (lifespan regulation) must be evolutionarily conserved and extensively regulated, (4) senescence is a stochastic byproduct of these regulated processes rather than a direct target of natural selection, and (5) genomic instability (an important stochastic component of senescence) plays no active role in lifespan regulation.

Keywords Lifespan regulation · Lifespan · Longevity · Potential lifespan · Essential lifespan · Warranty period

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Introduction

How to attain a long life has been a fascination for as long as there has been a record of human history (Gruman 2003). Advances in scientific knowledge have only intensified that search. A prerequisite for pursuing this worthy goal is an evidence based conceptual framework and a consistent terminology. There have been very good efforts to achieve the former (Vijg 2007), but the lack of the latter has created confusion that has thwarted consensus and impeded progress within the field of biogerontology.

Words have power because they represent concepts. An inconsistent or ill-defined terminology will be mirrored in the concepts they represent. Thus, one goal of this paper is to present a consistent terminology for examining aging and lifespan regulation. Achieving this goal involves a discussion of "aging", "lifespan" and "regulation" because each of these words has multiple meanings. After discussing terminology, an organismal perspective on the forces that made lifespan regulation necessary and the relationship between lifespan regulation and aging will be provided.

Aging

Aging is a term that creates considerable confusion because it has colloquial and scientific meanings, and the latter is further confounded by being applied to both individuals and populations. The term "senescence" was created to distinguish the colloquial from the scientific, but even here the highly regulated mechanisms of cellular senescence (Chang 2005; Fadeel and Orrenius 2005) are far different from the stochastic (random, non-deterministic) biochemical processes thought to be responsible for organismal senescence (Robert et al. 2010; Brunk and Terman 2002; Yin and Chen 2005).

Although numerous theories exist on how aging occurs, there is broad consensus on its consequences for individuals (Rattan 2006). As such, we can begin by declaring that biological aging or **senescence** is *the degradation of biological function that accompanies the passage of time*. When and how that degradation occurs and whether it can be slowed or reversed remains an area of controversy (Olshansky et al. 2002b). A stronger definition that resolves these controversies could be made if criteria for distinguishing between senescent and non-senescent changes could be identified.

Fortunately, these criteria can be found in a somewhat obscure but important paper that examined whether the "accelerated aging" effects observed in irradiated cells were caused by senescence or only mimicked senescence (Strehler 1959). Strehler proposed five criteria that must all be satisfied in order to attribute a change in biological function to senescence: Cumulative, Universal, Progressive, Intrinsic and Deleterious (forming the acronym CUPID). The addition of these criteria to the earlier definition of senescence converts a generic definition into a specific one capable of distinguishing senescent changes from non-senescent changes. Thus, **senescence** is *an intrinsic and inevitable degradation of biological function that accumulates over time at every level of biological organization from molecules to populations*.

Lifespan

Lifespan is another term whose meaning initially seems obvious but which suffers from a lack of specificity and overlaps with other terms like "duration of life" and "longevity". For example, lifespan is also applied to species as a characteristic or average age for members of that species which in demographic terms would be more aptly described as a "life expectancy". At the individual level, **lifespan** may be defined as *an individual's observed duration of life*. This definition acknowledges the equivalence of the older usage: "duration of life." **Longevity** is also defined as *length of life*, but the primary definition in both the Merriam-Webster and Oxford online dictionaries is *a long duration of life*. The latter meaning is important when examining the heritability of longevity which acknowledges the influence of genes (Carnes et al. 1999).

Lifespan has a more subtle problem that bears directly on lifespan regulation and is responsible for most of the controversies involving the efficacy of interventions for aging (Olshansky et al. 2002a). Namely, the "observed" lifespan is invariably less than the **potential lifespan** because nearly every death is premature (Carnes et al. 2008). Nobody spends their entire life in an ideal environment adhering to a perfect lifestyle while also successfully evading the detrimental consequences of chance. Further, human ingenuity (e.g., medicine, public health, dentistry, etc.) has invented countless ways to manufacture survival time (extend lifespan) for people who would otherwise have died at a younger age (Olshansky et al. 1998). Which lifespan is being regulated, the one subject to the vagaries of the environment and chance or a more fundamental lifespan linked to the intrinsic biology of a species (Carnes et al. 2003)?

Essential lifespan

A survey of life on Earth, past and present, reveals a simple reality: the environments of Earth are too hostile for any organism to escape death. If life was to persist, a solution to the absolute certitude of death had to be found. That solution became the defining characteristic of living matter; namely, the ability to replicate. This mortality scenario creates a race between reproduction and death. While the duration of this race varies by species, similar biological milestones (growth, development, maturation,

reproduction, nurturing and, for some species, grandparenting) must be achieved (Carnes 2007).

The logic presented here gives primacy to reproduction and the biology that makes it possible. There is considerable evidence to support this prioritization. One of the most influential theories of aging is the disposable soma theory (Kirkwood and Holliday 1979). It distills the allocation of physiological resources into two fundamental choices: maintaining the soma (living longer) or investing in reproduction (producing replicates). Since a greater allocation for maintenance detracts from the reproduction needed to compensate for mortality, reproduction must take precedence over maintenance. Other historically influential theories of aging such as the mutation accumulation theory (Medawar 1952) and antagonistic pleiotropy theory (Williams 1957) invoke the declining effectiveness of natural selection over the course of the reproductive period in order to explain the temporal kinetics and the biological consequences of senescence. Although the focus of these theories is the prediction of biological outcomes, they include an implicit biological timescale within which those events occur.

None of the terms discussed so far (lifespan, potential lifespan, longevity) accurately describe the window of time required to achieve Darwinian fitness (Carnes and Olshansky 1993, 1997) that is most relevant to lifespan regulation and life history strategies. It seems that a clarity of terminology requires a new term. Apt candidates, at least for multicellular organisms, would include **essential lifespan** (Rattan 2000) or **warranty period** (Carnes et al. 2003) both of which explicitly link the relationship between lifespan and reproduction.

Regulation

The biology responsible for *essential lifespan* is what Hayflick (2007) calls "**longevity determination**", but it might be more aptly described as "**lifespan determination**" or "**lifespan regulation**". To improve conceptual consistency, *longevity* should be reserved for concepts involving prolonged survival or extreme longevity while *lifespan* can be short or long. The intricate choreography of growth, development, maturation and reproductive biology that lies under the surface of the essential lifespan concept has been extensively examined (Ellison 2001; Gilbert and Raunio 1997; Rattan 1998, 2006). This biology is too critical to leave up to chance; it must be tightly regulated and evolutionarily conserved. However, regulated and conserved conjure up inaccurate images of biological rigidity.

To the contrary, phenotypic plasticity is an essential adaptive response to the innumerable threats to reproduction that exist in the capricious environments of earth (Williams 1966). The nematode *C. elegans* is an exemplar of plasticity. Environmental stress (crowding, food shortage) during the pre-adult stage triggers an alternate life history pathway that permits the nematode to more than double its typical adult lifespan (Partridge and Harvey 1993). Surviving a few extra days or weeks until an environmental mortality risk has passed or diminished could make the difference between reproducing successfully and Darwinian failure.

The obvious value of stress-induced extended survival in the race between reproduction and death suggests that mechanistic pathways for achieving this extension should be evolutionarily conserved and thus present as a generalized response in all taxa (Schumacher et al. 2008; Sinclair 2005). Indeed, such pathways have been described for taxa as distinct as yeast (Strauss 2003), fruit flies (Piper et al. 2005), rodents (Merry 2005; Guarente and Picard 2005) and humans (Prentice 2005). The question is not whether these life extending pathways exist, but whether there are costs or tradeoffs associated with invoking them (Holliday and Rattan 2010).

Caloric restriction (CR) extends life span in *Drosophila*, but it also reduces fecundity and diminishes physiological function (e.g., starvation resistance, oxidative stress, cold stress) at older ages (Burger et al. 2007). In addition, extreme CR gives rise to the detrimental reproductive and health consequences of anorexia. Conversely, there is no question that CR is the only effective intervention for combating the ongoing obesity pandemic and its health, mortality and longevity consequences (Olshansky et al. 2005). However, a legitimate problem with the CR story emerges from its presumed impact on the rate of senescence (Masoro 2006). It is here where the distinction between "observed" lifespan and "potential" lifespan becomes important (Carnes et al. 2008). Survival time that is reclaimed between the observed and potential lifespan has been

due to two types of intervention, those that reduce avoidable mortality risks (e.g., infection, obesity) and those that suppress (but do not cure) mortality risks arising from the intrinsic biology of the organism (e.g., some forms of cancer and heart disease). Reducing the mortality risks of overweight mice falls within the "avoidable" category; it extends their survival but has no effect on the rate of senescence. If this argument is plausible, then one would predict that naturally lean wild mice would not benefit from CR—a prediction that has now been experimentally verified (Harper et al. 2006).

Genomic instability

An increased focus on genomics has revealed that genomes accumulate damage at a far greater rate than previously thought and the "instability" arising from this damage is likely to be a significant stochastic contributor to senescence (Huberman 2003; Vijg 2007). This linkage to senescence is justified since the biological consequences of genomic instability fulfill Strehler's (1959) CUPID criteria, a point he reiterated 27 years after the publication of his seminal paper (Strehler 1986). Stochastic contributions to senescence may begin with the genome, but they do not end there; a growing body of evidence reveals a significant contribution from post-transcriptional and post-translational damage as well (Xu and Li 2006; Yin and Chen 2005; Carnes et al. 2010).

Notice, however, that there is an unequivocal consensus that the biological consequences of genomic instability are stochastic. Senescence is also considered to be a collection of largely if not exclusively stochastic phenomena (Vijg 2007; Carnes et al. 2010; Yin and Chen 2005). As such, genomic instability is likely to be an important contributor to senescence. It is here where clarity of terminology becomes important again; stochasticity and regulation are mutually exclusive concepts. Stochastic phenomena lack genetic regulation and coordination; they are not the direct targets of natural selection. However, longevity and especially extreme longevity are known to have a significant heritable component (Willcox et al. 2006; Gogele et al. 2010). Given the central role of "essential lifespan" in the life history strategy of every species, the complex genetic networks that give rise to it must be extensively regulated and coordinated (Witten 2007). Separating senescence from lifespan and longevity concepts makes it clear that the way to modify senescence is to modify genes and pathways within the biological domains (e.g., maintenance, repair, stress response) responsible for essential lifespan.

Demographic tangent

Thus far, my discussion has been exclusively biological and focused purely on metrics of time relevant to an individual. One of those, observed life span, is also used by population scientists like the actuaries and demographers who have developed most of the mathematical tools used to describe and predict the mortality consequences of aging (Gompertz 1825; Makeham 1860). The validity of these quantitative models is exceedingly important given the social and economic impacts of population aging already being felt around the globe and those that are yet to come (Olshansky et al. 1993).

Population aging means that not only more people but a larger fraction of people are surviving to older ages. In that regard, a relatively new demographic phenomenon has emerged; the rate of increase in death rates at older ages has slowed in developed countries. It has also been observed in non-human populations (Mueller et al. 2007). This so-called "mortality plateau" is a violation of the invariant increase in death rates predicted by traditional models like the Gompertz. As a consequence, the old models have been rejected (Carey et al. 1992) and new demographic models have been developed to quantify this new behavior and to conjecture on its implications for lifespan and longevity (Mueller and Rose 1996; Demetrius 2001).

Mathematical models impose a structure on data (Carnes and Gavrilova 2001). The problem is not fitting a model, but finding one that accurately reveals the underlying biology responsible for structures like a mortality plateau. Demographic models may not violate any mathematical assumptions but they often violate biological realities (Carnes et al. 1996; Carnes and Olshansky 2007). There are, in my view, two compulsory elements needed to transform a demographic model into a biodemographic model, cause-of-death and heterogeneity.

People die from different causes and a competing risk framework (Makeham 1860) using biologically motivated partitions of mortality (Carnes et al. 2006) captures a portion of this complexity. Also, populations (especially human) are a complex mixture of subpopulations with varying mortality dynamics (Carnes and Olshansky 2001) and a simple (two parameter) Gompertz model based on all-cause mortality cannot possibly capture this complexity. However, mixture models (e.g., a collection of distinct Gompertz subpopulations) generalized to incorporate competing risks are mathematically sound (Elandt-Johnson and Johnson 1980) and biologically reasonable (Strehler and Mildvan 1960).

So, what do these quantitative models tell us about mortality plateaus and their implications for longevity and aging? The answer, of course, depends on the model. One caution is to beware conflating actuarial aging with biological aging; the former is an age trajectory of all-cause death rates (a population phenomenon) and the latter is an age trajectory of physiological decline (an organismal phenomenon). Granted, one goes up and the other goes down but correlation does not necessarily imply causation. There is an extensive and well documented literature on mortality plateaus (nicely reviewed by Rauser et al. (2006)) and most of that literature addresses the issues just discussed.

The conundrum is that simple demographic models fail to capture biological realities and complex biodemographic models alienate the less mathematically inclined, are difficult for others to replicate, are often computationally unstable and invariably depend upon numerous strong biological assumptions. Nevertheless, in regards to mortality plateaus, I believe the model interpretations can be distilled down to two basic conclusions. One camp sees plateaus as evidence that mortality declines and life expectancy increases will continue to accelerate at late ages (e.g. Vaupel 1997). Others see plateaus as evidence that the longest lived subpopulations of our species are beginning to reveal themselves (Frank 2004; Charlesworth and Partridge 1997). If the latter is true, as I believe, then a mortality plateau is a harbinger that the survival time manufactured for individuals by human ingenuity may be approaching biological limits to how far longevity can be extended despite the dramatic breakthroughs in the future that I suspect will have profound beneficial effects on healthy life expectancy and quality of life.

Discussion

Many of the previous arguments have been made before, but the goal of this paper was to clarify terminology and the concepts they represent in order to provide greater insight into why lifespan regulation is important, how it works and how it might be modified. The question as to why it is important has been answered; *lifespan regulation* provides the time (*essential lifespan*) needed to accomplish reproduction and the phenotypic plasticity needed to adapt to environmental challenges that threaten reproduction.

There is an ecological maxim that declares "all organisms are a product of their environment". Hamilton's (1966) understanding of this truth is reflected in the title of his classic paper: "The moulding of senescence by natural selection". The forces of selection are the extrinsic mortality risks that make death a certainty, and it is the adaptation (biological response) to those risks that gives rise to the life history strategy of a species (Stearns 1992) and the biology needed to implement that strategy. In other words, the intrinsic biology of an organism is a byproduct of the environment, and senescence is, in turn, a byproduct of that intrinsic biology (Carnes and Olshansky 1997).

Clues as to how *lifespan regulation* is accomplished are scattered throughout this paper. Recall that growth, development, maturation and reproduction are a chronologically integrated series of highly regulated biological domains that define *essential lifespan* (Rattan 2000). The duration of essential lifespan and the means by which reproduction is accomplished varies dramatically between species. Semelparous organisms like Pacific salmon and many insects forego maintenance of the soma (longevity) for one massive reproductive effort. Iteroparous organisms (most fish, all reptiles, birds and mammals), on the other hand, spread their multiple births over time. In every case, however, there is an underlying species-specific race between reproduction and death that imposes a biological mandate to reproduce as early as possible. Adaptive responses to environmental stressors often do exactly the opposite; they modulate temporal kinetics within domains of essential lifespan (e.g., arrest growth, slow development and/or delay maturation, reduce fecundity). Although this plasticity (extension of lifespan) serves the reproductive mandate, it comes with a biological

cost that only humans can afford or would voluntarily pay—trading reduced Darwinian fitness for enhanced somatic maintenance.

This paper offers several take home messages that hopefully contribute to a better understanding of aging and longevity. One of those is that lifespan, longevity and aging are distinct entities. Another is that reproductive biology is the key to understanding the biology of any organism. A third is the value of using the Strehler criteria to distinguish changes in biological function due to senescence from those arising from non-senescent causes. Fourth, senescence is not a monolithic single entity, it is a massive collection of byproducts produced by the remarkable but messy chemistry of life (Carnes et al. 2008). Fifth, life can be extended without slowing senescence; the latter also requires delaying the onset age of disease (Olshansky et al. 1990, 2005; Carnes et al. 2008). Sixth, the function of the genome is to enable an organism to achieve its essential lifespan. As such, senescence is an inadvertent and unintended byproduct of physiological investments in reproduction having a higher priority than investments in somatic maintenance (Kirkwood and Holliday 1979). Finally, even the most complex quantitative models are far simpler than the biology they are intended to represent. As such, translating mathematical equations into biological expectations must be done with both caution and caveats.

Medawar (1952) described senescence as something revealed "by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence." Humans have taken that experiment to its extreme. Unless interventions can be found (and distributed on a broad scale) to modulate senescence, humans run the risk of trading longer life for worsening health. There is, therefore, some urgency to achieve the synthesis of knowledge needed to translate biomedical innovation into an improved quality of life for the rapidly growing number of people surviving beyond their essential lifespan.

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