Running out of developmental program and selfish anti-aging: a new hypothesis explaining the aging process in primates

Andrej Podlutsky

Received: 26 February 2019 / Accepted: 8 March 2019 / Published online: 26 March 2019
© American Aging Association 2019

Abstract Of the three complementary theories of aging, two (mutation accumulation and antagonistic pleiotropy) were formulated over fifty years ago before the introduction of molecular biology, and the third (disposable soma) is over thirty years old. Despite rigorous research in the past fifty years, none have gained substantial experimental support. Here, I review these theories and introduce a new hypothesis called the selfish anti-aging (SAA). Aging happens because natural selection is indifferent to the organism's life beyond reproduction; however, many mammalian species acquired anti-aging genes, which are providing instructions following completion of developmental, ontogeny, program. Such instructor-genes might be responsible for the elongation of lifespans of primates as a byproduct of parental care program. According to the SAA hypothesis, the animal models used in aging research could be divided into three groups, based on the degree of perceived presence and action of instructor-genes in each group. This new hypothesis is grounded in evolutionary theory and describes the unique primate aging process.

Keywords Aging · Aging theories · Evolution of aging · Instructor-gene · i-gene · Minimum lifespan requirement · Mutation accumulation · Disposable soma · Antagonistic pleiotropy · Selfish anti-aging

...opposition arises, as Darwin himself observed, not from what reason dictates but from the limits of what the imagination can accept.
George Williams, 1966

Introduction

In 1891, August Weismann, the first evolutionary biologist to systematically investigate aging, suggested aging is adaptive (Weismann 1891). In 1952, future Nobel Laureate Peter Medawar criticized Weismann's view and argued natural selection would not affect the aging process of wild populations because most individuals died before attaining advanced ages, and as such aging is not adaptive (Medawar 1952). Accordingly, "the functional performance of the adult body *should* deteriorate with age" (Rose and Graves 1989). Although sufficiently explaining aging from an evolutionary perspective, the most popular theory among aging researchers is George Williams's antagonistic pleiotropy (Williams 1957), which postulates that aging is an unfavorable character to be selected against. There, Williams reported, "It is remarkable that after a seemingly miraculous feat of morphogenesis, a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed." Comfort (1954) suggested that aging was a neutral evolutionary process but did not produce an independent theory. In 1977, Kirkwood introduced the disposable soma theory (Kirkwood 1977) to reunite evolutionary theory with the longevity-reproduction connection.

A. Podlutsky (✉)
College of Natural Science and Mathematics, University of Alaska
Fairbanks, Arctic Health Research Building, 2W04, Fairbanks,
AK 99775-7000, USA
e-mail: apodlutsky@alaska.edu

Over the past three decades, Medawar's mutation accumulation (MA), Williams's antagonistic pleiotropy (AP), and Kirkwood's disposable soma theories (DST) have been used for evolutionary studies of the genetic and molecular mechanisms of aging. However, despite progress in the field of aging, none of these theories present useful strategies to combat senescence in primates and postpone human aging. Recently, trying to bridge mechanistic and theoretical explanations of aging, Kirkwood (2005) attempted to reconcile the disposable soma theory with the oxidative stress theory of aging and other "mechanistic" theories of aging. The resulting explanation absorbed "everything" but did not shift evolutionary understanding of aging or offer a new research direction. The new hypothesis of aging should bring attention back to the evolutionary explanation of the senescent process, and the prediction that certain gene families are playing an important role in lifespan extension and could provide researchers with the testable experiments.

Mutation accumulation theory

Peter Medawar's famous publication *Unsolved Problem of Biology* (Medawar 1952) presented the first contemporary evolutionary perspective of the aging process. Firstly, he refuted Weismann's suggestion that the aging process was adaptive by asserting that most individuals in wild populations died before reaching an advanced age. Instead, Medawar emphasized that natural selection lost efficiency after reproduction, eliminating selective pressure on the aging process. This view was an *absolute* explanation of the evolution of aging: *aging existed because natural selection could not eliminate it*. This concept is the basis for all evolutionary theories of aging. Medawar's critiques of Weismann's adaptive view of aging remain valid in discussions with modern "programmed aging" supporters, who believe aging is beneficial for the species and thus programmed like other developmental processes (Libertini and Ferrara 2016).

Secondly, Medawar discussed the origin and evolution of senescence. To explain the genetic basis of aging, Medawar introduced the test tube metaphor. He suggested to imagine a population of test tubes, in which each test tube is potentially immortal. Due to poor handling, the population would experience extrinsic mortality, with breakage equivalent to death in natural

populations by external forces such as predation, starvation, infection, and hypothermia. Initially, tube fitness would be age-independent, and all tubes would have the same probability of breaking at any point in time. As the population is replenished by the birth of "young" test tubes, the proportion of "old" tubes in the population would decrease due to longer exposure to the constant breakage risk. As a result, the reproductive output of the "old" tube group would decrease due to fewer "old" tubes. Then, Medawar introduced mutations that affected the test tube population in an age-dependent manner: all tubes above a certain age would experience the activation of the mutated gene and would be eliminated from the population. If the mutations struck before the reproductive age, the test tube population would go extinct. If mutations struck after reproduction, fewer tubes were affected, and the mutation remained in the population. Thus, according to Medawar, mutations that presented early in life were subject to selective pressure while mutations that manifested later in life could accumulate. According to the mutation accumulation theory (MA theory), these late-life deleterious mutations produced a senescent phenotype in individuals that avoided extrinsic mortality.

However, the MA theory is not supported by contemporary genetics. Mutations are changes in the DNA sequence that can subsequently lead to changes in the protein structure and/or function. Many mutations have deleterious effects and are lost through purifying selection. According to the MA theory, late-acting mutations could accumulate in genes that would only cause problems later in life. However, if no selective pressure prevents mutation accumulation in these late-acting genes, there would also be an absence of selective pressure to keep them functional. In the absence of purifying selection, they would accumulate even more mutations and become pseudogenes. In contrast to the assumption that such genes would lead to the aging phenotype, the mutations accumulated in late-acting genes would result in pseudogenes that were no longer transcribed and/or translated. Many loci have accumulated mutations and become pseudogenes in some species, but devoid of such mutations remain functional in other species. For example, primate genomes contain approximately one thousand olfactory receptor genes that are typically expressed in the nasal epithelium for odorant detection. In the human genome, 60% of these receptors have acquired disrupting mutations during recent primate evolution, and they continue to

accumulate mutations (Gilad et al. 2003). In contrast to primates, rodents are “keeping” their smell-related genes functional and free of mutations. In primates, many olfactory receptor pseudogenes are not essential during the life of an organism, and because of this they no longer encode functional, expressed proteins. This example is an illustration: if a gene is not needed, it would accumulate mutations over time and become a pseudogene, not playing any role in the life of organisms. So, not surprisingly, to date, no late-acting genes have been identified that support the MA theory (Baudisch 2005).

Antagonistic pleiotropy theory

In “Pleiotropy, Natural Selection, and The Evolution of Senescence,” George Williams (1957) introduced the antagonistic pleiotropy theory (AP theory) and also criticized Weismann’s view that senescence is adaptive and Comfort’s senescence theory (Comfort 1956) that argued “senescence is selectively irrelevant.” Contrastingly, Williams attested that “senescence is an unfavorable character, and that its development is opposed by selection.” Williams suggested that senescence remains despite its negative fitness effect, and argued senescence arose by “selection of genes that have different effect on fitness at different ages.” In his view, the strength of selection declines after sexual maturity is attained; therefore, mutations that were beneficial at early life stages would persist regardless of their deleterious effects later in life.

According to Williams, “It is necessary to postulate genes that have opposite effect on fitness at different ages, or, more accurately, in different *somatic environments*” (emphasis by Williams). Thus, AP required “different somatic environments” a priori. In other words, differences between early and late cellular environments accounted for differences in fitness effects. However, Kirkwood and Holliday (1979) and Sacher (1982) both argue the division of life into an early and late period to explain aging is circular by nature and that “... a pleiotropic switch can only be a consequence of a prior aging process and not a primary cause”. The AP theory attempts to explain temporal somatic differences, so these changes could not be used to explain aging. Although genes have temporal changes in expression, these differences are secondary to other adjustments and therefore are not driving the aging process. To date,

no gene has been identified that supports the AP theory. Moorad and Hall (2009) proposed that adaptive evolution of aging via the AP theory might experience negative feedback. Hamilton (1966) provided rigorous theoretical support to the AP theory, but his conclusion was criticized by Baudisch (2005) who suggested that AP theory might be unimportant for the majority of species. Moorad and Promislow (2009) are in turn skeptical that pleiotropic mutations, if they are ever found, could be responsible for “enormous genetic variations for ageing that we observe in natural population.”

Disposable soma theory

In 1977, Kirkwood introduced the disposable soma theory (DST) (Kirkwood 1977), which postulated aging is a byproduct of a trade-off between reproduction and somatic maintenance. According to this theory, an organism uses energy for growth, maintenance, repair, storage, and reproduction to maximize fitness and survival. Because the amount of energy available to the organism during its lifespan is limited, there has to be a balance between reproduction and somatic maintenance. For most species, reproduction is of the higher priority, and, as a result, the importance of somatic maintenance is reduced, and the body gradually deteriorates following reproduction.

Initially, the DST complimented the MA and AP theories. Later, Kirkwood extended the DST to explain the physiological basis of aging through trade-offs between reproduction and maintenance. Trade-offs can be defined as a balance between two states that cannot be maintained simultaneously or as giving up one thing for another. However, based on these definitions, it is unlikely that a trade-off between reproduction and somatic maintenance exists. Surviving until the end of reproduction *requires* somatic maintenance, suggesting that these processes work together rather than against each other. Reproduction and maintenance are not two polar opposite tasks of the evolutionary process; instead, they exist in a balance that allows immediate reproduction in short-lived species and prolonged somatic maintenance for delayed reproduction in long-lived species. A trade-off between reproduction and somatic maintenance is unlikely because reproduction requires the body to be well-maintained. There is no reproduction-OR-somatic maintenance balance because maintenance *is* necessary to provide the best conditions *for* reproduction.

In an effort to reconcile the evolutionary theories of aging with the mechanistic theories of aging, Kirkwood suggested that oxidative stress and overall genomic instability (increased mutation frequencies, chromosomal aberrations, and mitochondrial DNA damage) were the underlying mechanisms of the DST. Unlike the MA and AP theories, which were based on the deleterious behavior of genes and proteins, the DST postulated that “aging evolved not through genes *doing* something, but because of genes *not doing* things” (Kirkwood 2008). This conclusion is echoed by the general evolutionary theory of senescence, which states that aging exists because natural selection does not concern itself with it. In a recent critique of the DST, Speakman and Król (2010) noted “a major problem with the DST is that while the existence of costly LAMs [longevity assurance mechanisms] was postulated over 30 years ago, it is still unclear what these LAMs are”.

Environmental effects on aging

Classical evolutionary theories of aging predict that aging would be delayed in safe environments. Based on the AP theory, Edney and Gill (1968) assumed that “specific longevity is determined by (1) *natural* selection tending to prolong it and (2) the sum of all environmental hazards tending to curtail it”. This conjecture assumes that as the environment becomes less hazardous, species longevity increases. In wild populations, most individuals die from external causes, largely age-independent sources of mortality, such as predation, extreme temperatures, or hunger, and the strength of natural selection on individuals declines after maturation (Kirkwood and Austad 2000). However, it is suggested that in a safe environment that is free of predation, mortality due to external causes would decline, resulting in longer individual survival and species longevity.

For example, at Sapelo Island, GA, a population of opossums has been separated from the mainland population for 4000–5000 years. Here, free from the threat of predators, the island opossum population evolved a significantly lower reproductive rate, slightly increased reproductive age, and a seemingly slower rate of aging (Austad 1993). Additionally, the island opossums had 20% smaller first litter sizes than the mainland opossums. At first glance, this case supports both the AP theory and DST by combining the AP-prescribed delay of late deleterious effects of pleiotropic genes and the

DST-prescribed decrease in reproduction that facilitate increased investment to somatic maintenance. Supposedly, because the island was a safe environment in the absence of predators, selection on the late-acting pleiotropic genes pushed their deleterious effects beyond the survival age of the mainland opossums. Simultaneously, selection for early reproduction was reduced in the island population. According to DST, lifespan increased due to a shift in the reproduction/somatic maintenance trade-off to allocate more energy to somatic maintenance. However, this trade-off is not the only explanation for the changes in aging and reproduction. The island population might have experienced alternative external pressures that limited reproduction and extended the developmental process, similar to the situation observed in some rodent species, where reproductive cycles are modulated by nutrition and population density (Drickmer 2007; Krebs et al. 2007; Randall 2007). In addition to the release from the threat of predation, the island population also experienced an increase in population density (adult female density on the island is 4.2 times higher than that on mainland and weaned offspring density on the island is 2.7 times greater than that on the mainland (Austad 1993)), which may lead to increased competition for food. In this situation, it could be advantageous for females to produce fewer pups per litter. Similarly, rodents with moderately restricted caloric intake have shown a decrease in reproduction and an increase in median and maximum lifespan. Thus, the difference between the two opossum populations may not be attributed to a “safe environment” on the island, but more likely resulted from increased competition for food in the island population.

In a comparison of two populations of guppies, one with predators and one with an absence of predators, Reznick and coauthors found no extension of lifespan in the community free of predation. By contrast, they found statistically longer intrinsic lifespans in guppies from populations that experience high predation rates (Reznick et al. 2004). Thus, the environmental effect on aging has a more complicated pattern of influence that has been suggested previously (Wensink et al. 2017).

Moreover, the notion that a “safe environment” is beneficial for the species longevity might be an oversimplification of a real life; as Charles Darwin stated, “Every being, which during its natural lifetime produces several eggs or seeds, must suffer destruction during some period of its life, and during some season or occasional year, as more individuals are

produced than can possibly survive, there must in every case be a struggle for existence, either one individual with another of the same species, or with the individuals of distinct species, or with the physical conditions of life” (Darwin 1859).

Aging: longevity vs. immortality

To develop my new hypothesis on the evolution of aging, I broke down the question “Why do we age?” into “Why are we not immortal?” and “Why do we live as long as we do?” The answer to the first part has been suggested by Medawar (1952) and Rose and Graves (1989); they suggested that because the strength of selection declines with age, evolution is not concerned with aging. In other words, long life and immortality are not under selective pressure. Interestingly, the opposite is also true, and regulating the aging process to limit the life span was also not under selective pressure. In the absence of selective pressure on aging, it is interesting that there are maximum species-specific life spans. Despite this apparent absence of selection on lifespan, there are no mice that live beyond 4 years or humans that live beyond 122 years. Understanding the genetic component of the species-specific aging rate would ultimately lead to a successful gerontological program (Hayflick 1988; Hayflick 2000; Sierra and Kohanski 2017). To investigate the genetic component of species-specific aging requires a new hypothesis.

The orchestra metaphor

According to the above critiques, none of the three theories of aging satisfactorily explains the aging process mechanisms. To explain the origin of aging, I have developed a new hypothesis, called the selfish anti-aging (SAA). To introduce this new hypothesis, I suggest a new metaphor of a philharmonic orchestra. Imagine a philharmonic orchestra playing Tchaikovsky’s Swan Lake every day for several years. Initially, the conductor would break up the music to make corrections or to switch musicians. In time, the performances become almost perfect. The length of time necessary to achieve perfection depends on the conductor’s talent, the number of artists in the orchestra, the talent of each artist, and the artists’ ability to adjust as a unit. After several months, the orchestra achieves the capacity to perform Swan Lake with little direction from the conductor by following the written notes and several key

players. Finally, after a few more months, the orchestra is playing Tchaikovsky without the conductor’s direction as brilliantly as it was playing with him. However, this orchestra is brilliant only when playing Tchaikovsky’s Swan Lake, and when all important artists are present. Imagine that one day, the conductor says, “You have been playing very well, and today you are going to do something different. After you are done playing Swan Lake, continue to play without the written notes. Do not stop playing at any cost! I want to see how well you have been trained during these months.”

Two possible endings for this hypothetical situation are envisioned. In one alternative, the music degrades over time, missed notes here and lost parts there, resulting in chaos. Alternatively, the key artists would retain order in some small portion of the music. They could potentially find equilibrium between chaos and order, resulting in a constant repetition of parts of the ballet requiring minimal instruments. Because the orchestra was trained to play only Swan Lake, it was a brilliant but specific orchestra. Repeated practice and performance of Swan Lake corrected and eliminated all mistakes. However, after Swan Lake concludes, mistakes will remain uncorrected, and harmony will collapse. These mistakes do not cause the chaos but are characteristics of the chaos. The cause of the chaos is that Swan Lake is finished, and no one knows or cares what happens next.

Let us replace our orchestra with a gene expression network in a living cell or organism and the conductor with the force of natural selection: each instrument is a gene or expression pathway, and Tchaikovsky’s music is the cellular or organismal ontogeny. This new orchestra is the biggest and most complicated gene network working together for correct ontogeny. During millions of years of evolution, cellular and organismal development have adapted within this gene network. These developmental patterns are flexible between species. At the completion of the developmental program, the aging process settles on and chaos or a small, simple repetition begins.

A new aging hypothesis: running out of program and selfish genes in anti-aging

According to Comfort (5), natural selection is indifferent to individual survival beyond reproduction. Although natural selection has led to some incredibly complex

developmental plans, complex development is not enough for the long-term individual survival. Organisms running out of the developmental program are as helpless as the Swan Lake-specific orchestra. They have the equipment to play any music but only learned to play Swan Lake.

Many organisms in the wild die soon after reproduction. For these species, life history is the constant cycle of egg-(development)-adult-(maturation)-egg. Arking (1998) described r-selected species as those with large numbers of offspring coupled with high mortality and k-selected species as those with a smaller number of offspring and a lower mortality rate. In r-selected species, death represented a statistical probability, and an individual might survive beyond the end of its developmental program and reproductive period. The random nature of this survival is not converted into inheritable benefits. Such post-reproductive survival is apparent when animals are reared in artificial environments devoid of natural pressures, such as predation or starvation. For example, in the wild, *Drosophila melanogaster* rarely survive more than two or three weeks, but in a lab, they survive up to two months (Linnen et al. 2001). Thus, natural selection selects for developmental programs that allow individuals to survive *at least* until the end of reproduction, but some survive beyond reproduction. This situation is similar to human-made devices with a warranty period. A Toyota or an iPod is manufactured with specific reliability, and both are supposed to operate during the warranty period, usually thirty-six months for cars and twelve months for iPods. However, this time limit does not indicate that the car or iPod will stop working after the warranty period. They often operate for a long time even after the warranty expires. In other words, cars are supposed to function, without significant problems, for *at least* three years and iPods for *at least* one year. For the animals, the “warranty period” is even more relevant. Natural selection selects for developmental programs that equip animals for survival during reproduction. While an animal is still reproductively active, its physical and physiological strength must be at peak level to compete in the “struggle for survival.” The developmental program readies the animal for reproduction, but many animals do survive after reproduction. Thus, completion of ontogeny—running out of the developmental program—does not automatically lead to immediate demise. For many species, the end of the reproductive period marks the beginning of gradual physiological

decline and deterioration, and aging begins when the developmental program ends.

However, running out of the developmental program does not completely explain aging. In the wild, many marine mammals and primates survive longer than a passive “built-in” reliability mechanism should permit. To account for this longevity, we return to the orchestra metaphor. Imagine that after each Swan Lake performance, one hundred CDs are produced. These CDs contain detailed information on how to organize an orchestra, choose instruments, play Swan Lake, and record new informational CDs. After CDs are produced, they are placed in a box at the theater entrance with the expectation that some disks will be taken and Swan Lake will be played again. On occasion, an orchestra is organized, and Swan Lake is performed, and a new batch of instructional CDs is recorded. After each performance, the musicians would pack up their instruments and disappear with no care of whether the CDs are taken. However, imagine the case when an instructor-artist (i-artist) offers that in return for food and shelter, she will take each CD and make sure that new orchestras would be organized, perform the music, and produce CDs. Unlike all other musicians in the orchestra, the i-artist plays a small role during the Swan Lake performance. Her primary role comes after the performance, with the CD distribution and the new orchestra formation. Soon the i-artist is irreplaceable, and her efforts to distribute the new CDs resulted in many subsequent performances of new Swan Lake orchestras. Now, let us substitute the CDs distribution with parental care and the i-artist with instructor-genes (i-genes) that are responsible for the safety of progeny. I-genes would account for the entire spectrum of physiological and social behavior responsible for progeny production and care. I-genes could be viewed as an extension of the developmental program into a parental care program. At the same time, these two programs are fundamentally different. The developmental program is evolutionarily much older and has evolved under strong selective pressures. By contrast, the parental care program is more flexible, including a broad spectrum of physiological and behavioral changes that begin in late development and remain through adulthood. The genetic basis for such changes is controlled by i-genes, which stabilize gene expression during a post-reproductive period, ensuring that chaos is postponed.

I-gene activity might evolve like Dawkins’ selfish gene action (Dawkins 2006). To ensure that i-genes are

necessary for the organism, they would change the developmental program so that they were indispensable for reproduction and progeny care. For example, i-genes might limit the number of eggs produced by ensuring the necessary hormonal changes are initiated. This situation corresponds to the i-artist limiting the CD production to 5–10 copies and being responsible for re-copying the CDs.

Generally, in the absence of parental care, genes are only maintained in the genome if they have a role during the developmental program. In the presence of parental care, incorporation into the genome is less restricted, and even genes that acted after ontogenesis could be maintained in the genome. I-genes would ensure their own survival by increasing progeny's dependence on parents and, as a byproduct, increase individual longevity. In return, the selfish action of i-genes provides organisms with a post-developmental program. By stabilizing gene expression, long-term parental care increased the chance that parents survive through the development of their offspring.

When compared to most land mammals, primates are characterized not only by more extended gestation periods and required parental care but also by increased longevity and post-developmental time (Wilson 2000). In most rodents, individuals in the wild only survive six to eight months (Phelan and Austad 1989). A reproductive strategy that includes a short gestation period and short developmental time can sustain a species even if all individuals of a generation die after a few months. During the evolution of great apes, in addition to an increase in body size and social complexity, species have gained longer gestation periods, extended parental investment, and increased longevity. In contrast to rodents, in many primate species, adults must survive at least 12–14 years after maturation. For example, with a long gestation period and three to four years between successful pregnancies, most female chimpanzees must stay fertile for 24–28 years to ensure species survival. This longevity depends on behavioral and physiological changes that occurred in the primate lineage. The group of i-genes likely facilitated the shift in primate's evolution from short pregnancies and little parental investment into long pregnancies and extended parental care. Successful identification of i-genes could ultimately lead to the development of therapies for age-related human diseases and aging itself.

Hamilton (1966) asserted that “if the organism practices parental care, ‘birth’ should be considered to occur

at the age at which the offspring becomes independent.” Unlike most animal species, primates, and hominids in particular, have an exceptionally long maturation period. In this sense, reproductive success and fitness of adults should be calculated from the number of offspring who themselves attain reproductive maturity.

Minimum lifespan potential

In aging research, species are characterized by the maximum lifespan of an individual. With this metric, a virtual “Methuselah’s zoo” could be created for the longest-lived animals (Austad 2010). However, information on maximum lifespan does not indicate when reproduction ends, and aging begins, which show for how long natural selection “cares” for the species. To determine this time point, I suggest using a value of species *minimum lifespan requirement*, defined as the length of time required to ensure species survival. The minimum lifespan requirement corresponds to the duration of time when the genes and behavior of a specific species are subject to the natural selection. Individual survival beyond the minimum lifespan requirement does not contribute to overall species survival. Minimum lifespan requirement would be calculated from age at maturation, the probability of survival until adulthood, the length of a gestation period, years under parental care, the number of young produced, the time between litters, and social structure. Wild female *Mus musculus* mature in ~30 days, have short gestation and weaning periods around 21–24 days each, and need to have 2 or 3 litters per female with a brief period between litters. Based on these numbers, I estimate its minimum lifespan requirement is 4 or 5 months. According to Phelan and Austad (1989), 50% of the wild mouse population survive to 130 days, and 10% survive to 279 days. Female chimpanzees first give birth at 14 years, have a 3-year weaning period, and have an average litter size of 1 (Hill et al. 2001). The probability of surviving to adulthood is 50%. To maintain a constant population size, females must average 4 or 5 offspring through their lives at the inter-litter interval of 2.5 years. Based on these numbers, I estimate the minimum lifespan requirement for the chimpanzee is 25–30 years. The difference in the minimum lifespan requirement for these two species highlights a significant challenge in aging research. To date, most aging research is conducted on model rodents even though they have a vastly shorter minimum lifespan requirement compared to

humans. These rodents are studied primarily because of convenience, limiting what we can learn about hominid aging, and specifically human aging. On the other hand, aging studies that focus on primates could lead to the identification of i-gene families, responsible for stabilizing the genome during a post-developmental stage and could lead to an understanding of human aging. If primates' longevity is due to the additional genetic organization by instructor-genes, then murine models would be inherently inadequate for the study of human aging.

Limitations of the current research

Current problems in aging research come directly from oversimplifications created by molecular biology. Importantly, we now know that Jacques Monod's statement (Monod and Jacob 1961) "what is true for *E. coli* is true for an elephant" does not apply to aging research. Although all life ends with death, choosing *any* animal model for aging research is not appropriate. Limitations of time and funding lead researchers to focus on aging in *Saccharomyces cerevisiae* (e.g., Lee et al. 2017), *Caenorhabditis elegans* (e.g., Scerbak et al. 2018), and *D. melanogaster* (e.g., Zhou et al. 2017). Although these model organisms are convenient, cheap, and short-lived, they offer little useful insight into mammalian aging in general, or human aging in particular (Austad and Podlutzky 2005; Austad 2001). Natural selection shaped those species to specific ecological niches, which are entirely different from mammalian niches. A similarity in genes or gene networks should not provide sufficient motivation to study a worm's aging process and project the results to humans; these types of studies would lead only to worm- or fly-specific knowledge. Unfortunately, few publications echo this critique of non-mammalian aging models (Gershon and Gershon 2001; Austad and Podlutzky 2005). Because i-genes would be a recent development in the vertebrate evolution, they are likely limited to mammals (primates in particular) and studies of yeast, worms, or flies would provide information of limited value on human aging. Aging research in the mouse is currently limited to the phenomenological observations between "young" and "old" animals with relatively few examples of life extension in knock-out mutants. Still, compared to primates, mice would have a limited number of i-genes, which might help in identifying them and understanding their role in the mammalian aging process.

Because of the difference between human and other primate's parental care, recent human evolution likely includes the rapid evolution of i-genes. For example, research on brain size and complexity (Dorus et al. 2004) found evidence for accelerated evolution in primate lineage compared to rodents. A similar approach might yield interesting results if one compares whole genomes instead of brain-related genes. For example, Nielsen et al. (2005) compared genomes of humans and chimpanzees for signs of positively selected genes and found that many genes of unknown biological processes exhibited accelerated evolution. It remains to be determined which of these genes are related to aging or i-gene groups.

Three groups of animal models for aging research

With an increase in the availability of whole-genome sequence data and the appreciation of comparative epigenetics of development, we need to know *where* to look and *what* to compare to understand human aging. As such, animal model organisms can be divided into three groups, according to their parental investment, i-gene action, and aging process in the wild.

Group A consists of animals that, in the wild, have short generation time and minimal or no parental care. Animals belonging to group A include *C. elegans*, *Drosophila melanogaster*, other insects, most fishes, and most rodents (e.g., Ashpole et al. 2017). Rodents are included in group A because they have minimal parental care after weaning.¹ These species likely have few i-genes. However, it is possible that some genes that are i-genes in primates still play an important role in aging in rodents or other lineages. Studying these i-gene homologs would reveal a gene-specific evolution of i-genes. Aging research in this group might uncover how animals in a safe lab environment can live 3–5 times longer than their wild counterparts. Comparative analysis of the genome maintenance systems between different rodent species might illuminate differences that increase their longevity in the lab. For example, the white-footed

¹ One rodent not in group A is the naked mole rat (*Heterocephalus glaber*). This rodent, approximately the size of a mouse, lives up to 30 years (Sherman et al. 1991; Edrey et al. 2011; Lewis et al. 2018; Olecka et al. 2018). However, specific physiological traits, such as poikilothermia, low body temperature, low respiration, low metabolic rate for an animal of its size, partial developmental arrest, and life at a low oxygen level, might significantly influence their longevity. Due to these unique characteristics, it is hard to place this animal in a particular group.

mouse (*Peromyscus leucopus*) occupies a similar ecological niche as a *M. musculus* but lives twice as long (up to eight years) in a protective lab environment (Sacher and Hart 1978). Finding differences between genome maintenance of *P. leucopus* and *M. musculus* would reveal which genes were subject to deviating evolutionary pressures and how these differences contributed to maximum longevity (Ungvari et al. 2008; Podlutzky et al. 2017).

Group B consists of species that have long maximum life spans with minimal parental care and short post-reproductive lifespan, such as birds and bats. In these cases, longevity is likely a byproduct of physiological characteristics associated with flight and energy utilization. The minimal parental investment in these species suggests that they are not required to have such long life spans, and they likely have few i-genes. In *Adaptation and Natural Selection*, Williams (1966) noted that not everything that is adaptive is an adaptation in the technical sense. Gould and Lewontin (1979) used the term “spandrel” for a phenotypic character that is a byproduct of the evolution of some other character. Longevity of many bats and birds species is a sort of spandrel of their ability to fly. During the flight, these animals rapidly burn energy resulting in elevated levels of reactive oxygen species (ROS) leaking from their mitochondria. However, these ROS do not damage DNA and other macromolecules due to free radical scavenging and DNA repair systems (Brunet-Rossini and Austad 2004; Alper et al. 2015), which potentially play a role in the longevity of the species. Group B species probably do not have advanced i-gene families due to limited parental care rarely extending beyond a single season. Aging studies in group B animals might reveal species-specific mechanisms to increase longevity, including robust DNA repair machinery or a sensitive ROS-scavenging system (Brunet-Rossini 2004; see also review by Davies et al. 2017).

Group C consists of species that have extensive parental investment, such as most primates and many whales. These species likely evolved many i-genes to facilitate adult survival beyond initial reproductive success. These genes would also help the adults survive until their progeny matures. Investigating genome evolution in closely related primates might reveal the genetic basis of increasing the gestation and weaning periods, the genetic basis of social structure and parental behavior. Research on this group will most likely bring information about mechanisms of human-specific i-

genes. Unlike group B, animal species belonging to group C have an extended period of life after reproduction. Understanding the underlying molecular mechanisms, identification of i-genes and their targets, would allow researchers to have a better view on human evolution. Identification of human-specific changes in i-genes will lead to the understanding and treatment of age-related diseases and, possibly, cancers.

Conclusion

Current evolutionary theories of aging, such as MA, AP, and DST, do not satisfactorily explain the underlying molecular mechanisms of aging. The new hypothesis developed here, SAA, explains the lack of immortality and the increase in primate’s longevity, by postulating that aging is a default process and a selfish action of the parental care program, respectively. Future research on aging should focus on identifying instructor-genes (or i-genes), which are active during maturation and then stabilize gene expression during the post-developmental period of organismal life. Comparisons of the molecular mechanisms involved with aging in primates will show these processes in closely related species, including humans. By comparing the whole-genome sequences of several primate species with different levels of parental care, we might identify i-genes that played a significant role in species evolution and anti-aging.

The September 2018 issue of the *Scientific American* was a special one: The Science of Being Human. However, none of the many articles have listed parental care as a unique or important characteristic of our species. Almost all animal groups have evolved degrees of parental care, from mouthbrooding cichlids to the crop milk secretion in birds; parental care seems to be universal and ubiquitous. That is probably why the parental care in humans seems to be a “nothing out of the ordinary,” many species do it, and we are as well. However, presented here is the new hypothesis linking primate’s parental care program with the anti-aging action of a family of instructor-genes, currently unidentified.

The role of i-genes in primate’s evolution and the origin of *Homo sapiens* could be even more prominent than the “simple” selfish anti-aging mechanism. The origin of conscious, the biological root of social structure and language, cooperation and altruism,

postponement of age-related diseases (including most cancers), all might be linked to the action of i-genes and the development and elaboration of parental care program.

Acknowledgements The author would like to thank friends and colleagues who contributed to the development of this article by discussions, criticism, or editing the manuscript: Zoltan Ungvari, Azhub Ibragimovich Gaziev, Nicola Raule, Alex and Sandra Pieke-Dahl, Steven Austad, Jeffrey Maycock, Robert Williams, Wendy Grus, and last but not least Natalia and Viktorija Podlutskaia. Special thanks to the anonymous reviewers of the manuscript, because of their critique, many useful suggestions have been addressed in the final version. However, only I can be blamed for any mistakes or deficiencies.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Alper SJ, Bronikowski AM, Harper JM (2015) Comparative cellular biogerontology: where do we stand? *Exp Gerontol* 71: 109–117. <https://doi.org/10.1016/j.exger.2015.08.018>
- Arking R (1998) *Biology of aging*. 2nd ed. chapter 4. Sinauer, Sunderland MA
- Ashpole NM, Logan S, Yabluchanskiy A, Mitschelen MC, Yan H, Farley JA, Hodges EL, Ungvari Z, Csiszar A, Chen S, Georgescu C, Hubbard GB, Ikeno Y, Sonntag WE (2017) IGF-1 has sexually dimorphic, pleiotropic, and time-dependent effects on healthspan, pathology, and lifespan. *Geroscience* 39(2):129–145. <https://doi.org/10.1007/s11357-017-9971-0>
- Austad SN (1993) Retarded senescence in an insular population of Virginia opossums. *J Zool Lond* 229:695–708. <https://doi.org/10.1111/j.1469-7998.1993.tb02665.x>
- Austad SN (2001) An experimental paradigm for the study of slowly aging organisms. *Exp Gerontol* 36(4–6):599–605
- Austad SN, Podlutsky A (2005) A critical evaluation of nonmammalian models for aging research. In: Masoro EJ, Austad SN (eds) *Handbook of the biology of aging*. Academic Press, San Diego, pp 449–469
- Austad SN (2010) Methuselah's Zoo: how nature provides us with clues for extending human health span. *J Comp Pathol* 142(1):510–521. <https://doi.org/10.1016/j.jcpa.2009.10.024>
- Baudisch A (2005) Hamilton's indicators of the force of selection. *PNAS USA* 102(23):8263–8268. <https://doi.org/10.1073/pnas.0502155102>
- Brunet-Rossinni AK (2004) Testing the free radical theory of aging in bats. *Ann N Y Acad Sci* 1019:506–508. <https://doi.org/10.1196/annals.1297.093>
- Brunet-Rossinni AK, Austad SN (2004) Ageing studies on bats: a review. *Biogerontology* 5(4):211–222. <https://doi.org/10.1023/B:GGEN.0000038022.65024.d8>
- Comfort A (1954) Biological aspects of senescence. *Biol Rev Camb Philos Soc* 29(3):284–329. <https://doi.org/10.1111/j.1469-185X.1954.tb00598.x>
- Comfort A (1956) *Biology of senescence*. Rinehart, New York
- Darwin C. On the origin of species. 1859; Chapter 3
- Dawkins R (2006) *The selfish gene*. 30th anniversary ed. Oxford Univ Press
- Davies JMS, Cillard J, Friguet B, Cadenas E, Cadet J, Cayce R, Fishmann A, Liao D, Bulteau AL, Derbré F, Rébillard A, Burstein S, Hirsch E, Kloner RA, Jakowec M, Petzinger G, Sauce D, Sennlaub F, Limon I, Ursini F, Maiorino M, Economides C, Pike CJ, Cohen P, Salvayre AN, Halliday MR, Lundquist AJ, Jakowec NA, Mechta-Grigoriou F, Mericskay M, Mariani J, Li Z, Huang D, Grant E, Forman HJ, Finch CE, Sun PY, Pomatto LCD, Agbulut O, Warburton D, Neri C, Rouis M, Cillard P, Capeau J, Rosenbaum J, Davies KJA (2017) The oxygen paradox, the French paradox, and age-related diseases. *Geroscience* 39(5–6):499–550. <https://doi.org/10.1007/s11357-017-0002-y>
- Dorus S, Vallender EJ, Evans PD, Anderson JR, Gilbert SL, Mahowald M, Wyckoff GJ, Malcom CM, Lahn BT (2004) Accelerated evolution of nervous system genes in the origin of *Homo sapiens*. *Cell* 119(7):1027–1040. <https://doi.org/10.1016/j.cell.2004.11.040>
- Drickmer LC (2007) Acceleration and delay of reproduction in rodents. In: Wolff JO, Sherman PW (eds) *Rodent societies*. University of Chicago Press, Chicago, pp 106–114
- Edney EB, Gill RW (1968) Evolution of senescence and specific longevity. *Nature* 220:281–282. PMID:5684860
- Edrey YH, Hanes M, Pinto M, Mele J, Buffenstein R (2011) Successful aging and sustained good health in the naked mole rat: a long-lived mammalian model for biogerontology and biomedical research. *ILAR J* 52(1):41–53
- Gershon H, Gershon D (2001) Critical assessment of paradigms in aging research. *Exp Gerontol* 36(7):1035–1047
- Gilad Y, Man O, Pääbo S, Lancet D (2003) Human specific loss of olfactory receptor genes. *PNAS USA* 106(6):3324–3327. <https://doi.org/10.1073/pnas.0535697100>
- Gould SJ, Lewontin RC (1979) The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. *Proc R Soc London B* 205(1161):581–598
- Hamilton WD (1966) The moulding of senescence by natural selection. *J Theoret Biol* 12:12–45. [https://doi.org/10.1016/0022-5193\(66\)90184-6](https://doi.org/10.1016/0022-5193(66)90184-6)
- Hayflick L (1988) Why do we live so long. *Geriatrics* 43(10):77–79
- Hayflick L (2000) The future of ageing. *Nature* 408(6809):267–269. <https://doi.org/10.1038/35041709>
- Hill K, Boesch C, Goodall J, Pusey A, Williams J, Wrangham R (2001) Mortality rates among wild chimpanzees. *J Human Evolution* 40:437–450. <https://doi.org/10.1006/jhev.2001.0469>
- Kirkwood TB (1977) Evolution of aging. *Nature* 270(5635):301–304. PMID:593350
- Kirkwood TB, Holliday R (1979) The evolution on aging and longevity. *Proc R Soc Lond B Biol Sci* 205(1161):531–546. PMID: 42059
- Kirkwood TB, Austad SN (2000) Why do we age? *Nature* 408(6809):233–238. <https://doi.org/10.1038/35041682>
- Kirkwood TB (2005) Understanding the odd science of aging. *Cell* 120(4):437–447. <https://doi.org/10.1016/j.cell.2005.01.027>

- Kirkwood TB (2008) Understanding aging from an evolutionary perspective. *J Intern Med* 263(2):117–127. <https://doi.org/10.1111/j.1365-2796.2007.01901.x>
- Krebs CJ, Lambin X, Wolff J (2007) Social behavior and self-regulation in murine rodents. In: Wolff JO, Sherman PW (eds) *Rodent societies*. University of Chicago Press, Chicago, pp 173–181
- Lee MB, Carr DT, Kiflezghi MG, Zhao YT, Kim DB, Thon S, Moore MD, Li MAK, Kaerberlein M (2017) A system to identify inhibitors of mTOR signaling using high-resolution growth analysis in *Saccharomyces cerevisiae*. *Geroscience* 39(4):419–428. <https://doi.org/10.1007/s11357-017-9988-4>
- Lewis KN, Rubinstein ND, Buffenstein R (2018) A window into extreme longevity; the circulating metabolomic signature of the naked mole-rat, a mammal that shows negligible senescence. *Geroscience* 40(2):105–121. <https://doi.org/10.1007/s11357-018-0014-2>
- Libertini G, Ferrara N (2016) Aging of perennial cells and organ parts according to the programmed aging paradigm. *Geroscience* 38(2):35. <https://doi.org/10.1007/s11357-016-9895-0>
- Linnen C, Tatar M, Promislow D (2001) Cultural artifacts: a comparison of senescence in natural, laboratory-adapted and artificially selected lines of *Drosophila melanogaster*. *Evol Ecol Res* 3:877–888
- Medawar PB (1952) *An unsolved problem of biology*. Lewis, London
- Monod J, Jacob F (1961) General conclusions: teleonomic mechanisms in cellular metabolism, growth and differentiation. *Cold Spr Harb Symp Quant Bio (Cellular Regulatory Mechanisms)* 26:389–401
- Moorad JA, Hall DW (2009) Age-dependent mutational effects curtail the evolution of senescence by antagonistic pleiotropy. *J Evol Biol* 22(12):2409–2418. <https://doi.org/10.1111/j.1420-9101.2009.01849.x>
- Moorad JA, Promislow DE (2009) What can genetic variation tell us about the evolution of senescence? *Proc R Soc B* 276(1665):2271–2279. <https://doi.org/10.1098/rspb.2009.0183>
- Nielsen R, Bustamante C, Clark AG, Glanowski S, Sackton TB, Hubisz MJ, Fledel-Alon A, Tanenbaum DM, Civello D, White TJ, Sninsky J, J, Adams MD, Cargill M (2005) A scan for positively selected genes in the genomes of humans and chimpanzees. *PLoS Biol* 3(6):e170. <https://doi.org/10.1371/journal.pbio.0030170>
- Olecka M, Huse K, Platzer M (2018) The high degree of cystathionine β -synthase (CBS) activation by S-adenosylmethionine (SAM) may explain naked mole-rat's distinct methionine metabolite profile compared to mouse. *Geroscience* 40(4):359–360. <https://doi.org/10.1007/s11357-018-0035-x>
- Phelan JP, Austad SN (1989) Natural selection, dietary restriction, and extended longevity. *Growth Dev Aging* 53:4–6
- Podlitsky A, Valcarcel-Ares MN, Yancey K, Podlitskaya V, Nagykalai E, Gautam T, Miller RA, Sonntag WE, Csizsar A, Ungvari Z (2017) The GH/IGF-1 axis in a critical period early in life determines cellular DNA repair capacity by altering transcriptional regulation of DNA repair-related genes: implications for the developmental origins of cancer. *Geroscience* 39(2):147–160. <https://doi.org/10.1007/s11357-017-9966-x>
- Randall JA (2007) Environmental constraints and the evolution of sociality in semifossorial desert rodents. In: Wolff JO, Sherman PW (eds) *Rodent societies*. University of Chicago Press, Chicago, pp 368–337
- Reznick DN, Bryant MJ, Roff D, Ghalambor CK, Ghalambor DE (2004) Effect of extrinsic mortality on the evolution of senescence in guppies. *Nature* 431(7012):1095–1099. <https://doi.org/10.1038/nature02936>
- Rose MR, Graves JL (1989) What evolutionary biology can do for gerontology. *J Gerontol* 44(2):B27–B29
- Sacher GA (1982) Evolutionary theory in gerontology. *Perspect Biol Med* 25(3):339–353
- Sacher GA, Hart RW (1978) Longevity, aging and comparative cellular and molecular biology of the house mouse, *Mus musculus*, and the white-footed mouse, *Peromyscus leucopus*. *Birth Defects* 14(1):71–96
- Scerbak C, Vayndorf E, Hernandez A, McGill C, Taylor B (2018) Lowbush cranberry acts through DAF-16/FOXO signaling to promote increased lifespan and axon branching in aging posterior touch receptor neurons. *Geroscience* 40(2):151–162. <https://doi.org/10.1007/s11357-018-0016-0>
- Sherman PW, Jarvis JUM, Alexander RD (1991) *The biology of the naked mole-rat*. Princeton University Press, Princeton
- Sierra F, Kohanski R (2017) Geroscience and the trans-NIH Geroscience Interest Group, GSIG. *Geroscience* 39(1):1–5. <https://doi.org/10.1007/s11357-016-9954-6>
- Speakman JR, Król E (2010) The heat dissipation limit theory and evolution of life histories in endotherms—time to dispose of the disposable soma theory? *Integr Comp Biol* 50(5):793–807. <https://doi.org/10.1093/icb/icq049>
- Ungvari Z, Krasnikov BF, Csizsar A, Labinskyy N, Mukhopadhyay P, Pacher P, Cooper AJ, Podlitskaya N, Austad SN, Podlitsky A (2008) Testing hypotheses of aging in long-lived mice of the genus *Peromyscus*: association between longevity and mitochondrial stress resistance, ROS detoxification pathways, and DNA repair efficiency. *Age* 30(2–3):121–133. <https://doi.org/10.1007/s11357-008-9059-y>
- Weismann A (1891) *Essay on heredity*, chapters 1 & 3 Clarendon Press, Oxford
- Wensink MJ, Caswell H, Baudisch A (2017) The rarity of survival to old age does not drive the evolution of senescence. *Evol Biol* 44(1):5–10. <https://doi.org/10.1007/s11692-016-9385-4>
- Williams GC (1957) Pleiotropy, natural selection, and evolution of senescence. *Evolution* 11(4):398–411. <https://doi.org/10.2307/2406060>
- Williams GC (1966) *Adaptation and natural selection*. Princeton Univ Press, Princeton
- Wilson OE (2000) *Sociobiology, the new synthesis*. 25th anniversary ed. Harvard Univ press, Cambridge, Massachusetts
- Zhou YZ, Yan ML, Gao L, Zhang JQ, Qin XM, Zhang X, Du GH (2017) Metabonomics approach to assessing the metabolism variation and gender gap of *Drosophila melanogaster* in aging process. *Exp Gerontol* 98:110–119. <https://doi.org/10.1016/j.exger.2017.07.020>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.