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Senescence in Animals: Why Evolutionary Theories Matter

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1. Introduction

Senescence, considered from the individual viewpoint can be characterized as a "progressive loss of fertility and increasing probability of death with increasing age"(Kirkwood & Austad, 2000). This phenomenon can also be considered from the populational perspective: senescent populations present increasingly higher death rates with increasing age (Masoro & Austad, 2006).

This is a clearly deleterious process, which seems difficult to conciliate with natural selection, which predicts evolution towards increasing fitness. Historically, the first evolutionary explanation able to conciliate these two processes is known as the mutation accumulation theory (Medawar, 1952). According to this theory, in age-structured populations the force of selection decreases with increasing age, allowing the accumulation of deleterious genes with age-specific effects on mortality rate (Hamilton, 1966). Under population genetics mechanisms, senescence is not necessarily deleterious: the original Medawar's proposition implies that the postponement of age-specific effects of harmful genes is equivalent to their elimination in such a way that they become effectively neutral. Hence, such postponement is beneficial and senescence can be regarded as a side effect of the process.

Medawar was convinced that these genes could only account for senescent manifestations encountered in protected populations after they reached ages not achievable in the wild and, therefore, that further explanation involving pleiotropy and linkage would be required to account for a gradual process of organic degeneration, but he did not elaborate on them. This was noted by Williams, who explained the maintenance of beneficial and deleterious traits together, giving rise to the antagonistic pleiotropy theory.

Essentially, the antagonistic pleiotropy theory relies on the existence of genes of a special kind, which are capable of increasing and decreasing fitness depending on the somatic environment and/or age. It is not necessary that the beneficial effects precede the deleterious effect as commonly believed e. g. (Futuyma, 1998; Masoro & Austad, 2006). Instead, Williams' original proposition only required an influx of pleiotropic alleles that may fixate in the population due to their overall beneficial effect. In this scenario, the observed senescence is understood as the composition of deleterious components from all present pleiotropic genes (Williams, 1957).

Instead of basing his arguments on genetics, a somewhat different view was offered by Kirkwood, elaborating on the error catastrophe of Orgel (Orgel, 1963). He approached senescence from an ecological argument in which energy resources may be allocated either

to somatic cell maintenance or to reproduction, thus generating some sort of soma-germ conflict. Called disposable soma theory, it ultimately relies on the existence of specific genes controlling the accuracy of the transcription/translation machinery in an age-dependent manner. Kirkwood himself regards his theory as a specialization of the antagonistic pleiotropy of Williams (Kirkwood, 1977; Kirkwood & Holliday, 1975a;b; 1979). The difference is that Williams invokes the existence of genes responsible for beneficial and deleterious effects, but Kirkwood's theory, while not denying the existence of these genes, does not require them. The conflicting destination of energy either to body or reproduction maintenance would suffice for the evolution of senescence.

Senescence is a process that causes animals to become progressively less fertile (Medawar, 1946) and more vulnerable (Comfort, 1956) with age. It has long been noticed that senescence-associated frailty causes population death rates to rise exponentially with age (Gompertz, 1825).

Although a number of evidences have since been collected in support of each of these theories, in the last decades some phenomena have challenged all of them. This includes the effect of caloric restriction on longevity, the late-life mortality deceleration and the longevity pathways controlled by either a single or a few genes, such as the insulin pathway and the effect of sirtuins on longevity.

2. Measuring senescence

Although generally considered together, it is useful to take some time to consider the effects of senescence on individuals' survival and fertility (physiological senescence) or on populational survival curves (demographic senescence) separetly. By not doing so, the researcher may unwittingly take the risk of assuming demographic senescence to stem directly from physiological senescence. Although it might well be the case, there is no theoretical reason why it must be so.

The fact is that the genetic architecture of senescence, i.e., which genes are related to which measurable effects that we call senescence and how they relate to each other, will dictate the relationship between physiological and demographic senescence(s).

2.1 What is the genetic architecture of senescence?

Genetic architecture refers to the genetic basis of a phenotypic trait. Beyond comprehending the map of the genes linked to a given trait, genetic architecture considers all phenomena through which such genetic map produces the phenotype Masoro & Austad (2006).

The most common definition of the senescent phenotype combines individual effects (decrease in functional and reproductive abilities) with an effect which is measurable only in a population (age-dependent increase in mortality). This often leads us to conclude that it is exactly the same phenomenon that makes us individually more fragile and at greater risk of dying as we age.

Figure 1 shows that this is only one of the possible relationships between physiological senescence (progressive fall on functional capacity and fertility) and demographic senescence (increased mortality accompaining chronological aging) (Promislow et al., 2006).

While it is not necessarily clear what the relationship between the physiological and demographic components of senescence is, most "aging genes" described in the literature are simply genes whose variations influence the longevity of the studied species regardless of their physiological effect, and few genes were shown to affect the Mortality Rate Doubling Time (MRDT) of populations of mutants for such genes, and, therefore, to affect the speed of senescence (de Magalhães et al., 2005). Additionally, when strains carrying alleles for many of the so called *longevity genes* are mixed with wild populations, generally the "beneficial" mutation is lost over a few generations, indicating that although such variants increase longevity, they may exert a deleterious effect for fitness (Promislow et al., 2006).

For these reasons, the first decision before staring to seek for "aging genes" should be which model of senescence to assume. Otherwise, we might not know how to interpret the findings in a coherent way: suppose that human carriers of a given mutation have an increase of 5% in their annual mortality from 30 years of age – are them carriers of a genetic disease or of a deleterious mutation in a senescence pathway?

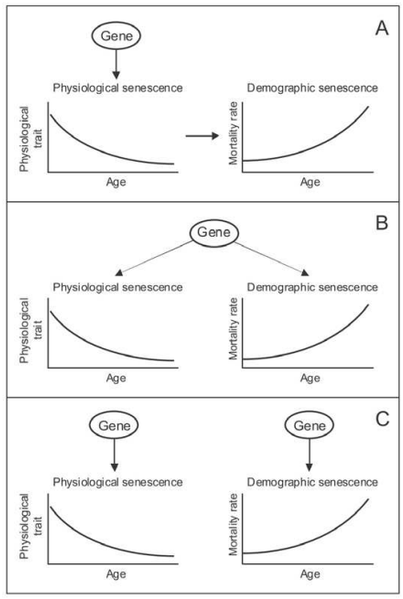

Fig. 1. Three different models for the relationship between physiological and demographic senescence on the genetic architecture of senescence. (a) Genes negatively influence physiological processes, which, then, lead to increasing effects on age-specific mortality. (b) The same genes that lead to physiological senescence independently lead to increasing age-dependent death rates, which are demografically measurable. (c) Different genes operate over physiological and demographic processes that are linked with senescence. Extracted from *Promislow, D. E. L. et al. Evolutionary Biology of Aging: Future Directions. In: Masoro EJ, Austad SN (Ed.). Handbook of the Biology of Aging. 6th. ed. San Diego: Academic Press, 2006. 217-242.*

If we suppose that senescence is a unique genetic phenomenon whose physiological effects lead to its demographic aspects (Figure 1 (a)), then "genes of senescence" should exert age-dependent deleterious effects in the physiology of organisms, and because more frail individuals are more prone to dye from a given insult, such genes would also increase mortality from their ages of onset.

On the other hand, genes that determine effects on demographic senescence may exert independent effects on the physiology of organisms. Such effects might not be linked to the demographic effects of the same genes (Figure 1 (b)).

Finally, physiological senescence could be genetically independent from demographic senescence, so that there would be a "genetic modularity" between the two phenomena, in which different groups of genes participate in each process (Figure 1 (c)).

This text assumes when necessary that genes linked to physiological senescence may impact probability of death (1 (a)). It does so relying on the fact that there is little evidence that there may be a genetic variability to the age-dependent physiological decline without its influencing on demographic senescence (Wessells et al., 2004).

Once delimited the senescent phenotype, we review some genetic phenomena that may have importance for the genetic architecture of senescence. Such phenomena include:

- Epistasis, when the expression of a gene negatively influences the expression of one another;
- Polygyny, where multiple genes contribute to a phenotypic trait;
- Pleiotropy, when multiple phenotypic characteristics are influenced by a single gene;
- Quasi-continuity, while a variation in a gene affects minimally a phenotype;
- Plasticity, when a single genotype can produce more than one distinct phenotype, such phenotypic diversity may occur among individuals of the same genotype, by action of different environmental influences on the same individual or *in the same individual at different ages*;
- Evolvability, when genotypic variations of a phenotype exist in a population and can lead to different degrees of adaptability, so that environmental changes will lead to readaptations.

Epistasis could function similarly to what is predicted on antagonistic pleiotropy theory: assuming two genes with positive effects for fitness, in which the first gene exerts a negative effect on the expression of the second gene, the first gene would have positive and negative effects on fitness The effect under selection, however, would be the average effect.

It is believed, since the formulation of the theory of mutation accumulation by Medawar, that senescence is a polygenic phenotype (Medawar, 1952). Indeed, recent decades have seen the description of "hundreds of aging genes" (Promislow et al., 2006). Summed to the fact that senescence is an early onset and gradually progressive phenotype in almost all of the species that has been described, it points to a polygenic inheritance with almost-continuity in organic response to genes that determine senescence.

3. The evolutionary theories of senescence

3.1 Introduction

It has always been difficult to conciliate senescence with natural selection, a biological mechanism generally expected to increase population fitness. Although acknowledged by Darwin (1872), the first tentative explanation for the evolution of senescence was offered by August Weismann in 1881. For Weismann, senescence had evolved for the good of species, in

that the removal of older, weaker and less fertile individuals from a population would enhance the survival of younger individuals and overall reproduction of the species (Weismann, 1889).

Realizing his argument was circular (since it depended on older individuals being weaker and less fertile for senescence to evolve) Weismann withdrew his theory (Weismann, 1892).

More than half a century later, Medawar proposed the mutation accumulation theory of senescence (Medawar, 1952). He realized that even in an imaginary non senescent population, older individuals would be very rare simply because the cumulative incidence of death is necessarily dependent of age. This means that late acting mutations will affect population fitness only in the proportion of surviving individuals after such late ages. In other words, the force of natural selection decreases with age and deleterious mutations with effects that are late enough are in fact neutral mutations, which could randomly accumulate.

For Medawar, this would explain the existence of deleterious mutations fixed in ages to which individuals of a given species are not expected to survive in nature. Senescence evolved through such a process would only be observable in protected species, such as laboratory animals or our own species. Medawar, nonetheless, believed that animals did senesce in nature and, therefore felt the need for an early benefit to explain how a not so late acting deleterious mutation could evolve to fixation.

This was developed into the antagonistic pleiotropy theory (Williams, 1957). In short, Williams proposed that the fitness associated to mutations with more than one effect is the average fitness. Therefore, a mutation with earlier beneficial effects and later deleterious ones could be fixed by natural selection if the overall fitness be positive. Deleterious effects early enough to impact mortality in nature could be compensated by beneficial effects. Williams' theory depended on the existence of such special, pleiotropic genes, in numbers sufficient to explain the observed progressive increase in the effects of senescence.

In 1977, elaborating on the mechanistic error catastrophe theory of Orgel (1963), Kirkwood proposed an ecological argument for the evolution of senescence (Kirkwood, 1977). Since evolution is centered on reproduction and not directly in survival, the energetic and metabolic cost of maintenance and repair could affect reproduction negatively if taken to perfection. Therefore, the level of body maintenance and repair that can evolve is the minimum to assure reproduction. Any deleterious mutation that do not decrease reproduction can not only be neutral, but can enhance fitness if it results in more reproductive resources. This is the disposable soma theory of senescence.

These three theories are not mutually excluding, and can explain different aspects of the evolution of senescence (Kirkwood & Austad, 2000).

3.2 The mutation accumulation theory of senescence

According to Haldane, a deleterious mutation with effect only on later ages may escape natural selection, because either most individuals will be dead or will have reproduced at such ages. For Haldane, this implies in the fall of the force of natural selection with advancing ages (Haldane, 1941). Nevertheless, he failed to turn this observation into a theory of senescence.

It was Medawar who would do so. The gap between Haldane's observation of the falling force of natural selection and an evolutionary theory of senescence relies on the requirement of an age structure on populations for the fell in the force of selection. It is natural to suppose an

age structure with many young individuals and rare older ones if senescence exists. In such a population, Haldane's explanation for Huntington's Disease works well, but such a model, which already pressuposes senescence, cannot acount for its evolutionary origins.

Medawar postulated that age-independent environmental hazards such as hunger, predation, accidents, etc. were a sufficient condition for the establishment of populational age structures. Older individuals, Medawar claimed, were rare because they have been exposed to such risks (termed extrinsic mortality) longer than young individuals. In other words, the existence of age structures in wild populations is a function of environmental hazards and not of senescence. Even a non senescent population would have an age structure (Medawar, 1952).

The importance of Medawar's reasoning is that older individuals in age structured populations, being necessarily rarer than younger ones, not only do not compete for environmental resources: they also don't contribute much offspring to newer generations. This is the key for Medawar's mutation accumulation theory of senescence – and also a basis for the next two hypotheses, antagonistic pleiotropy and disposable soma theories of senescence.

Figure 3 (age structured population)

Deleterious mutations, provided that it effects happen in sufficiently late ages, could accumulate in the genome According to mechanisms of population genetics, senescence is not necessarily harmful: Medawar's original proposition implies that the postponement of the effects of age-specific deleterious genes for late ages is equivalent to their elimination. Thus, these genes become effectively neutral (Medawar, 1952).

According to this theory, such evolutionary mechanism could only explain the manifestations found in senescent populations protected after individuals reach ages above those found in nature, since in nature, the age of accumulation would coincide with the maximum age of living individuals.

Medawar accepted that the effects of senescence also occurred at ages commonly found in nature. For this reason, he became convinced that another mechanism, involving either pleiotropy or linkage, would be necessary to explain the process of early and gradual degeneration which is charachteristic of senescence (Medawar, 1952). Medawar, however, didn't advance more details on this hypothesis.

3.3 The antagonistic pleiotropy theory

Although the accumulation of mutations justifies the existence of deleterious genes with late expression (and thus the already established senescent state), it didn't seem to explain the slow onset of senescence (Williams, 1957).

Seeking to understand how deleterious genetic effects expressed in relatively early ages could escape selection, Williams grounded his theory on four assumptions: the existence of a somatic cell line, i.e., non-transferable in whole or part by sexual or asexual reproduction, the natural selection of different alleles at a population, a decreasing probability of reproduction with increasing ages, the existence of pleiotropic genes with different effects on fitness at distinct ages (antagonistic pleiotropy). According to this idea, the evolutionary fundamental process to the establishment of senescence is a selective action on the inheritance of a gene with antagonistic effects on its carrier's fitness (Williams, 1957).

It is to note that the very existence of pleiotropic genes with antagonistic effects was not postulated by Williams. In a previous article, Sewall Wright describes an equation for calculating the impact of a pleiotropic gene on fitness:

$$W = (1 + S_1)(1 + S_2)...(1 + S_n) \, , \tag{1}$$

where W is the fitness of a gene and S_1, S_2 ... S_n are the separate selective coefficients for each age-specific effect of such gene on fitness (Wright, 1956).

Williams' merit was to note the implication of Wright's equation for the evolution of senescence in age structured populations. He applied to the Equation 1 the same reasoning applied by Medawar in relation to the age structure of populations: the magnitude of the effect of S_n of a gene may be reduced if it only starts at advanced ages. In a gene capable of expressing different effects on different ages, later effects will less be subject to natural selection than earlier effects.

By considering the effects of a given gene in distinct ages of expression, however, Williams proposed that the measure of the magnitude of each effect in question (advantages or disadvantages) is given by

$$S_n = m_n p_n \, , \tag{2}$$

where S_n is the effect under consideration, m_n its magnitude or impact on fitness and p_n is the proportion of a population's reproductive probability that is *relevant* to the age of manifestation of the effect S_n.

This allowed him to rewrite the Equation 1 considering the effect of age structure in the final selective coefficient of a pleiotropic gene:

$$W = (1 + m_1 p_1)(1 + m_2 p_2)...(1 + m_n p_n) \, . \tag{3}$$

From this equation we may extract the simplest case: the one of a pleiotropic gene with a late deleterious effect and a very early beneficial effect. To demonstrate the formula we need to know the values of p for each age.

Let us imagine a population (structured for simplicity on a human age-scale) with constant birth and death. This is necessary not to create an *ad hoc* argument, by starting with a previously non-senescent population and therefore with no age differences in mortality.

Let's say that this population has a constant mortality of 0.25 each 4 years, ie, 0.0625 per year, and that each 4-years extract is composed of 1000 individuals. This population age distribution is represented in Figure 2. The familiarity of this age distribution with any wild population is noticiable, as it is with any high-mortality human population (as an example, the Figure 3 represents the age distribution of the population of Afghanistan in 2008).

In this non-senescent population, organisms do not lose fertility with the progression of age and all individuals have the same reproductive probability. Therefore, p_x, i.e., the proportion of the reproductive probability associated with each age will be the proportion of remaining individuals with ages equal or superior to that in the population, since the effect of S remain after activated, i.e., be constant from its manifestation.

Williams could thus formulate an evolutionary hypothesis for the permanence (regardless of natural selection) of detrimental effects whose expression was sufficiently early to be influential in wild populations. It is important to notice that neither the equation nor any

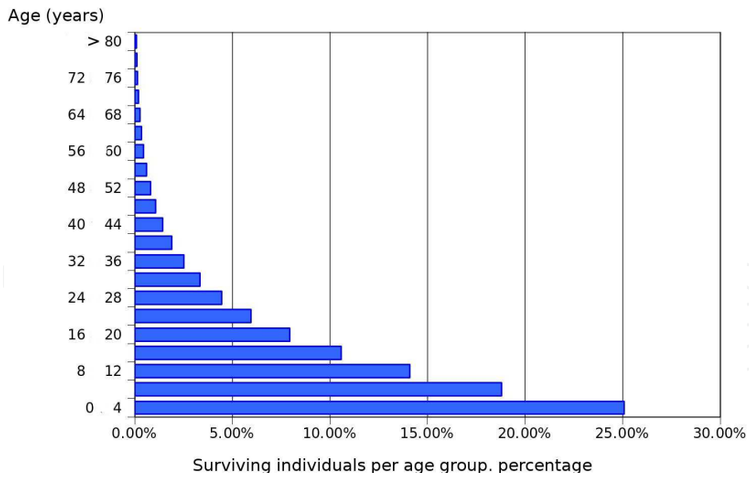

Fig. 2. Age distribution of an alleged non-senescent population exposed to a mortality of 6.25% per year.

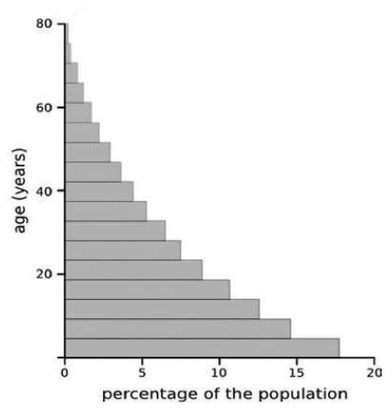

Fig. 3. Age distribution of the Afghan population in 2008 (data from U.S. Census, International Database, available at http://www.census.gov/).

comment on Williams' classic article (Williams, 1957) infer what the number of effects of a pleiotropic gene should be, nor which effect, beneficial or deleterious should happen earlier. While it is clear that the simplest case of antagonistic pleiotropy would be of a gene with an early beneficial effect and a late deleterious one, Equation 3 does not imply that this is the only possibility.

The literature, however, did not follow this conclusion. Williams' antagonistic pleiotropy came to be regarded precisely as the case in which a mutation with two actions, an early advantage and a later disadvantage, it is positively selected. It is worth quoting verbatim the concept of antagonistic pleiotropy found in the *Handbook of Biological Aging*, of 2006, in a chapter written by the editor of the book (Masoro, 2006):

"Another genetic mechanism, proposed by Williams (1957), is referred to as antagonistic pleiotropy. It proposes that those genes that increase evolutionary fitness in early life will be selected for, even if they have catastrophic deleterious effects in late life. Again, the deleterious

effects of these genes will be evident only in subjects in protected environments that enable a long life. ”

While Medawar discussed the age of onset of a characteristic deleterious and Williams called attention to the magnitude of genetic effects, no theory explicited discussed the influence of the magnitude of extrinsic mortality and random genetic drift on the selection of deleterious genes.

3.4 The disposable soma theory

From the 1970s, a new theory for the evolution of senescence was proposed by Thomas Kirkwood (Kirkwood & Holliday, 1975a;b), reasoning initially not about evolutionary mechanisms as maladaptive as Medawar or on pleiotropic genes as Williams, but on a strong ecological basis. Elaborating on the theory Orgell's “error catastrophe ” (Orgel, 1963), Kirkwood gave us a somewhat different view from what had previously been formulated on the evolution of senescence.

Kirkwood addressed the issue of senescence under an ecological constraint in which energy resources available to individuals could be allocated either for maintenance somatic cells or for reproduction, generating a soma-germ conflict. Called disposable soma theory, this ultimately depends on the existence of specific genes that either influence or control the precision of the genetic replication / transcription and translation machineries in an age-dependent fashion; Kirkwood himself considered his theory as a specialization of the antagonistic pleiotropy theory of Williams (Kirkwood, 1977; Kirkwood & Holliday, 1979). The difference is that Williams posits the existence of genes for beneficial and deleterious effects, but the theory of Kirkwood, despite not denying the existence of these genes, do not need them. If, under Williams theory, natural selection would act on the average effects of a selected gene's mutant alleles, under Kirkwood's assumption a single genetic effect, determining the distribution of resources between reproduction and body maintenance would be sufficient for the evolution of senescence. Senescence would be the inevitable result of selection for an “'ideal” energy allocation between reproduction and body maintenance.

This is the first theory to propose that the evolution of organisms can optimize the allocation of metabolic resources between the maintenance of the somatic lineage (the individual itself) and the effort of reproduction (investment in next generation). Under it, the physiological mechanisms that postpone senescence consume metabolic resources, which become less available for reproduction, and vice versa. As reproduction of the species by natural selection is prioritized, the body is “disposable” after its reproductive function has been sufficiently fulfilled, and the aging process may appear, without sufficient opposition from natural selection.

There is some experimental support for this theory. When fruit flies are selected for a longer life expectancy, there is decrease in fertility. Conversely, exposure of females to earlier reproduction was correlated with a decline in their lifetimes as compared to virgin females (Sgro & Partridge, 1999).

The disposable soma theory changes the fundamental question about the evolution of senescence: instead of questioning why we senesce, we could wonder why we, humans, live as much as we do (Kirkwood & Rose, 1991).

4. The evolutionary theories of senescence today

4.1 Is there senescence in the wild indeed?

Does anyone die of old age? The existence of senescence in wild populations in their habitats, which, as mentioned, led Medawar and Williams to think of antagonistic pleiotropy, was harshly questioned in the literature by influential researchers like Hayflick and Comfort (Comfort, 1956; Hayflick, 2000).

In a large study, however, Promislow described significant evidence of senescence in 26 species of mammals *in natura* (Promislow, 1991). In fact, in recent years, several studies have demonstrated demographic senescence (Austad, 1993; Bronikowski et al., 2002; Ericsson et al., 2001; Orell & Belda, 2002) and reproductive senescence in mammals and birds in their habitats (Austad, 1993; Broussard et al., 2003; Ericsson et al., 2001; Reid et al., 2003; Saino et al., 2003).

Finally, a strong indication that senescence does exist in wild populations comes from our species: if the data collected by Gompertz and those who followed him can be extrapolated to primitive humans, then our mortality progresses under a Gompertzian regime from around 12 years of age. Senescence starting in such an early age certainly would have impacted on mortality of early human populations (Gompertz, 1825).

Evidence is thus, that death due to senescence is actually happening in the wild. We must change the question from someone dies of old to " someone dies because of senescence '?"And the answer, backed by extensive literature is a resounding yes (Carey & Judge, 2000).

4.2 Findings supporting each evolutionary theory

Evidence for the genetic basis of senescence accumulate in the literature. With respect to the specific theories on the evolution of senescence, experimental evidence supports each of the three theories mentioned above (Hughes & Reynolds, 2005).

In Drosophila, it is possible to obtain two distinct lineages in relation the speed of installation of its senescence by systematically separating over generations, the first (beginning of reproductive life) or the last oviposition (immediately prior to reproductive senescence). The flies of the the second group senesce more slowly and live up to 50% longer than the first group flies (Baret & Lints, 1993; Fukui et al., 1995; Luckinbill & Clare, 1985; Rose & Charlesworth, 1980; 1981).

According to Rose, while the flies in the control group focus their greater efficiency in the early reproductive life, the group submitted to selective pressure for older reproduction requires the of the opposite strategy. In both groups, according to the evolutionary concept of senescence, mutations of late manifestation accumulate and propagate to the new generations. These changes will not affect the flies of the first group, but the second group will largely benefit if such manifestations are delayed. Mutations that make deleterious effects to occur later will improve fitness of individuals in the second group, but not in the first group. This mechanism, over generations, makes the senescent manifestations in the second group to become even later, so that the flies of this group evolve longevity. Interestingly, even with the suspension of the selective pressure, the difference persists, and the strains of flies arising from these experiments remain more long-lived than wild flies (Rose, 1991).

Hughes and others have found evidence in favor of mutation accumulation in the experimental evolution of accelerated senescence (decrease in MRDT) in fruit flies as the predominant phenomenon (Hughes et al., 2002), argument which is sustained by Cortopassi in relation to human senescence (Cortopassi, 2002). Physiological senescence in our species, however, is easily noticeable between the fourth and fifth decades of life. This is not incompatible with Medawar's observation (Medawar, 1952) that the accumulation of mutations explain only senescence in artificially protected populations: modern man is an excellent example of a protected population.

Pleiotropic mechanisms have currently been described. The gene for the juvenile hormone (JH) found in specimens of wild Drosophila is expressed early in its life cycle, and takes to an increase in fertility, early sexual maturation and augmented vitellogenesis. On the other hand, it undermines resistance to stress factors, reduces immunity and the maximum life expectancy (Flatt et al., 2005). In geese, artificial selection for early sexual maturation causes, as adverse effects, a faster reproductive senescence; quantitative analysis revealed a genetic correlation between these two features (Charmantier et al., 2006). Finally, several programmed cell death mechanisms known in mammals also perform "important vital functions such as energy production, metabolism differentiation or the cell cycle" (Ameisen, 2004; 2005). It was recently suggested that Alzheimer's disease, which appears to be specific to humans, could be an example of antagonistic pleiotropy (Bufill & Blesa, 2006).

Holliday argues that the mammals' life cycle strongly illustrates the idea behind the disposable soma theory: there is in mammals an inverse relationship between maximum reproductive potential and maximum longevity; small mammals are very short-lived and fertile, the great mammals are less fertile and very long-lived (Holliday, 1997; 2005). This contrast between longevity and reproduction also appears in a historical cohort analysis of demographic data of the aristocracy of Britain in which with female longevity correlated with a lower number of children (Westendorp & Kirkwood, 1998).

It is noteworthy that the evolutionary theories of senescence (mutation accumulation, antagonistic pleiotropy, and disposable soma) are not mutually exclusive. Although the three currently accepted evolutionary processes for the evolution of senescence can coexist, a current problem of the evolutionary research on senescence is to know how much each of the processes have contributed to the emergence of this phenomenon (Gavrilov & Gavrilova, 2006).

4.3 The evolutionary theories of senescence and the increasing knowledge on evolution

Charlesworth's cumulative effect model (Charlesworth, 2001). The potential effect of genetic drift and natural selection on deleterious and pleiotropic mutations: effective population size on age-structured populations(Charlesworth, 1980; Felsenstein, 1971), infinite sites model of molecular mutation (Kimura & CROW, 1964), infinite alleles model of polymorphism and the neutral theory of evolution (Kimura and Ohta).

4.3.1 Randon genetic drift

A greater effect of random genetic drift is expected in populations with age structure (where the effective population size, N_e is smaller than the real population size, N), than in populations without age structure (and where $N_e \approx N$). Suppose that a genetic effect in a population is expressed at an advanced age (arbitrarily defined as significantly higher than

the age of reproductive maturation of a species). We can use this to divide this population age into two subsets: that of individuals who have not expressed the genetic trait and those who have already expressed.

Let us consider what happens with the genetic trait in question under natural selection on these two subpopulations. Obviously, on the first subpopulation, the gene with the deleterious effect, not having expressed itself, is effectively neutral and therefore can evolve only by drift. In the second subpopulation, there is evolution by selection. Clearly, the effect of selection on the population as a whole will be less than what it would be if the mentioned gene was expressed at younger ages. This is just another way of saying that the force of selection falls with age.

Now let us consider the effect of genetic drift on the second subpopulation. Being it a fraction of the total population, its N_e will be considerably smaller than the the initial population's N_e. Thus, besides being subject to progressively smaller selection forces as a function of the age of onset, late onset of deleterious genes should be subject to progressively more intense phenomena of genetic drift. This point, not addressed in the current theories about the evolution senescence, might prove to be crucial.

This last aspect makes it fundamental to understand the roles of mutation, selection and drift as a whole in the evolution of senescence, since, at least in part, the force of selection declines with advancing ages precisely due to the decrease on the effective sizes of the subpopulations.

5. Conclusion

For decades, researchers in the field of senescence were divided between the proponents of proximal or mechanistic theories and the proponents of the distal or evolutionary theories of senescence (Masoro & Austad, 2006). Fortunately, recent decades have seen an excellent understanding of the importance of a joint reasoning between "mechanistic" and "evolutionary" thoughts: more and more studies focused on the evolution of senescence seek to understand its physiological mechanisms of onset and progression and researchers focusing on the mechanisms of senescence are increasingly seeking to understand the theoretical evolutionary basis of senescence (Masoro & Austad, 2006, Preface).

The evolutionary study of senescence seeks to explain why this phenomenon exists, providing researchers with mechanistic insights into what could be the proximal causes of senescence and how genetics produces the senescent phenotype (Kirkwood & Austad, 2000). By pointing to non-adaptive origins for senescence, the evolutionary theory may drive mechanistic researchers away from adaptive programs such as apoptosis as a plausible basis of senescence. After all, "nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973).

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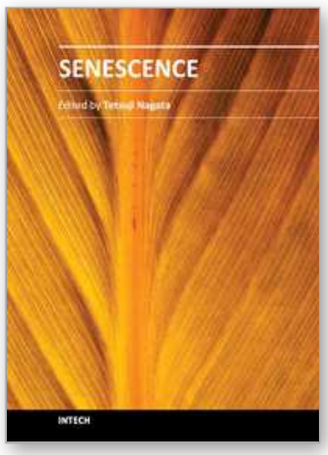

Senescence
Edited by Dr. Tetsuji Nagata

ISBN 978-953-51-0144-4
Hard cover, 850 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

The book "Senescence" is aimed to describe all the phenomena related to aging and senescence of all forms of life on Earth, i.e. plants, animals and the human beings. The book contains 36 carefully reviewed chapters written by different authors, aiming to describe the aging and senescent changes of living creatures, i.e. plants and animals.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Thiago Monaco, Daniel Silvestre and Paulo S. P. Silveira (2012). Senescence in Animals: Why Evolutionary Theories Matter, Senescence, Dr. Tetsuji Nagata (Ed.), ISBN: 978-953-51-0144-4, InTech, Available from: http://www.intechopen.com/books/senescence/senescence-in-animals-why-evolutionary-theories-matter-

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