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The evolution of mammalian aging

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Abstract

The incidence of aging is different between mammals and their closer ancestors (e.g. reptiles and amphibians). While all studied mammals express a well-defined aging phenotype, many amphibians and reptiles fail to show signs of aging. In addition, mammalian species show great similarities in their aging phenotype, suggesting that a common origin might be at work. The proposed hypothesis is that mammalian aging evolved together with the ancestry of modern mammals. In turn, this suggests that the fundamental cause of human aging is common to most, if not all, mammals and might be a unique phenomenon. Experimental procedures capable of testing these theories and how to map the causes of mammalian and thus, human aging, are predicted.

Keywords: Aging; Senescence; Evolution; Mammals; Reptiles; Birds; Longevity

1. Introduction

Aging affects all studied mammalian species: from mice living no more than a mere half-a-dozen years to humans capable of living over 120 years (Comfort, 1979, pp. 60–63; Hayflick, 1994, p. 21; Finch, 1994, pp. 150–153). Independent of average and maximum life span and trophic level, all studied mammals show an explicit aging phenotype shortly after their reproductive peek (Finch, 1994, pp. 150–202). In contrast, the data available for the ancestors of mammals (e.g. amphibians and reptiles—who evolved from amphibians 340 million years ago, see Fig. 1) shows both a much more feeble aging phenotype and the presence of apparently non-aging animals (Finch, 1994, 219–221): examples range from *Xenopus* with little over 15 years of maximum life span to Marion's tortoise capable of living over a century in captivity. Studies conducted in frogs failed to indicate any increase in mortality both in the wild (Plytycz et al., 1995) and in captivity (Brocas and Verzàr, 1961). In the case of the yellow-bellied toad, the fact that young individuals (2–4 years-old) were usually found in breeding pods did not prevent the oldest captured animals (of at least 11 years of age) from being fertile and showing little or no signs of aging—no increased mortality was found (Plytycz and Bigaj, 1993). The maximum reported longevity for individuals of this species in captivity is 27 years (Juszczyk, 1987). Studies amongst reptiles, both in the wild and in captivity, also failed to show a significant aging phenotype (Finch, 1994, pp. 219–221). One example is the long-lived Blanding's turtle: these relatively small animals, even though they reach a fixed size, can exceed 75 years of age (Breckle and Moriarty, 1989). In one field study, older turtles were found to have increased clutch size, reproductive frequency, and survivorship (Congdon et al., 2001).

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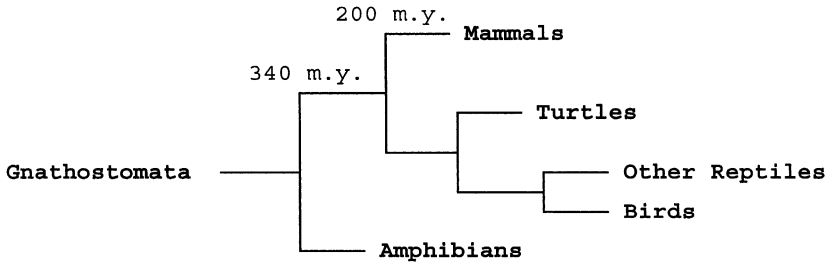

Fig. 1. Simplified version of the evolution of mammals and closely related taxa. Adapted from Maddison and Maddison, 1998.

Similar results have been reported in the three-toed box turtle (Miller, 2001). Even if some of these species eventually age, it is undeniable that aging's incidence and intensity decrease in reptiles when compared to mammals.

Mammalian species show little diversity in their aging phenotype (Finch, 1994, pp. 150–202). All true mammals or eutherians are iteroparous, show a gradual increase in mortality with age shortly after puberty, suffer the effects of aging in a multitude of organs, and, unlike many animals from different phyla, all mammals feature reproductive senescence. Except rodents and marsupials, the increase of mortality with age is within a very short range. This is in contrast with other phyla, such as teleosts, with some animals being semelparous, others featuring gradual aging, and others apparently not aging at all (Finch, 1994, pp. 136–143, 216 and 217). Mammals, in general, have a limited set of teeth, leading to a form of mechanical aging, and have limited cartilage regeneration, which leads to arthritis (Fox, 1938). Other forms of age-related diseases common to mammals include osteoporosis, an exponential increase of cancer with age, and neurodegenerative diseases amongst many of the studied species. Another strange feature of eutherians is the synchronization of many postnatal changes in approximate proportion to the life span, independent of how long this is. The aging pathologies of old mice are roughly the same in old humans or in any well-studied old mammal (Finch, 1994, pp. 150–202, 619). In fact, the aging changes of most well-studied mammalian species appear to be slightly distorted copies of each other, only timed at different paces. Finally, the observation of aged mammals in the wild (Nesse, 1988), such as senescent elephants or post-menopausal whales (Kasuya and Marsh, 1984), suggests that aging did not evolve in these long-lived mammals but instead persisted since their ancestry.

As for reptiles, the available studies not only describe some apparently non-aging species but also show contrasting features with mammals: oocyte regeneration, continuous tooth development, limb regeneration, and increased immune responses to infection. So why the large differences in the intensity of the aging phenotype between mammals and their ancestry? It is unlikely that so many deleterious genes are expressed in mammals and so few in reptiles. What makes mammals more susceptible to aging?

2. The evolution of mammalian aging

Since we witness cases of apparently non-aging species since our aquatic ascendancy (e.g. gnathostomes fishes (Cailliet et al., 2001)) and a sudden widespread burst of aging in mammals, it is implausible that aging developed independently in each species or sub-class of mammals. The simplest explanation to the overall differences between the incidence of the aging phenotype in mammals and their ancestry is that aging evolved to a large degree in the primordial mammals and then persisted throughout the generations until present time. This is the main hypothesis defended in this article.

Current evolutionary theories indicate that the first mammals to evolve from reptiles were small—little more than an inch-long—rodent-like animals, around 200 million years ago (Maddison and Maddison, 1998). Fossil records of early mammals support this view (Crompton and Jenkins, 1968; Luo et al., 2001). It is logical to assume that these first mammals had shorter life spans than their reptilian predecessors as adult body-size, to a certain degree, positively

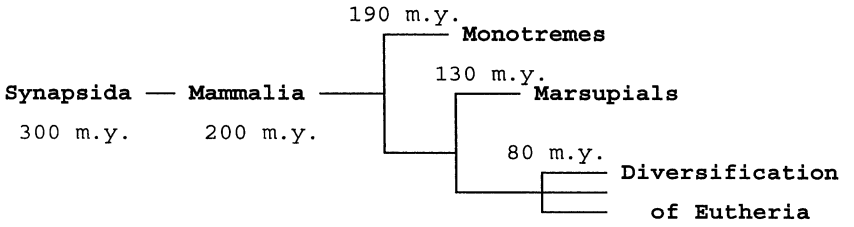

Fig. 2. Synapsids were the first species more closely related to mammals than to reptiles. The first mammals to resemble present species, however, only appeared about 200 million years ago. The branching of mammals began with monotremes (egg-laying mammals) and marsupials. Later, about 80 million years ago, began the branching of eutheria, or true mammals, whose radiation exploded after the mass extinction phenomenon, 65 million years ago. Adapted from Maddison and Maddison, 1998; Finch, 1994, pp. 603–619.

correlates with longevity and rate of aging amongst higher animals (Promislow, 1993; Ricklefs, 1998). Small animals they were until, about 65 million years ago, dinosaurs disappeared and paved the way for mammals (Bryant, 2000, chapter 2). Assuming, as it appears the most likely scenario, that the reptiles from which mammals evolved were slowly or non-aging creatures, we propose mammalian aging flourished during these times. Since aging is unlikely to evolve as an adaptive trait, the process by which this occurred could be: (1) a form of antagonistic pleiotropy as proposed by Williams (Williams, 1957), meaning that mammals possess certain essential function(s) not present in reptiles that as a by-product cause aging; or (2) genetic drift or mutation accumulation leading to the loss or mutation of protective and maintenance genes, caused by the abrupt decrease in life span of these early mammalian species. Female mammals have a limited stock of oocytes, apparently unlike many female reptiles and amphibians, which can even increase their reproductive output with age due to oocyte regeneration. Should this be universally true, it is a case where a loss of function occurred when mammals evolved from reptiles—a loss of function that immediately sets evolutionary pressure for a restriction on life span. Another example is continuous tooth replacement, common in many ancient and modern reptiles but generally absent from mammals (Finch, 1994, pp. 609 and 610). These examples support the hypothesis of short-lived primitive mammals selecting short generation cycles and consequently losing genes whose benefits increase with age as predicted in classical evolutionary theories (Medawar, 1952; Rose, 1991). In addition, the large evolutionary time as small, short-lived animals fostered aging to develop an intensity in mammals not seen in reptiles with similar life spans or body sizes.

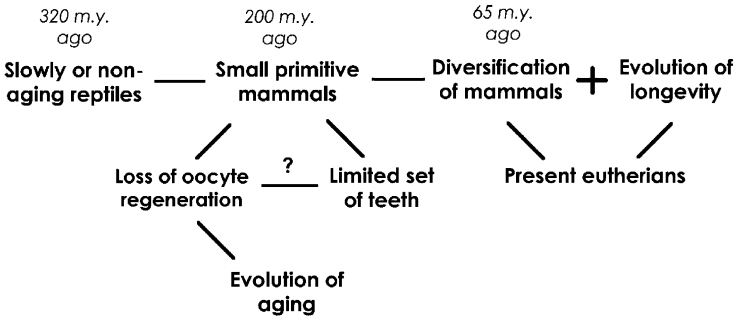

Fig. 3. Overview of the hypothesis for the evolution of mammalian aging. Millions of years as a short-lived species made primordial mammals develop reproductive senescence and consequently what we now call aging. (Although the possibility of a causal relation, one way or the other, between tooth erosion and reproductive senescence should not be ignored.) After the mass extinction in the late Cretaceous (about 65 million years ago), mammals took over the planet: diversifying, evolving new functions, conquering new environments, and generally evolving longevity.

3. Discussion

3.1. A common mammalian cause of aging?

The only documented case of an aging phenotype clearly different from other mammals is the Australian mice *Anthecinus* (Gosden, 1996, pp. 13–30; Finch, 1994, pp. 95–98). So it can be argued that most mammals share their causes of aging: The conquest of the world by mammals began about 65 million years ago, roughly when the dinosaurs disappeared. With exception of egg-laying mammals and marsupials, who diverged from eutherians, respectively, 190 and 135 million years ago (Fig. 2), eutherians evolved from that point to give the species we now know; from fossil records, most species increased in size and therefore evolved longevity, not aging (see Fig. 3). In contrast to the average mammal, elephants have up to six sets of molars (Finch, 1994, p. 199), a clear example of the evolution of a trait that permits a greater longevity. In fact, the first elephants to evolve, about 50 million years ago, were smaller than modern species, indicating elephants evolved longevity and suggesting the existence of senescent elephants in the wild as a consequence of evolving from a faster aging ancestry (see (Haynes, 1993)) for more on the evolution of elephants).

Assuming that aging evolved in the very small and vulnerable first mammals due to their high mortality, it is difficult to imagine greater increases in mortality and thus the aging mechanisms that evolved in mammals more than 65 million years ago remain the same. On the other hand, it was proposed (Strehler, 1986) that mammals with longer life spans obviated the causes of aging of short-lived mammals and therefore age for different reasons. Yet given the large similarities in physiology amongst mammals and their aging phenotype, the most likely scenario is that aging evolved in the primordial mammals and then, in certain species such as the modern long-lived mammals, longevity evolved as a result of a slowing of the basic aging process; but since even the longest-living mammals still age quite dramatically when compared to long-lived reptiles, this implies that they only slowed whatever mechanisms caused aging, not eradicated them, therefore making the causes of aging the same for all mammals independent of life span. *Anthecinus* and some rodents (Finch, 1994, pp. 608 and 616) are at present the only documented cases possible of being exceptions. But since aging has only been described in a fraction of the approximate 4600 species of mammals on the planet, it is possible that some mammalian species have divergent evolution regarding aging. For example, little is known about egg-laying mammals' aging, although, since egg-laying mammals diverged from eutherians 190 million years ago (see Fig. 2), it is not surprising to notice that the Australian spiny anteater has a 50-year life span and presumably a slow rate of aging (Finch, 1994, p. 606).

One hypothesis appears plausible: aging has the same causes in all primates. Although information is scarce regarding fossil records, the evolution of longevity in the first primates began about 60 million years ago (O'Neil, 1999, 2000). This is a good indicator that all primates share the same origin of aging since evolution of longevity and not evolution of aging was taking place.

3.2. How to test this hypothesis?

The ideal scenario to prove this hypothesis and, optimistically, to uncover the causes of mammalian aging would involve comparative biology of the mammalian, reptile, and/or amphibian genomes. Using as models apparently non-aging species, we might then be able to use bioinformatics to map the genes and proteins behind the reptilian secret of longevity. If mammals lost the genes that allow some reptiles to avoid aging, then genes mapped in these reptiles or some amphibians—assuming amphibians possess these genes too—could be used to create transgenic mammals capable of delaying and eventually eradicating aging. Alternatively, we might be able to make knock-ins of mammalian genes involved in whatever deleterious mechanism causes aging. Finally, determining expression profiles of genes theorized to be involved in aging, for example, DNA repair proteins at different ages amongst reptiles and mammals, or even between mammals with different rates of aging, might prove useful in determining what causes aging.

In order to obviate expensive and time consuming DNA sequencing methods, it might be possible to use cellular studies (Austad, 2001) to investigate the reasons behind, for example, reptilian longevity.

Cellular studies in cells from the Galapagos tortoise (Goldstein, 1974) show a large but limited replicative capacity (approximately 110 divisions from fibroblasts extracted from adult animals of unknown age); studies on amphibians demonstrated that cell differentiation does not need to involve loss of genomic totipotency (Gurdon et al., 1975); and the latent period of tissue extracts from frogs is dependant on donor age (Steinhardt, 1986). Unfortunately, cell senescence studies on reptiles have been mostly discarded and progresses made in culture and media conditions could lead to new observations. Information on cell cycle control (e.g. telomere maintenance and telomerase activity), oxidative defenses, stress-response mechanisms, DNA repair, etc., could prove useful to determine the differences in aging between mammals and their ancestry.

Although slowly progressing age-related changes have been reported in amphibians and reptiles (Perez-Campo et al., 1993; Finch, 1994, pp. 143 and 144; Townes-Anderson et al., 1998), there is a very limited amount of data regarding their aging phenotype. Slowly, but noticeable, aging reptiles might be relevant sources of information for they might allow us to find new clues as to the events leading to the evolution of aging from reptiles and possible similarities to human aging. It is probable that amongst the roughly 7000 species of reptiles and 4000 species of amphibians we find aging, even if a slower manifestation of the process found in mammals. For example, we do not know if the causes of death of old reptiles, animals, for example, in captivity, are similar to younger members of the same species.

Performing knock-outs of genes theorized to be involved in human aging in reptiles or amphibians might help clarify which pathways have the higher chances of being right. Werner's syndrome gene homologue in *Xenopus laevis* (Yan et al., 1998) is an excellent candidate, while other DNA repair genes also have a high potential due to their involvement in human progeroid syndromes (Martin and Oshima, 2000). Anti-oxidant enzymes, heat shock proteins, and other proteins involved in the stress response should be studied in these models as stress resistance often correlates with aging rates (Kirkwood and Austad, 2000).

3.3. Implications to gerontological research

If the evolution of aging in mammals was a singular process, then quickly aging evolutionary distant species (e.g. *Drosophila* or *C. elegans*) are dubious models for gerontological research. It can be argued that the mechanisms of aging can always be the same to evolve, i.e. the ones more susceptible to be deleted (Rose, 1991, p. 165). Although certain human aging mechanisms could be common to short-lived species, due to the large differences in physiology, mortality, and body plan between mammals and, for example, insects, it appears unlikely that insects and humans share the same cause of aging. Also, since aging phenotypes are quite diverse in nature, it is logical to assume different causes of aging can exist. Extrapolating, more complex aging phenotypes such as those seen in mammals might therefore be unique. (Obviously, if antagonistic pleiotropy is the reason why mammalian aging evolved then this arguing is useless). Caloric restriction (Weindruch and Walford, 1988), a method of increasing life span common to species such as monkeys (Ramsey et al., 2000), mice, and spiders (Austad, 1989), can be used to show similarities in the aging of many evolutionary distant organisms. It can be argued, however, that caloric restriction, as well as single-gene mutations affecting energy or developmental pathways (Flurkey et al., 2001), delays the entire genetic program, retarding the expression of genes associated with aging, whatever those may be.

If antagonistic pleiotropy is right, then perhaps aging in mammals has the same cause as in birds. Birds also evolved from reptiles; both mammals and birds are the only classes of endoderms, which in turn can lead to increased senses and intellectual capacity and, due to higher metabolic rates, aging as a by-product. It should be noticed that the aging phenotype is less expressed in birds than in mammals of the same size (Holmes and Austad, 1995; Martin, 2000; Holmes et al., 2001), as inferred by the life spans and mortality acceleration curves of most well-studied species. In fact, although oocyte regeneration has never been detected in birds, they might feature non-aging species (Gosden, 1996, pp. 55 and 56). In addition, fossil records do not indicate that present birds evolved from very small animals (Maddison and Maddison, 1998), making birds less receptive to

the evolution of aging. Yet even if low metabolic rates might help explain negligible aging in reptiles, they fail to explain the appearance of reproductive senescence in mammals. Moreover, marsupials, despite having lower metabolic rates, seem to age faster than eutherians of the same size (Austad and Fischer, 1991; Austad, 1997, pp. 88–90), which supports the view that eutherians evolved longevity and developed defense mechanisms not present in marsupials. In birds we witness the opposite (Martin, 2000). So, in conclusion, metabolic rates alone are not behind mammalian aging.

If the hypothesis presented in this paper is correct, then primates, and probably other eutherians too, are obvious choices for studying human aging: primates are effective models because their aging process probably shares its causes with humans; short-lived mammals can lead us to understand why the rate of aging differs between mammals; and long-lived mammals such as humans, whales, elephants, and bats, long-lived for their metabolic rate, can have evolved different mechanisms to retard aging and increase longevity.

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