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IDEAS & SPECULATIONS

Insights & Perspectives

The longevity bottleneck hypothesis: Could dinosaurs have shaped ageing in present-day mammals?

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Abstract

The evolution and biodiversity of ageing have long fascinated scientists and the public alike. While mammals, including long-lived species such as humans, show a marked ageing process, some species of reptiles and amphibians exhibit very slow and even the absence of ageing phenotypes. How can reptiles and other vertebrates age slower than mammals? Herein, I propose that evolving during the rule of the dinosaurs left a lasting legacy in mammals. For over 100 million years when dinosaurs were the dominant predators, mammals were generally small, nocturnal, and short-lived. My hypothesis is that such a long evolutionary pressure on early mammals for rapid reproduction led to the loss or inactivation of genes and pathways associated with long life. I call this the 'longevity bottleneck hypothesis', which is further supported by the absence in mammals of regenerative traits. Although mammals, such as humans, can evolve long lifespans, they do so under constraints dating to the dinosaur era.

KEYWORDS
DNA repair, evolution of ageing, life history, negligible senescence, reptiles

INTRODUCTION

How ageing – a detrimental phenotype that results in loss of function, degeneration and ultimately reproductive senescence and death – evolved has long fascinated scientists, and can be explained by the fading force of natural selection with age.[1,2] Because the greatest contribution to the next generation comes from young animals, selection favours alleles that confer survival at younger ages and reproductive fitness rather than survival at later ages. Species in different environments, in particular in regard to extrinsic mortality, must then evolve different life history strategies.[3] A mouse or a vole with high extrinsic mortality and a short lifespan will need to grow and mature very quickly if it is to reproduce, a so-called fast life-history; and if a given mutation, for example, causes cancer in 2-year-old mice it is unlikely to be selected against.

Although estimating the pace of ageing is not trivial, across populations it is possible to calculate the demographic rate of ageing, the rate at which mortality increases with age, which can be used for species comparisons.[4] Interestingly, a number of studies in recent years have shown very slow demographic ageing, and even numerous cases of negligible senescence, in dozens of species of reptiles, including many turtles, and in amphibians.[5,6] This is in stark contrast to what is observed in mammals that suffer from a clear and rapid degeneration.[7] Indeed, an exponential increase in mortality with age is a hallmark of mammalian ageing, unlike what is observed in other taxa where a greater diversity of demographic ageing rates is observed.[8] As such, when compared to reptiles, there is an absence of very slow ageing mammals and no evidence of negligible senescence,[6,9] but why?

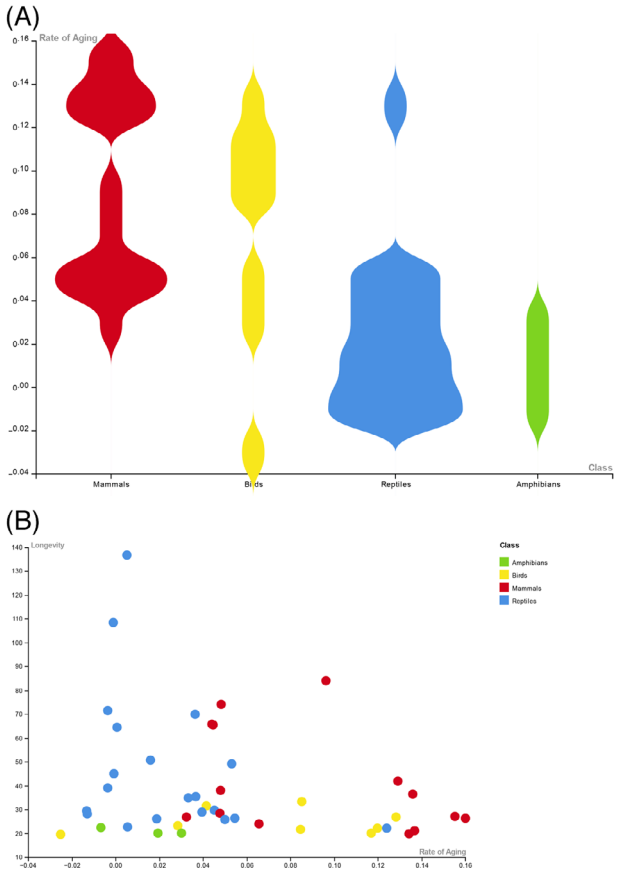

FIGURE 1 Distribution of rates of ageing (A) and rates of ageing versus longevity (B) for birds (yellow; $n = 8$), mammals (red; $n = 14$), amphibians (green; $n = 3$) and reptiles (blue; $n = 20$). Rate of ageing based on estimates of demographic ageing from ref. [6], filtered for species with a longevity of at least 20 years. Longevity refers to adult maximum longevity, as defined by ref. [6]. Figure created with RAWGraphs.

THE LONGEVITY BOTTLENECK HYPOTHESIS

One hypothesis is that the unique mammalian evolutionary history during the time of the dinosaurs shaped present-day mammalian ageing phenotypes. In addition to a slower rate of ageing, reptiles and amphibians feature traits largely absent from mammals, like oocyte regeneration, limb regeneration, continuous tooth replacement and cancer resistance.[10–12] By contrast, reproductive senescence and post-reproductive lifespans are common in mammals.[13] Therefore, it is not just that our closely related taxa can exhibit a slower rate of demographic ageing, it seems that the ageing phenotype is more marked in mammals, even in long-lived species like humans.

While fast ageing species can be found amongst reptiles, birds, amphibians and mammals, the slowest ageing species are non-mammals[6] (Figure 1). Indeed, examples of amphibians, fishes and reptiles exhibiting negligible senescence have been reported,[7,14,15] but no mammal. (Naked mole rats have been touted as exhibiting negligible senescence,[16] yet they show ageing changes like skin ageing,[17] sarcopenia and kyphosis,[18] and exhibit epigenetic ageing.[19]) It is plausible that all vertebrate species eventually age, and there might be biases in scientists studying mammals more than other taxa that result in mammalian ageing phenotypes being more characterised. Nonetheless, in studies spanning decades both in the wild and in captivity, rates of demographic ageing in some species of reptiles are lower than observed in any mammal;[5,6,20,21] not even long-lived humans age so slowly. Using data from a recent study,[6] it is clear that fast and slow ageing species can be found in all taxa, yet mammals are conspicuously absent amongst the slowest ageing and negligible senescence species, particularly when compared to reptiles (Figure 1).

Mammals evolved from synapsids, reptile-like animals that included large predators like the *Dimetrodon*, 300–250 million years ago (mya). Dinosaurs first appeared in the Triassic period and became the dominant terrestrial vertebrate during the Jurassic (200 mya) until their mass extinction at the Cretaceous–Paleogene boundary 66 mya (Figure 2). It is a subject of debate when the first mammals appeared, but eutherians diverged from monotremes and marsupials about 180 and 160 mya, respectively.[22] Although many extinct lineages of early mammals diversified,[23,24] including larger sizes,[25,26] by and large early mammals during the time of the dinosaurs were preyed upon and therefore small, nocturnal, short-lived animals.[24,27] Indeed, ancestral eutherians have been estimated to weight between 6 and 245 g and were likely insectivorous.[28] Therefore, due to predation, the ancestors of modern mammals spent more than 100 million years during the dinosaur-era as small, short-lived animals (Figure 2).

The long evolutionary pressure on early mammals for a fast life-history and rapid reproduction resulted, I hypothesise, in the loss or inactivation of genes and processes related to repair and regenerative mechanisms. In other words, the short-lived, rapidly reproducing early mammals lost traits associated with long life. This may or may not have happened in all early mammals, but I propose it occurred in the ancestral lineage leading to modern mammals. Remarkably, there is molecular evidence in support of this hypothesis in the form of the photolyase DNA protection system that was lost in the eutherian mammalian lineage during the time of the dinosaurs.[27,29] Inspired by the 'nocturnal bottleneck hypothesis',[30] which states that the early evolution of mammals under the reign of the dinosaurs left a lasting legacy on the anatomy and physiology of present-day mammals, I put forward the 'longevity bottleneck hypothesis'. My hypothesis is that modern mammals – particularly long-lived species – age more markedly and rapidly than reptiles, birds or amphibians because of our unique evolutionary history during the time of the dinosaurs.

Once the dinosaurs disappeared and mammals became the dominant terrestrial vertebrate, mammals diversified to fill many ecological niches and were able to grow in size.[31] For example, the earliest fossil record of primates, purgatoriids that lived shortly after the Cretaceous–Paleogene extinction event that destroyed the dinosaurs, suggests a small body size and a reliance on insects.[32] By contrast, abundant fossil and phylogenetic evidence shows that after the Cretaceous–Paleogene extinction event there was a rapid diversification and increase in mammalian body size,[33–35] which one study estimated levelled off 40 mya.[31] Interestingly, pantodonts, the first mammals 62 mya to achieve a large size (~42 kg) lived at a fast pace as

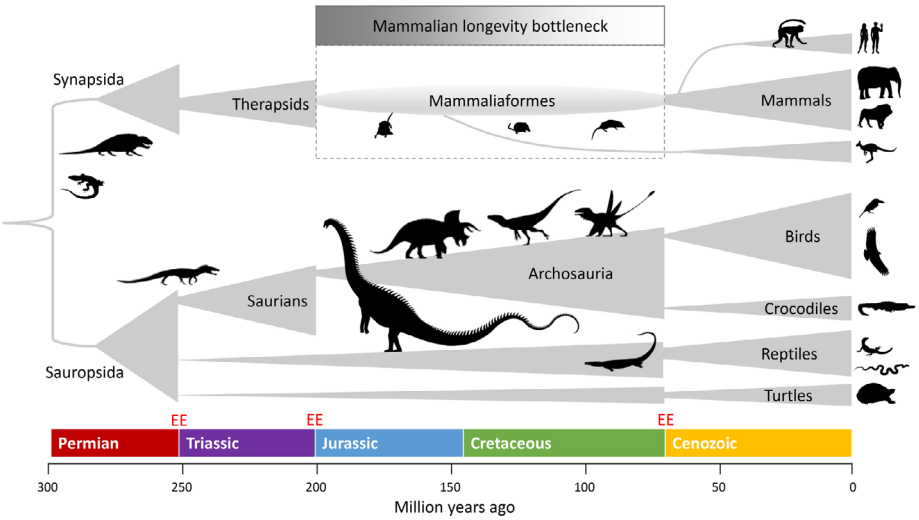

FIGURE 2 The evolution of mammals and the longevity bottleneck hypothesis. Synapsids, reptile-like ancestors to mammals, diverged from sauropsids, the ancestors to dinosaurs, birds and reptiles, over 300 mya. After the Triassic–Jurassic extinction event, about 200 mya, dinosaurs became the dominant predators. By contrast, mammals survived by becoming small nocturnal insectivores, but growing in size once the dinosaurs disappeared, after the Cretaceous–Paleogene extinction event, about 66 mya. The longevity bottleneck hypothesis states that early mammals spending over 100 million years as small, short-lived animals led to gene loss or inactivation of traits associated with longevity and left a legacy that is observed in the marked ageing phenotype of modern mammals, in particular in long-lived species such as humans. Figure inspired by ref. [27]. EE, extinction event. The Cenozoic is featured for simplicity but encompasses three periods (Paleogene, Neogene and Quaternary). Silhouettes from phylopic.org.

they have been estimated to have a shorter lifespan than expected for their body size,[36] which in light of the longevity bottleneck hypothesis is tempting to speculate resulted from their evolution from small, short-lived ancestors.

In the over 60 million years since the extinction of the dinosaurs, the diversification of mammals resulted in a huge variety of species with fast and slow life histories, including many large, long-lived species, like elephants, whales and humans. Clearly, extinct and extant mammals have evolved amazing traits and adaptations, including longevity and tumour suppression mechanisms; yet I argue that this occurred under constraints that are remnants from the time of the dinosaurs, as evidenced that even the longest-lived mammals, such as humans, age faster than many reptiles (Figure 1B). The importance of constraints in evolution has long been recognised but often also overlooked in lieu of the role of adaptation,[37] including in the context of ageing.[38] Here, I make the case that some ageing phenotypes of modern mammals, such as reproductive senescence and tooth erosion, as well as the absence of negligible senescence in mammals, may reflect biological constraints dating to the dinosaur era.

CAVEATS AND PROSPECTS

While the longevity bottleneck hypothesis may help explain observed differences in ageing between modern mammals and other taxa, there are other possible contributors for such differences. Of note, because mammals, unlike reptiles or amphibians, are poikilotherms, it is possible that body temperature is a contributor to the shorter lifespan of mammals as an example of antagonistic pleiotropy,[12] given that in poikilotherms a lower temperature results (up to a certain degree) in a longer lifespan.[39] One study, in fact, estimated that early Jurassic stem-mammals (~200 mya) had longer lifespans than expected for their body size and reptile-like metabolic rates.[40] Although temperature can impact on longevity, birds have by and large higher temperatures and longer lifespans than mammals.[41] Therefore, whether the higher body temperature of mammals might contribute to their faster ageing when compared to reptiles and amphibians remains unknown.

Given that cancer is so prevalent in mammals, and many species of reptiles and amphibians exhibit negligible senescence, one intriguing possibility is that cancer is in general more frequent in mammals. There are cases of cancer in reptiles and amphibians,[42] but it is unclear if the exponential increase in cancer incidence observed in humans and many other mammals is also observed in reptiles or amphibians. Anecdotal reports suggest that cancer incidence in reptiles and amphibians is lower than in mammals,[10,42] but further studies are needed.

Intriguingly, development appears to be more plastic in reptiles and amphibians than in mammals; in the context of the developmental theory of ageing,[43] I speculate this might also reflect mammalian constraints resulting from their evolutionary history that impact tissue regeneration and ageing. Moreover, species exhibiting indeterminate growth and/or increased reproduction with age have been observed amongst reptiles, amphibians and fishes,[7,21] traits absent from mammals that evolutionarily may help explain negligible senescence in non-mammalian vertebrates.[44] Clearly, more studies of ageing, longevity, regeneration and age-related diseases across the tree of life are warranted to better understand the evolution of ageing and its impact on present-day species, including humans (Box 1).

Box 1

Testing the longevity bottleneck hypothesis with evolutionary genomics. With the rapidly growing number of sequenced vertebrate genomes, it should be possible to test the longevity bottleneck hypothesis using comparative genomic approaches, including ancestral reconstructions of genomes and traits.[45] We already know of one repair pathway, the photolyase DNA protection system, that was lost in the eutherian lineage and improves repair in transgenic mice.[29] Although our knowledge of genes and processes involved in repair and regeneration is incomplete, evolutionary genomic analyses may uncover other losses of genes and pathways in mammals compared to other vertebrates and, in particular, compared to reptiles. Moreover, it is possible that repair and regeneration genes were not lost but rather inactivated in mammals due to mutations or downregulation. Analyses of gene expression patterns and gene regulation across species, as already shown to provide insights in the context of longevity,[46,47] may therefore also be employed to test the longevity bottleneck hypothesis. Furthermore, we need more phenotypic data on ageing traits and tissue regeneration across the tree of life, so we can map these traits using comparative methods and better understand the underpinning evolutionary processes.

CONCLUSIONS

Overall, the longevity bottleneck hypothesis has several important implications. It may explain traits observed in human and mammalian ageing, like reproductive senescence, the absence of very slow demographic ageing, and tooth erosion. Moreover, it raises the question of whether other cases of longevity bottlenecks caused by predation or other ecological constraints may have occurred in other taxa, perhaps over shorter timescales than the dinosaurs' rule. As such, studying the pace by which longevity (or ageing rates or phenotypes) evolved across taxa may reveal other longevity bottlenecks. In addition, future studies are warranted to investigate whether other repair, defence or regeneration systems were lost or inactivated in mammals, and obtaining more evidence to support the proposed – and admittedly speculative – hypothesis is necessary. Recent genome sequencing efforts have opened the door for large-scale comparative analyses of longevity evolution (Box 1), and it should be possible to test the longevity bottleneck hypothesis using evolutionary genomics in the years ahead.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest

DATA AVAILABILITY STATEMENT

The data that support the findings of this article are available in ref. [6]. The author welcomes readers to contact him for further questions and information.

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