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Review

Slow aging in mammals—Lessons from African mole-rats and bats

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ABSTRACT

Traditionally, the main mammalian models used in aging research have been mice and rats, i.e. short-lived species that obviously lack effective maintenance mechanisms to keep their soma in a functional state for prolonged periods of time. It is doubtful that life-extending mechanisms identified only in such short-lived species adequately reflect the diversity of longevity pathways that have naturally evolved in mammals, or that they have much relevance for long-lived species such as humans. Therefore, some complementary, long-lived mammalian models have been introduced to aging research in the past 15–20 years, particularly naked mole-rats (and to a lesser extent also other mole-rats) and bats. Here, I summarize and compare the most important results regarding various aspects of aging – oxidative stress, molecular homeostasis and repair, and endocrinology – that have been obtained from studies using these new mammalian models of high longevity. I argue that the inclusion of these models was an important step forward, because it drew researchers' attention to certain oversimplifications of existing aging theories and to several features that appear to be universal components of enhanced longevity in mammals. However, even among mammals with high longevity, considerable variation exists with respect to other candidate mechanisms that also must be taken into account if inadequate generalizations are to be avoided.

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1. Introduction

Mammals exhibit great variability in longevity: species such as shrews, mice, and rats almost certainly die before they reach the age of 3 years even if they are maintained under optimal conditions and without any predators, whereas other species can live for more than 100 (e.g., humans) or even 200 years (e.g., the bowhead whale *Balaena mysticetus*) [1]. Some very simple yet important lessons based on this variation are the following: *a*) maximum longevity is species-specific *b*) being species-specific, it must have a genetic basis which is subject to evolutionary change; *c*) evolutionary change has led to effective mechanisms of maintaining a functional soma into old age in some species, but not in others. Given these facts, it is an important achievement of modern biogerontology that (mammalian) lifespan variation is increasingly represented in the model organisms used to explore the mechanisms of (mammalian) aging. The inclusion also of long-lived model organisms is of great importance because most if not all theories about why organisms age have been developed on the basis of a very few short-lived model organisms, mainly yeast, nematodes, flies, and laboratory mice. It has been argued that the continuous self-limitation brought about by the use of only a few short-lived models could cause the results of such research to be misleading in the long run if the aim is to understand aging in general [2–5]. It is also questionable whether candidate genes or pathways of aging identified only in short-lived organisms are necessarily also representative of long-lived species such as humans [6,7].

Here I review the ways in which studies that included uncustomary, long-lived model species have modified and refined our understanding of (mammalian) aging mechanisms since the start of the new millennium. I will demonstrate that the inclusion of such new models has contributed substantially to necessary adjustments of even long-standing, well-established theories. I also address the question of the universality of mechanisms that may slow the aging process in mammals, i.e., to what extent a given mechanism is unique to the species (or lineage) that exhibits it, or whether that mechanism can explain the aging phenotype even of distinct long-lived mammalian lineages, at best including humans. The main focus will be on naked and other African mole-rats (Bathyergidae) and on bats (Chiroptera). Some of the most extreme longevities in relation to body size among mammals have evolved in these two unrelated taxa, and because most representatives of these lineages are small, they are principally more suited for broader-scale aging studies than are, for example, elephants or whales. In addition, studies using mole-rats or bats raise fewer ethical and regulatory problems than do studies using primates. Consequently, these lineages have received special attention from aging researchers during the past 15–20 years.

2. Systematics, ecology, and longevity patterns of African mole-rats and bats

2.1. Heterocephalus glaber *and other African mole-rats*

The naked mole-rat *Heterocephalus glaber* is the smallest (ca. 40 g) representative of African mole-rats (Bathyergidae), a strictly subterranean rodent family which is endemic to sub-Saharan Africa. The family is traditionally subdivided into the 6 genera [8,9]. The lineage leading to *Heterocephalus* diverged from the common ancestor of all other bathyergid species in the early Oligocene, approximately 31 million years ago (Mya) [8,10]. Because of this long independent evolution, it has been suggested that naked mole-rats should be placed into their own family, Heterocephalidae [10]. Regardless of nomenclature, monophyly of the clade containing all living African mole-rats, including *Heterocephalus*, is undisputed. Here I follow the traditional classification based on previous studies [8,9] (Fig. 1).

All Bathyergidae live in self-dug burrow systems where they feed mainly on tubers and roots and rarely emerge above-ground. Three genera (*Heliophobius*, *Georhychus,* and *Bathyergus*) contain only solitary species, whereas the other three genera (*Cryptomys*, *Fukomys,* and *Heterocephalus*) contain species that are highly social. Animals in these genera typically live in extended family groups in which reproduction is monopolized by a few individuals (usually the founder pair), whereas the other family members forego their own reproduction in the confines of their natal colonies, even after reaching full maturity [11].

The longevity of African mole-rats appears to be generally high. The extraordinarily long lifespan of naked mole-rats was first described some 15 years ago [12,13] and is now known to exceed 30 years [1], making this species the longest-lived rodent species known to date despite its small adult body size. Species of the social genus *Fukomys* are also very long-lived for their body size: at least two (the Ansellís mole-rat, *F. anselli*, and the giant mole-rat *F. mechowii*) can live longer than 20 years [1,own unpublished data]. *Fukomys* species are of particular interest to biogerontologists because breeders of both sexes live on average approximately twice as long as their non-reproductive counterparts [14–16]. This feature, unique among mammals, offers researchers the opportunity to study highly divergent aging rates within one genotype, without the inevitable shortcomings of inter-species comparisons.

2.2. Bats

After rodents, bats (Chiroptera) are the second most speciose mammalian order. More than 1200 species with a nearly worldwide distribution are currently recognized [17]. The order contains 20 families that are subdivided into the two suborders Yinpterochiroptera (including fruit-eating megabats, formerly classified as Megachiroptera, plus four insectivorous families) and Yangochiroptera (containing the other 15 bat families) [18]. Some megabats weigh as much as 1.6 kg, but bats are typically small; for example, the adult body mass of little brown bats (genus *Myotis*) ranges from 3 to 30 g [19]. This genus has received particular attention from biogerontologists in the past 20 years because it contains the small bat species with the highest longevities recorded so far: *M. brandti* (41 years), *M. myotis* (37.1 years), *M. lucifugus* (34 years) and *M. blythii* (33 years) [1,20]. No other mammals live longer for their body size [1]. However, longevity is generally high in all bat lineages, and several other bat genera contain species with recorded lifespans of more than 30 years, too [1,19,21].

3. Aging studies involving African mole-rats and bats

3.1. Oxidative stress

The oxidative stress theory of aging was proposed in 1956 [22] and soon became one of the most widely accepted proximate theory of aging. In brief, this theory posits that reactive oxygen species (ROS), which are produced in the mitochondria during aerobic metabolism, cause continuous damage on macromolecules such as DNA, proteins, and lipids. This damage would accumulate with advancing age (if not counteracted by defense or repair mechanisms), thereby compromising cellular and tissue integrity in the long run and eventually leading to tissue degradation and organ failure. When species with different longevities are compared, the predictions of the theory are straightforward: longer-lived species should produce fewer ROS, have better defenses against ROS, or both, ultimately resulting in less molecular damage (or slower accumulation of damage) than that seen in shorter-lived species.

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