

Unlocking the secrets of naked mole-rat longevity

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ABSTRACT

Renowned for extreme longevity and extraordinary cancer resistance, the naked mole-rat (*Heterocephalus glaber*) serves as a powerful biological model to uncover novel healthy aging mechanisms. Fourteen hallmarks have been proposed to describe the core features of biological aging; however, whether their direct enhancement contributes to longevity remains unclear. Here, we summarize current knowledge on the differential regulation of these aging hallmarks in the naked mole-rat and their potential roles in its exceptional lifespan. We also discuss current research limitations and suggest future directions to better elucidate the basis of naked mole-rat longevity, ultimately enabling the development of strategies to promote healthy aging in humans.

Key words: Naked mole-rat; Longevity; Aging; Comparative biology; Intervention



INTRODUCTION

Biological aging manifests as the interaction of multiple core hallmarks. These hallmarks are categorized into three hierarchical tiers: primary, antagonistic, and integrative (Kroemer et al., 2025). While the age-associated manifestation of these hallmarks and their roles in driving aging onset are established, whether directly targeting them can delay aging and extend lifespan and health span remains unresolved. Although traditional animal models have advanced our understanding of these aging hallmarks, emerging noncanonical models, particularly those exhibiting extreme resistance to aging and age-related diseases, offer fresh insights (Brunet, 2020). Among diverse animal models, the naked mole-rat occupies a unique position due to its negligible senescence, characterized by mortality rates that do not increase with age (Ruby et al., 2018). This species also exhibits extreme cancer resistance (Delaney et al., 2016; Oka et al., 2022; Seluanov et al., 2009; Shepard et al., 2026; Taylor et al., 2017; Tian et al., 2013), maintains cardiac function under ischemia/hypoxia conditions with minimal tissue damage (Faulkes et al., 2024), and retains reproductive capacity throughout its exceptionally long lifespan (Edrey et al., 2011). Collectively, these exceptional traits make naked mole-rats an ideal system for studying how aging hallmarks are regulated to promote longevity. Beyond naked mole-rats, other long-lived mammals, such as bats, bowhead whales, and elephants, have also evolved unique anti-aging mechanisms (Abegglen et al., 2015; Firsanov et al., 2025; Koh et al., 2019), providing complementary insights into the regulation of aging hallmarks. The particular significance of whales and elephants lies in their remarkable resistance to age-related diseases like cancer. While their longevity is expected given their size, this resistance is what makes them increasingly valuable models for understanding healthy aging. Here, we summarize research on how the primary, antagonistic, and integrative hallmarks of aging are differentially regulated in naked mole-rats and other long-lived species, highlighting potential avenues for developing innovative interventions targeting these hallmarks to combat aging and age-



related diseases.

THE PHYSIOLOGICAL CHARACTERISTICS OF THE NAKED MOLE-RAT

Basic information

The naked mole-rat is a pink, nearly hairless, mouse-sized rodent that inhabits arid subterranean burrows in eastern Africa (Figure 1). It is exceptionally long-lived for its size, with a documented maximum lifespan of approximately 40 years (Buffenstein & Amoroso, 2024; Patel et al., 2025; Ruby et al., 2024; Tanes et al., 2026). Naked mole-rats feed primarily on roots and tubers (Braude et al., 2020; O'connor et al., 2002).

Naked mole-rats are one of the few eusocial mammals, living communally in colonies of up to 300 individuals. Within these colonies, only the queen and a few males engage in reproduction, while the remaining females are reproductively suppressed and function as workers responsible for tasks such as foraging, nest building, and pup care (Jarvis, 1981; Yamakawa et al., 2025). They are also xenophobic and utilize a colony-specific soft chirp for member recognition, which helps maintain colony cohesiveness. This distinct dialect is shaped by the queen and transmitted across generations; however, dialects change following queen replacement (Barker et al., 2021).

In an excellent review, Buffenstein et al. (2022) systematically address long-standing misconceptions and contentious hypotheses in naked mole-rat biology. For instance, despite its name, the naked mole-rat is not completely hairless, it possesses approximately 40 vibrissa-like tactile hairs along its flanks. These specialized sensory hairs are highly sensitive and aid in environmental navigation (Crish et al., 2003). Another example is its visual function. The naked mole-rat is described as functionally blind, as its visual system is severely degenerate, although it retains the ability to respond to changes in luminance (Catania & Remple, 2002; Hetling et al., 2005; Nikitina et al., 2004;



Vice et al., 2021). Previous studies have suggested that naked mole-rats exhibit poikilothermic traits and have a limited capacity for thermoregulation (Riccio & Goldman, 2000). Similar poikilothermic traits have been reported in other species, such as Mashona mole-rat (Bennett et al., 1993). However, Mikhilchenko et al. (2026) propose that naked mole-rats represent a unique thermoregulatory category, distinct from traditional classifications. They possess functional nonshivering thermogenesis and UCP1 but fail to maintain homeothermy due to excessive heat loss. Exogenous substrates can support body temperature during cold exposure, and artificial insulation partially restores their thermoregulatory capabilities.

Naked mole-rats have evolved pronounced tolerance to the chronic hypoxic and hypercapnic conditions characteristic of their subterranean habitat (Oka et al., 2023; Park et al., 2021), enabling survival under extreme hypoxia without apparent injury (Larson et al., 2014; Park et al., 2017; Peterson et al., 2012). Moreover, they have a reduced pain pathway (Browe et al., 2020). In addition, representations of the upper and lower incisors occupy 31% of the primary somatosensory cortex, and their somatosensory cortex expands to encompass virtually the entire neocortical area normally reserved for vision (Catania & Remple, 2002). Additionally, because naked mole-rats have lived underground, they naturally lack vitamin D. However, they maintain calcium balance through efficient intestinal absorption that does not rely on vitamin D (Buffenstein & Yahav, 1991). These adaptations are closely linked to their underground lifestyle. Remarkably, their intestinal microbiota remains stable across different age groups (Rakhimov et al., 2026; Tanes et al., 2026).

The naked mole-rat immune system exhibits striking remodeling features. This species retains functional thymic tissue up to at least 11 years of age and possesses additional ectopic cervical thymi (Emmrich et al., 2021). Notably, the myeloid-to-lymphoid cell ratio in its peripheral blood and lymphoid tissues is



substantially higher than that in mice, and it completely lacks conventional natural killer (NK) cells (Hilton et al., 2019; Patel et al., 2025). Functionally compensating for this lack of NK cells, its peripheral blood and spleen are enriched with abundant circulating $\gamma\delta$ T cells (Lin et al., 2024). $\gamma\delta$ T cells are not particularly abundant in lymphoid organs and have thus received less attention in the past; however, recent findings demonstrate they play pivotal roles in regulating both innate and adaptive immunity, as well as tumor immunosurveillance (Bychkov & Wiest, 2025; Sanchez Sanchez et al., 2024). A subset of these $\gamma\delta$ T cells in naked mole-rat highly expresses NK cell cytotoxicity-related genes, potentially enabling them to exert NK cell-like tumor immune surveillance functions (Sanchez Sanchez et al., 2024). Based on these findings, researchers propose that the evolution of the naked mole-rat immune system was driven less by frequent viral exposure and more by adaptation to its closed subterranean habitat. This adaptation optimizes tissue homeostasis, potentially contributing to their exceptional longevity (Patel et al., 2025). However, the physiological function of naked mole-rat $\gamma\delta$ T cells and their contribution to cancer resistance lack substantial experimental evidence and represent an important future direction.

Evidence of healthy aging

The naked mole-rat does not exhibit the typical age-associated acceleration of mortality risk that characterizes other mammalian species and may therefore be the first reported mammal exhibiting negligible senescence over the majority of its long lifespan (Buffenstein, 2008). Physiologically, regardless of age, naked mole-rats maintain low levels of body temperature, metabolic rate, cardiac output, and kidney concentrating ability under basal conditions, which may enable better preservation of organ and cellular function (Buffenstein & Craft, 2021). Regarding reproduction, no obvious age-related decline in reproductive capacity has been observed (Buffenstein, 2008; Buffenstein &



Jarvis, 2002). At the molecular level, the protein degradation mechanisms remain unchanged during aging, with no accumulation of polyubiquitinated or oxidized proteins (Pérez et al., 2009). Collectively, the naked mole-rat has successfully avoided the age-related functional decline commonly observed in other mammals through multiple adaptation mechanisms, thereby providing a valuable natural model for studying healthy aging and extending health span.

Broad disease resistance

The naked mole-rat exhibits remarkable resistance to both spontaneous and chemically induced tumorigenesis, with only limited cancer cases reported in captive breeding populations (Delaney et al., 2016; Oka et al., 2022; Seluanov et al., 2009; Shepard et al., 2026; Taylor et al., 2017; Tian et al., 2013). This observed resistance is attributed to multiple unique mechanisms (Wang et al., 2025a). In 2013, Tian and colleagues first reported that exceptionally high levels of high-molecular-mass hyaluronan (HMM-HA) in naked mole-rat tissues effectively suppress malignant transformation by enhancing early contact inhibition (Tian et al., 2013). Building on this, the same research group demonstrated, using a transgenic mouse model expressing the naked mole-rat hyaluronan synthase 2 gene (*nmrHAS2*), that these mice exhibited significantly elevated HMM-HA levels. These transgenic mice displayed a reduced incidence of spontaneous tumors, enhanced resistance to chemically induced skin cancer, a 4.4% increase in median lifespan, and a 12.2% extension in maximum lifespan (Zhang et al., 2023). These findings indicate that HMM-HA plays a significant role in regulating cancer resistance and promoting healthy longevity. In addition to naked mole-rats, several other species exhibit tumor resistance phenotypes, including elephants and greater horseshoe bats. Although changes in hyaluronan pathways have not been reported in them, other shared and unique mechanisms contribute to this resistance. For instance, specific amino acid substitutions in the gene *ALDH6A1* have been identified in naked mole-rats, elephants, and greater horseshoe bats, potentially inhibiting



tumor cell migration (Li et al., 2023). Species-specific mechanisms also exist. For example, efficient drug efflux mediated by the ABC transporter ABCB1 has been shown to underlie the improved response to genotoxic agents in bats, contributing to their reduced cancer incidence (Koh et al., 2019). ABC transporter-mediated drug efflux appears to be a conserved mechanism across species (Fischer et al., 2013; Li et al., 2022; Suominen et al., 2025). However, whether changes in the ABC transporter family is associated with cancer resistance in other species remains to be further validated.

In terms of cardiovascular health, naked mole-rat do not show age-associated cardiac hypertrophy, diastolic dysfunction, or a decline in functional cardiac reserve up to 24 years of age (Grimes et al., 2012; Grimes et al., 2014), nor do their blood vessels lose their elasticity in middle age (Csiszar et al., 2007). Interestingly, naked mole-rat express high levels of A β in the brain throughout life. However, a unique 88 kDa tau protein as well as its axonal localization have been proposed to confer exceptional microtubule stability and neuroprotection to naked mole-rats (Orr et al., 2015).

Thus, the naked mole-rat's remarkable resistance to cancer, age-related cardiovascular decline, and neurodegeneration underscores its unparalleled value as a comparative model for healthy aging research.

HOW ARE HALLMARKS OF AGING REGULATED IN THE NAKED MOLE-RAT?

Fourteen hallmarks of aging have been proposed (Kroemer et al., 2025). We focus here on summarizing research on how the primary, antagonistic, and integrative hallmarks are differentially modulated in naked mole-rats (Figure 2; Table 1).

Resistance mechanisms against primary hallmarks of aging



Genomic instability: Genomic stability ensures the complete and accurate transmission of genetic information, thereby preventing the accumulation of mutations, cellular aging, and decline in tissue function (Wu et al., 2024; Zheng, 2022). The naked mole-rat exhibits multiple unique adaptive mechanisms to maintain this stability. In a systematic comparative study of 16 mammalian species, including the naked mole-rat, Cagan et al. (2022) found that its annual somatic mutation rate is exceptionally low (approximately 93 mutations per year), only about one-eighth that of the house mouse (796 mutations per year). DNA repair serves as a conserved mechanism protecting against genomic instability. However, DNA repair capacity downregulates with age (Chen et al., 2023; Li et al., 2016). Conversely, fibroblasts from long-lived species (such as naked mole-rats and bowhead whales) or long-lived humans exhibit enhanced DNA repair capacity (Evdokimov et al., 2018; Onn et al., 2020; Tang et al., 2025; Tian et al., 2019). Interestingly, amino acid substitutions in factors related to DNA damage checkpoint and repair pathways, such as *ATRIP* and *RPA1*, have been identified in naked mole-rats and are associated with increased stress resistance (Zhou et al., 2020). Recently, our work demonstrated that unique amino acid alterations have shaped the DNA repair function of cGAS in this species, reversing the homologous recombination (HR) repair-suppressing role characteristic of the human cGAS ortholog (Chen et al., 2025). While oxidative stress poses a critical threat to genomic stability, several studies report that naked mole-rat longevity is independent of oxidative stress parameters (Andziak & Buffenstein, 2006; Andziak et al., 2005; Andziak et al., 2006). However, research on the molecular mechanisms underlying DNA repair in the naked mole-rat remains limited, and its species-specific regulatory networks are still not fully elucidated. Interestingly, enhanced genomic maintenance has been reported as a shared mechanism underlying longevity across species. For instance, long-lived bats have undergone positive selection in genes involved in DNA repair pathways, such as *ATM* and *TP53* (Zhang et al., 2013). Similarly, bowhead whale exhibits mutations in the DNA repair factor *ERCC1*,



duplications of *PCNA*, and enhanced expression of *CIRBP* (Firsanov et al., 2025; Keane et al., 2015). Although DNA repair activation contributes to delayed aging and reduced age-related diseases (Chen et al., 2020; Jiang et al., 2025), whether naked mole-rat DNA repair mechanisms can be applied to other species remains unexplored (Chen et al., 2026).

Telomere attrition: Telomere attrition serves as a core molecular clock that determines cellular replicative lifespan and systemic aging. It triggers the DNA damage response, induces cellular senescence, and drives tissue functional decline (Deboy et al., 2023; Jones-Weinert et al., 2025). The naked mole-rat maintains exceptional genomic stability via a unique telomere protection system. Telomere dynamics, particularly the rate of age-related attrition, are considered a reliable predictor of lifespan (Whittemore et al., 2019). Unlike most species, studies reveal that telomere length in naked mole-rat blood cells does not shorten with age but instead exhibits slight elongation, suggesting an effective age-buffering mechanism *in vivo* (Adwan Shekhidem et al., 2019). It has been reported that the naked mole-rat possesses two copies of the *TINF2* gene, potentially facilitating more stable anchoring of other protective proteins to telomeres (Macrae et al., 2015b). As a core shelterin component binding directly to telomeric DNA, naked mole-rat TRF1 has been found to bind telomeres better than its mouse ortholog, protecting telomeres during replication under hypoxia (Augereau et al., 2021). Moreover, genes encoding telomere-associated proteins in the naked mole-rat genome, such as *TEP1*, show signatures of positive selection (Kim et al., 2011). Notably, patterns of age-related telomere dynamics also vary within the Bathyergidae family. For instance, the Damaraland mole-rat, a close relative of the naked mole-rat, displays significant age-dependent telomere shortening (Leonida et al., 2020). Long-lived bats, in contrast, possess unique mechanisms for telomere stability, which are closely associated with positive selection of telomere-related genes such as *DKC1* and *TERT* (Morgan et al., 2013), and the expression of genes



involved in the alternative lengthening of telomeres pathway (Foley et al., 2018). This suggests that telomere protection mechanisms may have followed independent evolutionary trajectories among different long-lived species.

Epigenetic alterations: Epigenetic alterations establish a dynamic link between the environment and genetics by regulating DNA methylation, histone modification, and chromatin remodeling. Their drift with age can directly drive disordered gene expression, loss of cell identity, and accelerated aging (Kim et al., 2016; Yang et al., 2023b). Despite not exhibiting typical phenotypic signs of senescence, the naked mole-rat undergoes systematic changes in its DNA methylation patterns over time, indicating epigenetic aging at the molecular level (Horvath et al., 2022). Studies have successfully constructed a DNA methylation-based epigenetic clock for naked mole-rats, providing a crucial molecular tool for investigating their longevity mechanisms (Lowe et al., 2020). The rate of age-related DNA methylation change in this species is lower than in most mammals, aligning with their respective documented maximum lifespans (Kerepesi et al., 2022). Furthermore, the reproductively active queen exhibits a slower epigenetic aging rate compared to non-reproductive females in the colony (Horvath et al., 2022). This finding challenges the traditional notion that reproductive investment shortens lifespan, indicating the complex interplay between eusocial structure, reproduction, and longevity. Interestingly, studies demonstrate that naked mole-rat cells possess a highly stable epigenome compared to mouse cells, conferring significant resistance to cellular reprogramming induced by the Yamanaka factors (Tan et al., 2017). This stability may more effectively preserve cell identity throughout their extended lifespan. Naked mole-rat-derived induced pluripotent stem cells exhibit pluripotency without tumorigenicity (Miyawaki et al., 2016). However, how the naked mole-rat achieves precise regulation of this stable epigenome, and how this stability contributes to its remarkable cancer resistance, remain unclear. Furthermore, the influence of external signals (such as hypoxia, nutrition, and



social stress) on epigenome stability, and how this responsiveness changes with age, warrant further investigation.

Loss of proteostasis: The loss of protein homeostasis leads to the accumulation of misfolded proteins and the formation of protein aggregates, directly damaging cellular functions and driving tissue degeneration. Naked mole-rats demonstrate an exceptional ability to maintain proteostasis (Azpurua et al., 2013; Pérez et al., 2009). Azpurua and coworkers (2013) found that, compared to mouse cells, naked mole-rat cells exhibit higher translational fidelity, characterized by a lower rate of amino acid misincorporation. Concurrently, they possess a unique fragmented 28S ribosomal RNA structure. However, this characteristic is not consistently present in their close relative, the Damalaland mole rat (Fang et al., 2014). Notably, structural changes in 28S ribosomal RNA have been documented in other rodents such as America's tuco-tucos (*Ctenomys*) and the degu (*Octodontomys gliroides*) (Melen et al., 1999), as well as in insects and plants (Winnebeck et al., 2010). However, whether and how these changes impact aging in these species remains to be further studied. Furthermore, naked mole-rat proteins exhibit heightened resistance to chemical denaturation, and their tissues show no age-related accumulation of oxidized or ubiquitinated proteins (Pérez et al., 2009). In addition, Rodriguez et al. found that naked mole-rats, compared to mice, have higher 20S proteasome activity, along with higher activity and abundance of the 26S proteasome, resulting in enhanced proteasome function (Rodriguez et al., 2012). Collectively, these features indicate that the naked mole-rat possesses superior systems for both protein synthesis and clearance, maintaining proteome stability and functional integrity. Similarly, bats express major heat shock proteins at higher levels. This may enable them to withstand the elevated temperatures associated with flight while safeguarding proteome homeostasis (Chionh et al., 2019).



Disabled macroautophagy: Disabled macroautophagy leads to impaired clearance of damaged proteins and organelles, accelerating aging and promoting various aging-related diseases (Hansen et al., 2018; Weindruch et al., 1982). Research indicates that naked mole-rats maintain relatively high levels of autophagic activity. Autophagy levels in their hepatic stellate cells are elevated compared to those in age-matched juvenile mice (Zhao et al., 2014). Kim et al. demonstrated that naked mole-rat fibroblasts exhibit significantly higher levels of the Atg12-Atg5 complex than mouse fibroblasts. Knocking down Atg5 in these cells resulted in damaged mitochondrial accumulation, impaired proliferation and adhesion, and increased apoptosis/anoikis (Kim et al., 2020). Furthermore, proteomic analysis reveals that the LC3II/LC3I ratio shows no significant age-related changes in the naked mole-rat brain, while Beclin-1 levels only decrease significantly in the oldest age group (Triplett et al., 2015). Notably, Manskikh et al. (2025) recently reported a progeroid syndrome characterized by autophagic dysfunction, termed idiopathic cachexia, in a subset of naked mole-rats. Affected animals exhibited a decreased LC3II/LC3I ratio, p62 protein accumulation, systemic lipofuscin deposition, myocardial degeneration, cataracts, and amyloid body formation in the brain. This finding highlights the critical role of functional autophagy in maintaining naked mole-rat health. Enhanced autophagy is a key common mechanism underlying extreme longevity (Yang et al., 2023a). For example, bats also exhibit enhanced autophagic activity with advancing age (Huang et al., 2019). Collectively, active autophagy acts in concert with other defense mechanisms, such as proteostasis, to form an integrated proteome protective network. However, its functional role in determining the exceptional health span of the naked mole-rat remains to be investigated.

Regulation mechanisms of antagonistic hallmarks of aging

Deregulated nutrient-sensing: Organisms sense nutrients in the environment to coordinate growth and development. Disruption of this process causes age-



related functional decline and chronic diseases such as cancer, diabetes, cardiovascular disorders, and neurodegeneration. Throughout evolution, naked mole-rats have developed distinctive cardiometabolic and genetic adaptations that enable their survival in the extreme conditions of their subterranean habitat (Faulkes et al., 2024). Studies have also shown that naked mole-rats can survive for 18 minutes in total oxygen deprivation (Park et al., 2017). Mechanistic studies have revealed that they can utilize fructose for glycolysis under hypoxic conditions, dependent on the specific expression pattern of the fructose transporter GLUT5 and the enzyme ketohexokinase (KHK) (Park et al., 2017). Under hypoxic conditions, naked mole-rats can remain metabolically active in part by reducing oxygen use for thermogenesis (Ilacqua et al., 2017). It has also been reported that exposure to hypoxia correlated with a tissue-specific differential regulation of components of the Akt/mTOR signaling pathway in naked mole-rats (Al-Attar et al., 2020). mTORC1 activation may protect cells by enhancing glycolytic capacity through metabolic reprogramming. Moreover, naked mole-rats employ an energy conservation strategy: under chronic hypoxic conditions, they actively suppress global energy metabolism and modulate cell membrane cholesterol levels to maintain membrane integrity and function, thereby ensuring cell survival in low-oxygen environments (Farhat et al., 2020). Attenuated GH/IGF1 signaling confers resistance to diabetes and cancer in humans and mice (Guevara-Aguirre et al., 2011). Naked mole-rats exhibit lower hepatic expression of insulin/IGF1 pathway genes than mice (Ma & Gladyshev, 2017). Interestingly, IGF-mediated glucose signaling in naked mole-rats is caste- and tissue-specific. Under hypoxia, subordinates and juveniles maintain glucose transport to sustain activity, whereas queens adopt an energy-conserving phenotype suited for their sedentary reproductive function (Ojaghi & Pamenter, 2026). In bats, unique amino acid changes in *IGF1R* and *GHR* have been identified and may represent mechanisms contributing to their exceptional longevity (Seim et al., 2013). While targeting nutrient-sensing pathways shows promise in delaying aging (Castillo-Quan et



al., 2019), whether alterations in these pathways in naked mole-rats, which primarily represent adaptations to their environment, also cause the beneficial side effect of longevity remains to be validated.

Mitochondrial dysfunction: Mitochondrial dysfunction triggers energy metabolism imbalance, excessive production of reactive oxygen species (ROS), and dysregulation of apoptosis signaling (Pavlović et al., 2025). In contrast, the mitochondria of the naked mole-rat demonstrate exceptional adaptive and protective mechanisms (Cheng et al., 2021; Cheng et al., 2024; Munro et al., 2019; Stoll et al., 2016). Mitochondrial ultrastructure is well-preserved in aged naked mole-rats, with stable expression and activity of mitochondrial Complex IV. Collectively, this stability may contribute to maintaining skeletal muscle integrity during aging and protect against sarcopenia (Stoll et al., 2016). Naked mole-rat brain mitochondria exhibit a calcium-buffering capacity more than double that of mouse mitochondria, effectively preventing calcium overload and cell death during hypoxia. This enhanced function is attributed to their unique ultrastructural features, including larger volume and higher cristae density (Cheng et al., 2024). Moreover, the extraordinary longevity of the naked mole-rat may also be attributed to its specialized mitochondrial antioxidant defense mechanisms, which enable effective resistance against oxidative damage and maintenance of mitochondrial homeostasis (Munro et al., 2019). Under hypoxic stress, functional parameters of naked mole-rat skeletal muscle mitochondria, such as respiration and ROS production, exhibit minimal change, contributing to the maintenance of functional stability (Cheng et al., 2021). Supporting this, previous study has demonstrated that the amount of hydrogen peroxide produced by isolated heart mitochondria is negatively correlated with species maximum lifespan (Lambert et al., 2007). Specifically, mitochondria from certain bat species produce less hydrogen peroxide per unit of oxygen consumed (Brunet-Rossinni, 2004). However, it remains unclear how the unique ultrastructural features of naked mole-rat mitochondria arise, whether



they are mechanistically linked to calcium buffering capacity, low ROS production under hypoxic stress, and energy metabolism, and whether they collectively underpin healthy longevity. Additionally, the heterogeneity of these mechanisms across tissues and their age-related dynamics remain to be elucidated.

Cellular senescence: Cellular senescence, an irreversible state of cell cycle arrest characterized by active secretion of senescence-associated secretory phenotype (SASP) factors, drives deterioration of the tissue microenvironment and impairment of tissue functions. It has been proven to be one of the key drivers of organismal aging, as implanting senescent cells into young mice is sufficient to induce physical dysfunction in the recipients (Knoedler et al., 2025; Wu et al., 2025). Zhao et al. (2018) confirmed that naked mole-rat cells undergo developmental programmed senescence, as well as senescence induced by oncogene activation and DNA damage. Moreover, prolonged cell culture induces premature senescent phenotypes in naked mole-rat mesenchymal stromal cells, making them more similar to human mesenchymal stromal cells than to mouse ones (Emmrich et al., 2024). Accumulation of senescent cells is also reported in aged naked mole-rat skin (Fatima et al., 2022). These data indicate that naked mole-rat longevity does not stem from a simple evasion of senescence mechanisms. Interestingly, Kawamura et al. revealed that senescent cells in naked mole-rats rapidly initiate programmed cell death via the INK4a-RB pathway. This mechanism of clearance upon induction effectively prevents the long-term persistence of senescent cells and their deleterious paracrine effects (Kawamura et al., 2023). This finding suggests the existence of an endogenous senescent cell clearance mechanism in naked mole-rats, which may contribute to their exceptional health span. Notably, this intrinsic strategy conceptually parallels an emerging therapeutic approach: the use of senolytic drugs to clear senescent cells has proven effective in combating age-related pathologies and improving health outcomes (Gasek et



al., 2021; Jaros & Melk, 2025). Interestingly, research shows that bat fibroblasts exhibit attenuated stress-induced senescence with a dampened secretory phenotype (Athar et al., 2025). This suggests that species have evolved diverse strategies to modulate cellular senescence. However, whether the mechanisms underlying the efficient clearance of senescent cells in naked mole-rats could be harnessed in humans warrants further investigation.

Regulation mechanisms of integrative hallmarks of aging

Stem cells exhaustion: The depletion of stem cells leads to a decline in tissue regeneration capacity and deterioration of organ function, driving aging and the onset of age-related diseases. Unlike other mammals, naked mole-rat tissues retain stem cell function and regenerative potential with age, preventing the age-associated exhaustion of stem cells (Emmrich et al., 2022; Yang et al., 2024). Research has shown that the intestinal Lgr5⁺ stem cell pool is markedly expanded in naked mole-rats. However, these cells divide at a slower rate than in mice, resembling the human pattern. Rather than entering a quiescent (G0) state, they decelerate the cell cycle by extending G1/G2 phase arrest (Montazid et al., 2023). Furthermore, the population of stem cells within naked mole-rat skin remains stable throughout aging. Cellular compartments and differentiation trajectories in the skin remain stable throughout life, with no age-related decline in wound-healing capacity (Savina et al., 2022). Similarly, a comprehensive characterization of their hematopoietic system revealed an expanded quiescent hematopoietic stem and progenitor cell (HSPC) compartment and an absence of age-related functional decline (Emmrich et al., 2022). This sustained resistance to stem cell exhaustion contributes to the long-term maintenance of regenerative capacity across tissues. However, the mechanisms that balance stem cell senescence resistance with tumor suppression require further investigation.

Altered intercellular communication: Disrupted intercellular communication



causes dysregulation of the tissue microenvironment, reduced systemic integration, and ultimately disrupts homeostasis. Research has revealed that naked mole-rat cells exhibit exceptional sensitivity to contact inhibition (Seluanov et al., 2009). This heightened responsiveness is mechanistically grounded in their abundance of HMM-HA (Tian et al., 2013). At cell densities that still permit proliferation in other mammals, the presence of HMM-HA is sufficient to trigger activation of the p16^{INK4a} pathway in naked mole-rat cells. The evolution of HMM-HA production is associated with their subterranean lifestyle (Zhao et al., 2023). Furthermore, very-high-molecular-mass hyaluronan (vHMM-HA; >6.1 MDa) exhibits superior cytoprotective properties compared to shorter-chain HMM-HA, mediated by the major HA receptor, CD44 (Takasugi et al., 2020; Takasugi et al., 2023). Considerable variability exists regarding its precise molecular weight. While some reports suggest a molecular weight of 6-12 MDa, Del Marmol et al. (2021) reported approximately 2.5 MDa. Moreover, this high-molecular-mass hyaluronan is attributed to the unique sequence of the naked mole-rat hyaluronan synthase. Several critical residues regulating hyaluronan biosynthesis have been identified in hyaluronan synthase (Agarwal et al., 2019). Whether alterations occur in these residues across other species remains to be explored. Additionally, how HMM-HA-triggered early contact inhibition signals integrate with other forms of intercellular communication, such as gap junctions and paracrine signaling, remains unclear. Furthermore, the relationship between p16^{INK4a} pathway activation and cellular senescence warrants further investigation.

Chronic inflammation: Chronic inflammation is a key driver of aging, accelerating cellular and tissue damage and thereby promoting functional decline and the onset of age-related diseases. The naked mole-rat effectively evades inflammaging through a multi-layered, systemic anti-inflammatory defense network. At the molecular level, its extracellular matrix is enriched with HMM-HA, which forms a physicochemical anti-inflammatory barrier by inhibiting



canonical pro-inflammatory signaling pathways (Zhang et al., 2023). In response to tissue damage, naked mole-rats exhibit a unique anti-inflammatory reaction. Although chemical carcinogens induce levels of DNA damage and cell death comparable to mice, inflammatory immune cell infiltration is markedly reduced. This characteristic may stem from loss-of-function mutations in the necroptosis regulators *RIPK3* and *MLKL*, which disrupt this highly inflammatory cell death pathway and thereby delay carcinogenesis (Oka et al., 2022). At the immune system level, single-cell sequencing reveals significant alterations in the immune system of naked mole-rats (Hilton et al., 2019; Lin et al., 2024; Sanchez Sanchez et al., 2024). Notably, their youthful blood and marrow cell compositions are well maintained until middle age (Emmrich et al., 2022). Under systemic inflammatory conditions (e.g., LPS stimulation), iNOS activity and NO production in naked mole-rat myeloid cells are substantially lower than in mice, and the arginine metabolic pathway undergoes species-specific regulation, contributing to acute inflammation tolerance and reduced tissue damage (Gorshkova et al., 2025). Furthermore, naked mole-rats exhibit intrinsic resistance to potent inflammatory stimuli. For instance, topical imiquimod application fails to induce psoriasis-like inflammation in their skin (Kisipan et al., 2020). They also lack pain behaviors and thermal hyperalgesia in response to inflammatory agents like acid and capsaicin, potentially aiding adaptation to their acidic subterranean habitat (Park et al., 2008). Collectively, the naked mole-rat has thus constructed a multidimensional anti-inflammatory network. However, the mechanisms balancing inflammation induction with immune defense efficacy warrant further investigation. Bats have also evolved multiple anti-inflammatory strategies, including suppression of NLRP3 inflammasome activity (Ahn et al., 2019), inhibition of TNF signaling (Banerjee et al., 2017), and dampened responses to cytoplasmic DNA (Xie et al., 2018).

Dysbiosis: Gastrointestinal dysbiosis accelerates multi-organ aging and promotes age-related diseases by disrupting intestinal barrier function,



triggering systemic chronic inflammation, and interfering with host metabolic homeostasis (Abahussin et al., 2025; Chittimalli et al., 2023). Previous analysis has revealed a lower total microbial load coupled with higher diversity within the naked mole-rat gut (Debebe et al., 2016; Rakhimov et al., 2026). This structural profile may be linked to the high polyphenol content in its primary diet. Polyphenols, known for broad-spectrum bioactivity including antimicrobial, anti-inflammatory, antioxidant, and anticancer effects, are likely key drivers shaping this unique microbial environment. A 2017 study further revealed that the naked mole-rat gut microbiota is enriched with sulfate-reducing bacteria supporting anaerobic metabolism, likely as an adaptation to the subterranean environment. This facilitates increased production of beneficial metabolites such as short-chain fatty acids (Debebe et al., 2017). Subsequent high-throughput sequencing of microbial communities in the intestinal and respiratory tracts confirmed enrichment of bacterial genera associated with cellulose degradation and short-chain fatty acid production in the gut (Cong et al., 2018), substantiating their potential role in host energy acquisition and intestinal health maintenance. Furthermore, studies have found little difference in the microbiota of naked mole-rat from different age cohorts (Rakhimov et al., 2026; Tanes et al., 2026). Interestingly, analysis of fecal samples collected from toilet chambers revealed that fecal microbiota composition is highly correlated with gut microbiota composition (Chua et al., 2022). Observed differences in microbial communities between distinct colonies may be associated with social structure factors, such as the presence of a queen. These findings provide new insights for non-invasive monitoring of microbial dynamics and for exploring the relationship between social behavior and the microbiome. In addition, studies indicate that naked mole-rats possess a more robust intestinal barrier than mice, characterized by lower gut permeability, a greater number of goblet cells, and higher mucus content (Aguilera-Lizarraga et al., 2024). This physical barrier is critical to maintaining a stable intestinal microenvironment and preventing infiltration of harmful substances and inflammatory triggers. Consistently,



transgenic mice expressing *nmrHAS2* exhibit a significant increase in goblet cells and Paneth cells (Zhang et al., 2023). Therefore, gut health in the naked mole-rat is achieved through the combination of a unique microbiota and a robust physical barrier. Notably, research reveals that bats also exhibit remarkable stability in their gut microbiota, showing no significant differences in microbial composition between adults and juveniles (Hughes et al., 2018). This highlights the importance of gut microbiota in regulating longevity. Moreover, the regulatory network governing microbiota-host crosstalk, as well as the mechanisms by which microbial metabolites systemically influence distal organ aging, warrant further investigation. Although gut microbiota has received the most attention, the regulation of microbiomes in other organs, such as the oral cavity (Ren et al., 2024; Wang et al., 2025b), also remains to be explored.

Extracellular matrix changes: Changes in the extracellular matrix (ECM) disrupt tissue mechanical stability, weaken intercellular signal transmission, and promote the formation of an inflammatory microenvironment (Mavrogonatou et al., 2023). As mentioned previously, the ECM of naked mole-rat cells is exceptionally enriched with HMM-HA. By binding to the CD44 receptor, HMM-HA triggers early contact inhibition, contributing to the cancer resistance and longevity observed in this species (Tian et al., 2013; Zhang et al., 2023). Analysis of the temporomandibular joint revealed that naked mole-rats possess an articular disc containing a hyaluronan-rich, cartilage-like layer with directionally aligned collagen fibers. This structure effectively mitigates mechanical stress, protecting the mandibular bone from wear (Adachi et al., 2025). Interestingly, under ischemic conditions, the brain extracellular space in naked mole-rat exhibits a unique adaptive response. Unlike in rats, their extracellular space within the ischemic core region expands rather than contracts. This expansion maintains diffusion permeability for both small and large molecules and significantly attenuates the accumulation of extracellular potassium ions (Thevalingam et al., 2021). This dynamic response helps



preserve brain function under extreme hypoxia. However, the underlying molecular mechanisms are unclear. Additionally, the composition of other ECM components in naked mole-rats and how they change with age remains to be investigated.

Psychosocial isolation: Psychosocial isolation is a newly proposed hallmark of aging which has been neglected for a long time. It has been posited that highly ordered social structures create a favorable environment for longevity (Giraldo et al., 2016; Giraldo et al., 2021). The eusocial structure of the naked mole-rat may protect individuals from psychological isolation, potentially forming the macro-environmental foundation for their exceptional longevity. Experiments have shown that social isolation triggers a sharp surge in stress hormone levels in naked mole-rats, particularly in females (Blecher et al., 2020), indicating that group living serves as a critical buffer, shielding individuals from environmental uncertainties. Moreover, oxytocin signaling is implicated in promoting prosocial behaviors, playing a crucial role in maintaining long-term stability and cooperation within their large, complex colonies (Mooney et al., 2014). It is noteworthy that bats also exhibit diverse social behaviors (Kerth & J, 2012; Tietge et al., 2025). However, how signals triggered by social activity or isolation are translated into cellular and molecular processes that regulating aging, and how we can intervene in this process, remains unclear.

PERSPECTIVES

Need for enhanced naked mole-rat research tools

Although the field has made significant progress in elucidating the mechanisms underlying naked mole-rat longevity, the lack of specific research tools, such as antibodies, hampers exploration of these underlying mechanisms. Furthermore, while preliminary analyses of the 14 hallmarks of aging have offered rich clues for understanding naked mole-rat longevity, the functional relevance of these hallmarks does not imply causality. Rigorous proof of their contribution to



extreme longevity would necessitate systematic *in vivo* gain- and loss-of-function experiments in naked mole-rats that involve activating or inhibiting key pathway genes and monitoring outcomes, yet the current lack of technical approaches represents a principal barrier. This is partly due to their unique reproductive social structure, in which only the queen and a few males can reproduce. This constraint has complicated establishing gene-editing techniques comparable to those well-established in mice. Consequently, rigorous causal evidence is currently lacking in the naked mole-rat model. Excitingly, a recent study established a native lung cancer model in naked mole-rats by introducing the oncogenic *Eml4-Alk* fusion gene using CRISPR-mediated genome editing (Shepard et al., 2026). Nevertheless, establishing robust genetic editing approaches in this species remains a critical future direction. Moreover, when discussing these various longevity-promoting mechanisms in naked mole-rats, core questions remain unanswered: How much do these mechanisms respectively contribute to their extremely long lifespan? And do they interact with one another? It is well established that hallmarks of aging are interrelated in other model organisms. For example, genomic instability is related to cellular senescence, while cellular senescence is closely linked to chronic inflammation in mice. However, a systematic analysis of these interactions in naked mole-rats is currently lacking, primarily due to the absence of mature *in vivo* tools for genetic perturbation. Such tools are essential for determining whether a specific pathway regulates the resistance of another hallmark, and for assessing their relative importance to longevity.

Species complexity in naked mole-rats

Naked mole-rats are traditionally considered a single species. However, Faulkes et al. analyzed mitochondrial DNA from wild colonies across multiple countries and found significant genetic differentiation among populations. Notably, Cytochrome-*b* gene sequence divergence between populations from



Ethiopia and southern Kenya reached 5.8%, a value approaching levels typical of interspecific differences observed among other Bathyergidae species (Faulkes et al., 1997). Subsequent studies have further validated this genetic divergence (Wright et al., 2025; Zemlemerova et al., 2020a), identifying geographic barriers such as rift valleys and rivers as key drivers of population separation (Wright et al., 2025). Furthermore, a recent analysis confirmed intraspecific genomic variation between the genomes of naked mole-rats from Japan and existing reference genomes (Toga et al., 2026). Despite these significant molecular genetic differences, Zemlemerova et al. found that naked mole-rats exhibit a consistent karyotype (2N=60) throughout their entire distribution range (Zemlemerova et al., 2020b). Recent genomic analysis has revealed three highly divergent lineages: *H. phillipsi*, *H. g. glaber*, and *H. g. ansorgei* (Uhrová et al., 2025). Each lineage occupies distinct environmental conditions. *H. phillipsi*, which inhabits extremely harsh habitats, shows deep genetic divergence and distinct morphology, while *H. g. glaber* and *H. g. ansorgei* show less pronounced morphological differentiation. This finding holds significant implications for future studies investigating heterogeneity in anti-aging mechanisms across these lineages.

Complementary long-lived rodent model from China

Given that the naked mole-rat is native to East Africa, could we establish a complementary long-lived rodent model from China? The plateau zokor (*Eospalax baileyi*), a subterranean rodent native to the Qinghai-Tibetan Plateau, inhabits an environment characterized by low oxygen and elevated carbon dioxide levels. Through evolution, zokors have developed unique molecular adaptations to these extreme conditions (An et al., 2024). This subterranean niche is highly similar to that of naked mole-rats. However, whether plateau zokors can be considered as long-lived and whether they exhibit disease resistance remain to be determined. Given the current scarcity of naked mole-



rat research resources, developing alternative longevity models using native Chinese species offers a pathway to overcome these limitations while leveraging local resources.

The cost of living long

The exploration of extreme longevity mechanisms in the naked mole-rat ultimately points to an evolutionary biology question: Is this anti-aging phenotype a “free lunch” shaped by natural selection, or a “trade-off” incurring corresponding costs? Classic trade-off theory posits that, due to limited resources, allocating energy to somatic maintenance and repair necessarily comes at the expense of other functions, such as reproduction (Kirkwood, 2002). Based on this, it is reasonable to speculate that naked mole-rat longevity is likely not an isolated advantage but rather the result of sacrificing certain conventional physiological functions. However, female naked mole-rats demonstrate no decline in fertility for the vast majority of their long lifespan (Edrey et al., 2011), attributed to an exceptionally large ovarian reserve and postnatal oogenesis (Briño-Enríquez et al., 2023). Interestingly, their reproductive strategy is fundamentally reshaped, as the vast majority of colony members remain in a state of reproductive suppression throughout their lives. A study found higher plasma oxidative stress in breeders than non-breeders, indicating a potential trade-off (Jacobs et al., 2021). Although enhanced function in multiple organs has been identified, some “degenerations” exist, including visual function (Hetling et al., 2005) and thermoregulation (Vandewint et al., 2019). Understanding these potential trade-offs is not only an intriguing evolutionary biology question but also crucial for evaluating the risks of translating these mechanisms into humans. However, current experimental evidence regarding this trade-off is lacking. Establishing techniques such as genetic manipulation in the naked mole-rat is an important step towards systematically evaluating this phenotypic trade-off *in vivo*. If a trade-off does exist, whether these mechanisms can be separated from their associated costs



is another intriguing question. If the answer is yes, then anti-aging strategies translated from naked mole-rats to humans might circumvent the corresponding negative effects. Conversely, if these mechanisms are tightly coupled with specific physiological deficits, the potential risks of applying them to humans would be significantly increased and would require careful consideration.

Translational potential of naked mole-rat mechanisms

Can longevity mechanisms discovered in naked mole-rats finally translate into human anti-aging clinics? As a proof-of-concept, Zhang et al. successfully introduced the *nmrHAS2* gene into mice, demonstrating that it significantly reduced tumor incidence, extended both median and maximum lifespan, and improved multiple health span parameters, thereby laying a solid foundation for HMM-HA-based anti-aging interventions (Zhang et al., 2023). Furthermore, delphinidin, a natural plant compound found in fruits and vegetables that functions as a potent hyaluronidase inhibitor, has been reported to reduce migration and invasion behavior of cancer cells both *in vitro* and *in vivo*, confirming the potential of targeting hyaluronidases to reduce metastasis (Mcguire et al., 2024). Another example involves the four specific amino acid mutations at the C-terminus of the naked mole-rat cGAS protein. Introducing these four mutations into human cGAS reverses its inhibitory effect on HR repair. Furthermore, transgenic expression of naked mole-rat cGAS in fruit flies extends lifespan, and its overexpression in aged mice mitigates multi-organ aging phenotypes (Chen et al., 2025). However, naked mole-rat longevity is attributed to multiple mechanisms. Identifying additional translatable mechanisms and exploring combinatory intervention strategies are among the key future directions.

In summary, as a long-lived and disease-resistant rodent model, naked mole-rats are uniquely positioned to help us understand the biological basis of aging and longevity, inspiring the development of interventions. As discussed, they



decelerate aging by synergistically targeting multiple key nodes across the fourteen hallmarks. Notably, adaptations to some hallmarks have been extensively studied, while others remain less explored. Moreover, direct evidence linking their distinct manifestation and regulation of these hallmarks to lifespan extension or disease resistance is largely lacking. Nevertheless, this characteristic suggests that translating naked mole-rat longevity mechanisms to humans may require targeting multiple aspects, including genomic, epigenomic, metabolic, intercellular, and environmental factors, as targeting single pathways may have limited efficacy. Against the backdrop of global population aging, we anticipate that advanced experimental techniques and comprehensive studies on naked mole-rats, alongside complementary rodent models native to China, will ultimately pave the way for translating safe and effective interventions to human health.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.Z.: Writing - Original draft. Y.C.: Conceptualization, Funding acquisition, Writing - Revising & Editing. Z.M.: Conceptualization, Writing - Revising & Editing. All authors read and approved the final version of the manuscript.



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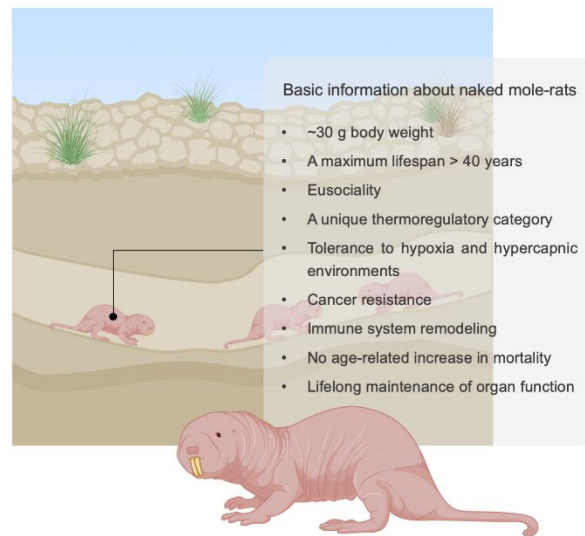


Figure 1. Basic information of naked mole-rats. Created with BioRender.com.

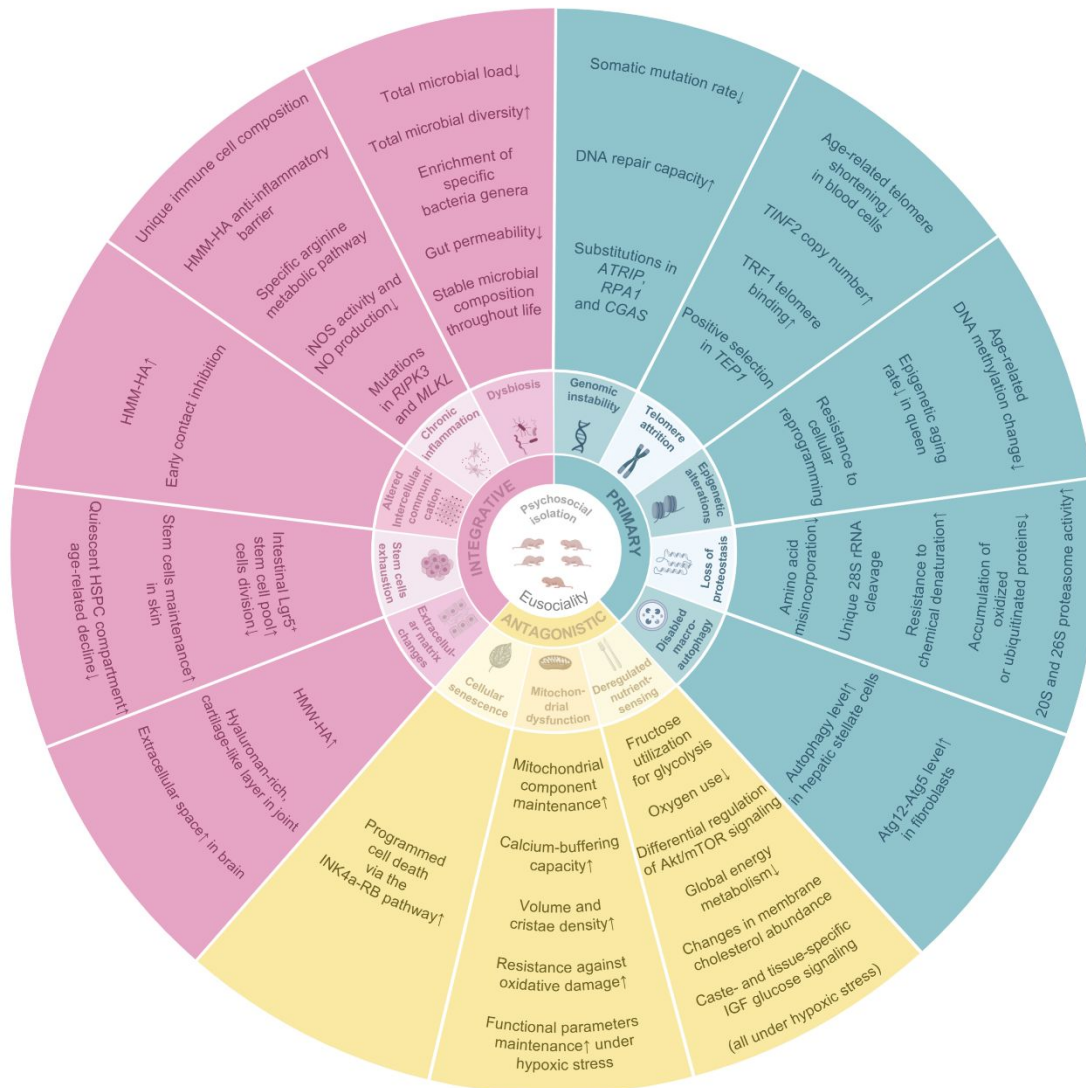


Figure 2. The figure illustrates the unique mechanisms by which naked mole-rats resist the primary, antagonistic, and integrative hallmarks of aging. Adapted from (Kroemer et al., 2025). Created with BioRender.com.

Table 1. A comparison of unique features in long-lived animals and short-lived animals

	Age-related changes in short-lived animals (e.g., mouse)	Resistance mechanisms in long-lived animals			References
		Naked mole-rat	Long-lived bats	Long-lived whales	
Genomic instability	DNA repair capacity↓	Substitutions in <i>ATRIP</i> , <i>RPA1</i> & <i>CGAS</i>	Positive selection in <i>ATM</i> & <i>TP53</i>	Substitution in <i>ERCC1</i> ; <i>PCNA</i> duplication; <i>CIRBP</i> expression↑	(Chen et al., 2025; Firsanov et al., 2025; Keane et al., 2015; Macrae et al., 2015a; Zhang et al., 2013; Zhou et al., 2020)
Telomere attrition	Telomere shortening and instability↑	<i>TINF2</i> duplication↑; TRF1 telomere binding↑; Positive selection in <i>TEP1</i>	Positive selection in <i>DKC1</i> & <i>TERT</i>	Insufficient evidence	(Augereau et al., 2021; Kim et al., 2011; Macrae et al., 2015b; Morgan et al., 2013; Tharmapalan and Wagner, 2024)
Epigenetic alterations	Fast change in DNA methylation	Slow DNA methylation change with age	Slow DNA methylation change with age	Insufficient evidence	(Kerepesi et al., 2022; Wilkinson et al., 2021)
Loss of proteostasis	Misfolded proteins↑; Protein aggregates↑	Unique 28S rRNA cleavage; 20S and 26S proteasome activity↑	Insufficient evidence	<i>PSMD4</i> & <i>UCHL3</i> duplications	(Keane et al., 2015; Pérez et al., 2009; Rodriguez et al., 2012)
Disabled macroautophagy	Autophagy level ↓	Atg12-Atg5 level↑	Age-related autophagy↑	<i>CREG1</i> expression↑	(Huang et al., 2019; Kim et al., 2020; Pride et al., 2015; Toren et al., 2020)
Deregulated nutrient-sensing	Insulin/IGF-1 signaling↑; mTORC1	Fructose utilization; Different	Substitutions in <i>IGF1R</i> & <i>GHR</i>	Substitution in <i>LAMTOR1</i>	(Al-Attar et al., 2020; Buffenstein

	pathway↑	Akt/mTOR regulation; Insulin/IGF1 pathway↓			and Craft, 2021; Guevara-Aguirre et al., 2011; Keane et al., 2015; López-Otín et al., 2013; Ma and Gladyshev, 2017; Mota-Martorell et al., 2020; Park et al., 2017; Seim et al., 2013)
Mitochondrial dysfunction	ROS production ↑; Mitochondrial integrity and biogenesis↓	Unique mitochondrial structure; ROS production↓and functional maintenance↑ under hypoxic stress	ROS production↓	Insufficient evidence	(Cheng et al., 2021; Cheng et al., 2024; Eaton et al., 2023; Munro et al., 2019; Vyssokikh et al., 2020)
Cellular senescence	Senescent cell generation↑; Senescent cell clearance↓	Programmed cell death via the INK4a-RB pathway	Stress-induced senescence↓	Insufficient evidence	(Athar et al., 2025; Kawamura et al., 2023; López-Otín et al., 2013; Wang et al., 2009)
Stem cells exhaustion	Stem cell quantity and function↓	Stable and functional stem cell pool	Insufficient evidence	Insufficient evidence	(Montazid et al., 2023; Savina et al., 2022)
Altered intercellular communication	Neurohormonal signaling deregulation	HMM-HA-triggered early contact inhibition	Insufficient evidence	Insufficient evidence	(Yaghmaie et al., 2010; Zhao et al., 2023)
Chronic inflammation	Inflammasome and pro-inflammatory pathways↑	Unique immune cell composition; Substitutions in <i>RIPK3</i> & <i>MLKL</i> ; iNOS activity &	NLRP3 inflammasome activity↓; TNF signaling↓	SASP factor induction↓	(Ahn et al., 2019; Banerjee et al., 2017; Firsanov et al., 2025;

		NO production↓			Gorshkova et al., 2025; Oka et al., 2022; Talley et al., 2024; Thevaranjan et al., 2017; Xie et al., 2018; Zhang et al., 2023)
Dysbiosis	Microbial diversity↓	Enrichment of specific bacteria genera; Gut permeability↓; Stable microbial composition throughout life	Stable microbial composition between adults and juveniles	Insufficient evidence	(Aguilera-Lizarraga et al., 2024; Cong et al., 2018; Hughes et al., 2018; Jiao et al., 2025; Tanes et al., 2026)
Extracellular matrix changes	Age-related ECM stiffening, with elasticity/compliance↓	HMM-HA↑	Insufficient evidence	Insufficient evidence	(Wood et al., 2014; Zhang et al., 2023)
Psychosocial isolation	Progressive (self-)exclusion from societal activities	Eusociality	Insufficient evidence	Sociality in certain species	(Blecher et al., 2020; Boyer et al., 2019; Collinge et al., 2025; Kerth and J, 2012; Mooney et al., 2014; Tietge et al., 2025; Würsig and Koski, 2021)



探秘裸鼯鼠的长寿机制

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摘要

裸鼯鼠（*Heterocephalus glaber*）以极长的寿命和强大的抗癌能力而闻名，是揭示健康衰老新机制的重要模式生物。目前已有 14 项衰老标志被提出，用于描述生物衰老的核心特征；然而，直接增强这些标志是否有助于延长寿命仍不清楚。本文总结了目前对裸鼯鼠中这些衰老标志差异性调控的认识，并探讨它们在裸鼯鼠超常寿命中可能发挥的作用。同时，我们还讨论了当前裸鼯鼠研究的局限性，并展望未来方向，以更好地阐明裸鼯鼠长寿的机制，进而为开发促进人类健康衰老的策略提供依据。

关键词：裸鼯鼠；长寿；衰老；比较生物学；干预

