OPEN ACCESS Freely available online

Journal of Aging Science

Review Article

Healthy Aging Biology, Powerful Insight from the Long-Lived Naked Mole-Rat

Frédéric Saldmann[1,2], Mélanie Viltard[1*], Christine Leroy[3,4], Patrice Codogno[4], Gérard Friedlander[3,4]

[1]Fondation Pour La Recherche En Physiologie, Brussels, Belgium; [2]Service de Médecine Vasculaire, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France; [3]Department of Medicine, University of Paris, Paris, France; [4]INSERM U1151 CNRS UMR8253 Institut Necker-Enfants Malades (INEM), Paris, France

ABSTRACT

The naked mole-rat, Heterocephalus glaber, is the longest-lived rodent known with a lifespan in captivity >30 years, 10 times longer than mice, a comparable size rodent. In addition to a particularly long life, it exhibits exceptional resistance to many age-related diseases: cancer, cardiovascular, neurodegenerative, and metabolic diseases. It resists many forms of stress: hypoxia, oxidative stress, and strikingly maintains adequate body composition, fertility, bone quality, and mineral density throughout their long life. The naked mole-rat is a non-traditional animal model that defies the law governing the processes of aging and mortality and provides a powerful tool for the discovery of endogenous molecular anti-aging pathways. Over the past decades, much possible resistance and anti-aging mechanisms have been discovered. These include exclusive physiological mechanisms involved in cellular senescence and its clearance, telomere attrition, genome and proteome stability, stress resistance and metabolism flexibility... This review aims to summarize the many identified anti-aging strategies of the naked mole-rat to better grasp some of the main theories that have been generated. However, many of these theories remain to be fully investigated and confirmed to further understand the complex biology of the naked mole-rat.

Keywords: Naked mole rat; Aging; Cancer; Physiology; Senescence

INTRODUCTION

Aging is defined by a progressive, yet physiological decline of the biological functions of an organism that leads to senescence and ultimately death. Aging occurs in every cell, tissue, and organ of nearly every living organism. Interestingly and unlike most, one mammal does not seem to age: the naked mole-rat, Heterocephalus glaber. Discovered in 1842 by the naturalist Eduard Rüppell, and native of East Africa, the naked mole-rat is a small poikilothermic rodent that lives strictly underground and is one of the only mammals known to exhibit eusociality. The naked mole-rat is the longest living rodent that can live up to 37 years in captivity, and more than 17 years in the wild [1,2], without facing any increased age-related hazard of mortality, challenging Gompertz's mortality law [3]. Their subterranean environment in extremely dry regions of Africa is a challenge: food scarcity, low amount of oxygen, complete darkness, poor gas exchanges, harmful chemicals and soil pollutants.

Despite an awfully hostile environment, naked mole-rat appears remarkably resistant to a variety of age-related diseases, such as cancers, neurodegenerative, cardiovascular, or metabolic diseases. In addition, naked mole-rat, unlike most mammals, do not show any typical aging signs such as changes in basal metabolism, changes in body composition or bone density, reduction of fertility, until very late in their life (>31 years), suggesting a delay in the rate of aging [4]. This review aims to summarize and classify the numerous studies on the different endogenous anti-aging strategies of the naked mole-rat, as an overview of the current research progress.

LITERATURE REVIEW

Simply avoid cellular senescence accumulation

Cellular senescence is generally defined as a permanent cell cycle arrest accompanied by metabolic alterations. It is triggered by a

Correspondence to: Dr. Mélanie Viltard, Fondation Pour La Recherche En Physiologie, Brussels, Belgium, E-mail: mviltard@fondationphysiologie.org

Received: July 30, 2021; **Accepted**: August 13, 2021; **Published**: August 20, 2021

Citation: Saldmann F, Viltard M, Leroy C, Codogno P, Friedlander G (2021) Healthy Aging Biology, Powerful Insight From the Long-Lived Naked Mole-Rat. J Aging Sci. 9: 258.

variety of stresses, including oxidative stress, telomere shortening, genotoxic stress, inflammation, DNA damages... By stopping the proliferation of damaged cells, cellular senescence is a powerful anti-cancer strategy, but on the other hand, the excessive accumulation of senescent cells during aging can also contribute to the alteration of tissue repair and regeneration leading to many age-related diseases. Clearance of senescent cells can reverse the age-related decline and increase lifespan in transgenic mice [5]. Currently, research has been focused on senolytics, drugs that can clear senescent cells from the organism with a clear aim to prevent age-related phenotypes [6].

A study has shown that naked mole-rat cells have the potential to become senescent and can undergo several types of senescence, such as developmentally programmed senescence, stress-induced premature senescence, and oncogene-induced senescence [7]. However, naked mole-rat induction of senescence required a higher dose of DNA damage compared with the mouse.

Up until recently, it was still unclear whether senescent cells accumulate in the naked mole-rat body during aging. Indeed, a recent study suggests that naked mole-rat could be resistant to senescent cell accumulation during aging due to activation of Senescent Cell Death (SCD), causing spontaneous death of senescent cells [8]. These results suggest that senescent naked mole-rat cells are preferentially eliminated by apoptosis rather than by the immune system. In addition, a recent study showed that the naked mole-rat immune system lacks the canonical natural killer cells, an important element in the recognition and removal of senescent cells [9,10]. In addition, a recent study has demonstrated that naked mole-rat skin fibroblasts were protected from cellular senescence through an enriched β-catenin activity inducing the accumulation of cholesterol-enriched lipid droplets [11]. These observations were consistent with previous results showing the role of cholesterol in delaying senescence in mice [12].

The telomere length/telomerase system with its beneficial/detrimental duality is intricately related to cellular senescence and cancer. A recent study showed that, in naked mole-rat, telomere length does not decrease with age suggesting evolution toward increased telomere maintenance [13,14]. A study comparing telomerase genes and their promoter regions between naked mole-rat and different organisms showed specific polymorphisms in the functional domains that could cause increased telomerase expression, thus reducing telomere attrition [15]. In addition, another study showed that the naked mole-rat presented an extra copy of the gene TINF2, a protector of telomere integrity [16]. Finally, another study showed that a gain-of-function mutation of naked mole-rat TRF1 enhanced telomeric and metabolic functions specifically under conditions of hypoxia [17].

These results suggest that one powerful anti-aging mechanism of the naked mole-rat is its ability to delay cellular senescence and prevent its accumulation by triggering senescent cell death. However, more research should address the exact mechanisms by which the naked mole-rat prevents the accumulation of senescent cells.

Natural mechanisms to resist stress and cancer

Naturally, the naked mole-rat seems resistant to many age-related pathologies, and in particular cancer. Indeed, after almost 29 years in captivity, researchers have not observed any incidence of cancer [18]. Only recently, a small number of cancerous lesions have been reported in zoo-raised naked mole-rats [19-21]. Although these small numbers are probably underestimated, as more cases could be unreported, these statistics support the idea that the naked mole-rat show extremely high resistance to cancer.

An important naked mole-rat anti-cancer mechanism is early contact inhibition triggered by a very High-Molecular-Mass Hyaluronan (vHMMH) produced by a unique Hyaluronan Synthase 2 (HAS2), enzyme causing the increase in the size of the naked mole-rat hyaluronan [22-24]. Degrading vHMMH abrogated the early contact inhibition and renders naked mole-rat cells susceptible to malignant transformation [23]. In addition, naked mole-rat high-molecular-mass hyaluronan has enhanced cytoprotective properties in a p53-dependent manner, especially against oxidative stress [25]. However, vHMMH might not be the only anti-cancer mechanism in the naked mole- rat and the precise mechanisms remain elusive.

DNA damages occur on a daily basis as a result of intracellular and extracellular stresses. If left unrepaired, these damages result in genomic mutations that can contribute to the decline in organ functions and multiply the risk of cancer [26]. Evidence showed that naked mole-rat repair DNA damages more efficiently than the short-lived mouse, with more efficient base and nucleotide excision repair systems [27,28]. In addition, the expression of genes encoding for DNA repair enzymes and most DNA repair signaling pathways are significantly up-regulated in the naked mole-rat as compared to the short-lived mouse [29]. PARylation activity, an early sensor and mediator of DNA damage repair, is significantly higher in the naked mole-rat as compared to mice [28]. Finally, a study showed that SIRT6 could be responsible for a more efficient DNA repair in long-lived species, including the naked mole-rat [30]. Overall, these results suggest a more efficient DNA repair in naked mole-rats but yet to confirm the exact mechanisms. As a result, several studies suggest that naked mole-rats have a genome persistently stable most of their life [16,31,32]. In addition, naked mole-rat exhibits not only a stable genome but a stable epigenome as well [33].

Another view is that aging can result from a decline in protein quality-control systems that lead to the accumulation of damaged proteins and loss of proteostasis [34]. Indeed, the accumulation of misfolded proteins is one of the root causes for many age-related diseases such as degenerative and neurodegenerative diseases [35]. In the naked mole-rats, evidence suggests the existence of strong mechanisms preventing proteostasis loss. Indeed, naked mole-rats are more resistant to protein unfolding and more generally can maintain better protein structure, integrity, and function during aging than mice [36]. In addition, naked mole-rat translates protein more accurately than the mouse [37]. Naked mole-rat shows high levels of proteasome activity, possibly reflecting superior protein turnover, in response to oxidative stress [38]. Indeed, naked mole-rat exhibits high levels of oxidative stress, particularly

protein carbonylation, DNA damages, and lipid peroxidation even at a young age [39-41]. One probable link could be that two cytoprotective proteins Nrf2 and NFκB, both triggered by oxidative stress and highly expressed in the naked mole-rat, could be key modulators of naked mole-rat proteasome activity. In addition to the proteasome, autophagy also plays a crucial role in proteostasis by eliminating potentially toxic damaged proteins inside cells. A study suggests that, unlike mice, autophagic responses are higher in naked mole-rat tissues throughout their life, as a strategy to maintain proteostasis by removing damaged proteins and lowering the overall metabolic demand of the cells [42-45]. In addition, a recent proteomic analysis showed that the detoxifying pathways were increased in the naked mole-rat, suggesting that it might contribute to its higher stress resistance [46,47].

Phylogenetic analysis from 65 different mammals reveals that the naked mole-rat possesses 17 copies of the Phosphatase and Tensin Pseudogene (PTENps), suggesting a unique regulation of tumor suppressor genes in the naked mole-rat [48]. In addition, p53, another major tumor suppressor, is also uniquely regulated. p53 is highly stable in naked mole-rat with an extremely long half-life and displays a high basal level of nuclear localization [49]. The role of this nuclear p53 in the absence of DNA damage and how naked mole-rat avoids the deleterious effect of p53 constant activation is still enigmatic and future studies investigating in detail the tumor suppressor regulation are necessary.

Powerful metabolism adaptations

For many years, researchers have been investigating the relationship between the endocrine system and the aging processes. The endocrine system plays a major role in the regulation of cellular interactions, cellular growth, and metabolism and is an established player influencing aging.

The Growth Hormone (GH)/Insulin-Like Growth Factor-1 (IGF-1)/insulin system plays an important role in the control of the lifespan and aging [50]. And many studies strongly suggest that this signaling pathway plays a major role in the pathogenesis of several age-related diseases including neurodegeneration, many cancers, metabolic and cardiovascular diseases [50-52]. Several studies suggest that GH/IGF-1/insulin pathway might be down-regulated in the naked mole-rat. Indeed, transcriptome analysis of the naked mole-rat liver showed decreased expression of genes involved in the insulin/IGF-1 pathway compared to mice [31]. In addition, a previous study showed an untraceable level of circulating IGF-1 (<12ng/ml) in naked mole-rat blood [18]. Interestingly, in the African mole-rats branch, IGF-1 was identified as a positively selected gene and its expression is down-regulated during aging in the naked mole-rat [53]. In addition, another study shows slight variations in the IGF signaling pathway when comparing naked mole-rats, humans, and mice, including the down-regulation of IGF-1 during naked mole-rat aging [54]. These results suggest that small variation from a fine-tuned IGF-1 system could have a major impact on longevity in the naked mole-rat, and more studies are warranted.

Caloric Restriction (CR) is a highly conserved mechanism delaying aging and age-related diseases resulting in lifespan extension in numerous species [55]. In recent years, researchers have demonstrated that many of the effects of caloric restriction on aging and longevity have been linked to the reduced intake of certain specific essential amino acids (EAAs). Among those, two EAAs have been extensively investigated: low tryptophan [56,57] and methionine [58-60] intake have been shown to increase lifespan. Interestingly, both levels of tryptophan and methionine were very low in the naked mole-rat plasma as compared to mice [61,62]. The beneficial effects of CR or amino acid restriction is mediated through modulation of specific signaling pathways including GH/IGF-1, NRF2, mTOR, and FOXO [63-65]. Many of these signaling pathways are known to be modulated in the naked mole-rat and it could be interesting to analyze in more detail the complex mechanisms involved. In addition, a long-term reduction in dietary branched-chain amino acids (valine, leucine, and isoleucine) can increase lifespan in mice in a sex-dependent manner [66], while its supplementation in old animals could be beneficial [67]. In naked mole-rat, metabolites involved in the leucine, isoleucine, and valine metabolism were strongly down-regulated when compared to mice [62]. Interestingly, the small intestine is very short in the naked mole-rat, compared to the mice [68]. As the small intestine is the main organ responsible for the catabolism of dietary amino acids, this phenotype could explain the low levels of certain amino acids in the naked mole-rat. Conversely, supplementation in certain amino acids increased lifespan, for example, an increase in glutamate results in lifespan extension in yeast and worm [69,70]. Levels of glutamate are significantly higher in the naked mole-rat [62,71,72]. As an essential component of glutathione synthesis, glutamate could be an important mediator of oxidative stress occurring during aging. All these results strongly suggest that the balance of nutrients in the naked mole-rat diet might be an important factor for healthy aging.

It is well known that proteins involved in zinc metabolism are altered during aging, leading to alteration in zinc homeostasis and causing multiple human diseases such as neurodegenerative diseases [73-75]. Interestingly, the naked mole-rat has very high levels of aging-related Alpha2-Macroglobulin (A2M) in blood and liver compared to humans and mice [76,77]. A2M is found both in the blood and tissues and is the main transporter of zinc. A recent study has demonstrated the anti-cancer properties of A2M, through interferences with PTEN and its upstream modulator miR-21 and AKT signaling pathways [78]. In the naked mole-rat, the high expression of A2M could help maintain zinc homeostasis through life and have a role in their extreme resistance to cancer.

The naked mole-rat lives in an extremely challenging environment and as a result, has developed an extreme metabolic plasticity allowing it to quickly respond to specific needs. As an example, the naturally hypoxia-tolerant naked mole-rat is capable of metabolic reprogramming under hypoxic insult. Indeed, naked mole-rat is able to switch from glucose to fructose-driven glycolysis in the brain [79] and to use glycogen as a source of ATP in the heart [72].

DISCUSSION

Stay young and cool

Pedomorphy or neoteny is the ability to maintain juvenile characteristics well into adulthood [80]. The maintenance of processes essential for the early development of life could be linked to both prolonged healthspan and prolonged lifespan. Indeed, these juvenile traits could provide more efficient biological functions while also facilitating better tolerance of stressors and metabolic flexibility. Pedomorphy has been observed in many different species including insects [81], birds [82,83], amphibians [84-87], reptiles [88], humans [89-92], mice and naked mole-rats [90,92,93] and may contribute to prolonged longevity. Many organs and cellular systems, in the naked mole-rat, display pedomorphic traits including the heart, the lung, the brain, the reproductive organs, the immune system, that theoretically could lead to its extreme longevity.

Another interesting example is the influence of body temperature on aging and longevity. Temperature is a key environmental factor that dramatically affects the lifespan of many organisms. A century ago, a study showed that longevity in Drosophila was temperature dependent [94]. More recently, several studies showed, in fish models, that a 3-5°C decrease in water temperature prolongs lifespan, delayed the onset of cognitive deficits and senescence [95-97]. Similarly, lowering the temperature increases longevity of the rotifer [98]. The effect of lowering temperature on longevity, while more difficult to study, are also observed in homeotherms. Indeed, using a transgenic mouse model, a study demonstrated that a modest reduction in core body temperature increases lifespan [99].

Another way to lower body temperature in homeotherms is calorie restriction. Numerous studies show that calorie restriction leads to a drop in body temperature by 1 to 2°C, in part due to a slower metabolism [95,100,101]. Calorie restriction leads to an extended lifespan in many species including humans, and this prolongation of life may be in part due to lower body temperature [102]. In men, a 25% calorie restriction for 6 months significantly decreased body temperature and is associated with less DNA damage, a known marker of aging [103].

Naked mole rats are also unique among mammals as they are imperfect homeotherms and as such have naturally a much lower body temperature than most other mammals at 32-33°C (compared to 37-38°C for most other mammals) [104,105]. One study suggests the important role of temperature in the exceptional longevity of the naked mole rat [105].

CONCLUSION

In the past decade, scientific advances have suggested that aging could be a reversible and flexible process. Undoubtedly, the naked mole-rat represents a model of successful aging in mammals and holds the keys to reverse aging. In the recent years, studies have unraveled several anti-aging mechanisms in the naked mole-rat, but more research is greatly needed to gain further insights into these mechanisms or a combination of these mechanisms on the naked mole-rat longevity, and to better clarify their applicability to humans. Finding the molecular or metabolic pathways capable of manipulating human aging would bring unprecedented benefits to human health and create new opportunities for anti-aging therapy. The naked mole-rat, an exceptional animal whose aging is negligible, appears to be the ideal model for understanding how to slow down human aging.

CONFLICTS OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Buffenstein R, Ruby JG. Opportunities for new insight into aging from the naked mole-rat and other non-traditional models. Nat Aging. 2021;1: 3-4.
2. Hochberg ME, Noble RJ, Braude S. A Hypothesis to Explain Cancers in Confined Colonies of Naked Mole Rats. BioRxiv. 2016.
3. Ruby JG, Smith M, Buffenstein R. Naked mole-rat mortality rates defy gompertzian laws by not increasing with age. Elife. 2018;7: e31157.
4. Buffenstein R. Negligible senescence in the longest living rodent, the naked mole-rat: Insights from a successfully aging species. J Comp Physiol B. 2008;178(4): 439-445.
5. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan. Nature. 530(7589): 184-189.
6. Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, giorgadze N, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell. 2015;14(4): 644-658.
7. Zhao Y, Tyshkovskiy A, Muñoz-Espín D, Tian X, Serrano M, Demgalhaes JP, et al. Naked mole rats can undergo developmental, oncogene-induced and DNA damage-induced cellular senescence. Proc Natl Acad Sci U S A. 2018;115(8): 1801-1806.
8. Kawamura Y, Oka K, Takamori M, Sugiura Y, Oiwa Y, Fujioka S, et al. Senescent cell death as an aging resistance mechanism in naked mole-rat. BioRxiv. 2020.
9. Hilton HG, Rubinstein ND, Janki P, Ireland AT, Bernstein N, Fong NL, et al. Single-cell transcriptomics of the naked molerat reveals unexpected features of mammalian immunity. PLoS Biol. 2019;11.
10. Antonangeli F, Zingoni A, Soriani A, Santoni A. Senescent cells: Living or dying is a matter of NK cells. J Leukoc Biol. 2019;105(6): 1275-1283.
11. Chee WY, Kurahashi Y, Kim J, Miura K, Okuzaki D, Ishitani T, et al. β-catenin-promoted cholesterol metabolism protects against cellular senescence in naked mole-rat cells. Commun Biol. 2021;4: 357.
12. Zhang M, Du Y, Lu R, Shu Y, Zhao W, Li Z, et al. Cholesterol Retards Senescence in Bone Marrow Mesenchymal Stem Cells by Modulating Autophagy and ROS/p53/p21 Cip1/Waf1 Pathway. Oxid Med Cell Longev. 2016;2016: 1-10.
13. Shekhidem HA, Sharvit L, Leman E, Manov I, Roichman A, Holtze S, et al. Telomeres and longevity: A cause or an effect? Int J Mol Sci. 2019;20(13): 3233.
14. Leonida SRL, Bennett NC, Leitch AR, Faulkes CG. Patterns of telomere length with age in African mole-rats: New insights from quantitative fluorescence in situ hybridisation (qFISH). PeerJ. 2020;8: e10498.
15. Evfratov SA, Smekalova EM, Golovin AV, Logvina AV, Zvereva MI, Dontsova OA. Structural features of the telomerase RNA gene in the naked mole rat Heterocephalus glaber. Acta Naturae 21. 2014;6(4): 41-47.

16. MacRae SL, Zhang Q, Lemetre C, Seim I, Calder RB, Hoeijmakers J, et al. Comparative analysis of genome maintenance genes in naked mole rat, mouse, and human. Aging Cell. 2015;14(2): 288-291.
17. Augereau A, Mariotti M, Pousse M, Filipponi D, Libert F, Beck B, et al. Naked mole rat TRF1 safeguards glycolytic capacity and telomere replication under low oxygen. Sci Adv. 2021;7(8): eabe0174.
18. Buffenstein R. The naked mole-rat: A new long-living model for human aging research. J Gerontol - Ser A Biol Sci Med Sci. 2005;60(11): 1369-1377.
19. Delaney MA, Ward JM, Walsh TF, Chinnadurai SK, Kerns K, Kinsel K, et al. Initial Case Reports of Cancer in Naked Mole-rats (Heterocephalus glaber). Vet Pathol. 2016;53(3): 691-696.
20. Taylor KR, Milone NA, Rodriguez CE. Four Cases of Spontaneous Neoplasia in the Naked Mole-Rat (Heterocephalus glaber), A Putative Cancer-Resistant Species. Journals Gerontol Ser A Biol Sci Med Sci. 2017;72(1): 38-43.
21. Cole JE, Steeil JC, Sarro SJ, Kerns KL, Cartoceti A. Chordoma of the sacrum of an adult naked mole-rat. J Vet Diagn Invest. 2020;32(1): 132-135.
22. Seluanov A, Hine C, Azpurua J, Feigenson M, Bozzella M, Mao Z, et al. Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. Proc Natl Acad Sci U SA. 2009;106(46): 19352-19357.
23. Tian X, Azpurua J, Hine C, Vaidya A, Myakishev-Rempel M, Ablaeva J, et al. High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. Nature. 2013;499(7458): 346-349.
24. Faulkes CG, Davies KTJ, Rossiter SJ, Bennett NC. Molecular evolution of the hyaluronan synthase 2 gene in mammals: implications for adaptations to the subterranean niche and cancer resistance. Biol Lett. 2015;11.
25. Takasugi M, Firsanov D, Tombline G, Ning H, Ablaeva J, Seluanov A, et al. Naked mole-rat very-high-molecular-mass hyaluronan exhibits superior cytoprotective properties. Nat Commun. 2020;11: 2376.
26. Hoeijmakers JHJ. DNA Damage, Aging, and Cancer. N Engl J Med. 2009;361(15): 1475-1485.
27. Evdokimov A, Kutuzov M, Petruseva I, Lukjanchikova N, Kashina E, Kolova E, et al. Naked mole rat cells display more efficient excision repair than mouse cells. Aging (Albany NY). 2018;10(6): 1454-1473.
28. Kosova AA, Kutuzov MM, Evdokimov AN, Ilina ES, Belousova EA, Romanenko SA, et al. Poly(ADP-ribosyl)ation and DNA repair synthesis in the extracts of naked mole rat, mouse, and human cells. Aging (Albany NY). 2019;11(9): 2852-2873.
29. MacRae SL, Croken MMK, Calder RB, Aliper A, Milholland B, White RR, et al. DNA repair in species with extreme lifespan differences. Aging (Albany NY). 2015;7(12): 1171-1181.
30. Tian X, Firsanov D, Zhang Z, Cheng Y, Luo L, Tombline G, et al. SIRT6 Is Responsible for More Efficient DNA Double-Strand Break Repair in Long-Lived Species. Cell. 2019;177(3): 622-638.
31. Kim EB, Fang X, Fushan AA, Huang Z, Lobanov AV, Han L, et al. Genome sequencing reveals insights into physiology and longevity of the naked mole rat. Nature. 2011;12(479): 223-227.
32. Petruseva IO, Evdokimov AN, Lavrik OI. Genome stability maintenance in naked mole-rat. Acta Naturae. 2017;9(4): 31-41.
33. Tan L, Ke Z, Tombline G, Macoretta N, Hayes K, Tian X, et al. Naked Mole Rat Cells Have a Stable Epigenome that Resists iPSC Reprogramming. Stem Cell Reports. 2017;9(5): 1721-1734.
34. Santra M, Dill KA, De Graff AMR. Proteostasis collapse is a driver of cell aging and death. Proc Natl Acad Sci U S A. 2019;116(44): 22173-22178.
35. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci. 2018;21(10): 1332-1340.
36. Perez VI, Buffenstein R, Masamsetti V, Leonard S, Salmon AB, Mele J, et al. Protein stability and resistance to oxidative stress are determinants of longevity in the longest-living rodent, the naked mole-rat. Proc Natl Acad Sci U S A. 2009;106(9): 3059-3064.
37. Azpurua J, Ke Z, Chen IX, Zhang Q, Ermolenko DN, Zhang ZD, et al. Naked mole-rat has increased translational fidelity compared with the mouse, as well as a unique 28S ribosomal RNA cleavage. Proc Natl Acad Sci U S A. 2013;110(43): 17350-17355.
38. Rodriguez KA, Edrey YH, Osmulski P, Gaczynska M, Buffenstein R. Altered composition of liver proteasome assemblies contributes to enhanced proteasome activity in the exceptionally long-lived naked mole-rat. PLoS One. 2012;7(5): e35890.
39. Saldmann F, Viltard M, Leroy C, Friedlander G. The naked mole rat: A unique example of positive oxidative stress. Oxid Med Cell Longev. 2019;2019: 7.
40. Lewis KN, Andziak B, Yang T, Buffenstein R. The Naked Mole-Rat Response to Oxidative Stress: Just Deal with It. Antioxid Redox Signal. 2013;19(12): 1388-1399.
41. Andziak B, O'Connor TP, Qi W, Dewaal EM, Pierce A, Chaudhuri AR, et al. High oxidative damage levels in the longest-living rodent, the naked mole-rat. Aging Cell. 2006;5(6): 463-471.
42. Zhao S, Lin L, Kan G, Xu C, Tang Q, Yu C, et al. High autophagy in the naked mole rat may play a significant role in maintaining good health. Cell Physiol Biochem. 2014;33: 321-332.
43. Zhao S, Luo H, Kan G, Zhao Y, Lin L,Tang Q, et al. The protective role of autophagy in heterocephalus glaber hepatic stellate cells exposed to h2o2 or nutritional stress. Cell Physiol Biochem. 2014;34: 463-473.
44. Kim J, Chee W-Y, Yabuta N, Kajiwara K, Nada S, et al. Atg5-mediated autophagy controls apoptosis/anoikis via p53/Rb pathway in naked mole-rat fibroblasts. Biochem Biophys Res Commun. 2020;28(1): 146-153.
45. Triplett JC, Tramutola A, Swomley A, Kirk J, Grimes K, Lewis K, et al. Age-related changes in the proteostasis network in the brain of the naked mole-rat: Implications promoting healthy longevity. Biochim Biophys Acta. 2015;1852(10): 2213-2224.
46. Heinze I, Bens M, Calzia E, Holtze S, Dakhovnik O, Sahm A, et al. Species comparison of liver proteomes reveals links to naked mole-rat longevity and human aging. BMC Biol. 2018;16(1): 82.
47. Lewis KN, Mele J, Hornsby PJ, Buffenstein R. Stress resistance in the naked mole-rat: The bare essentials - A mini-review. Gerontology. 2012;58(5): 453-462.
48. Tang J, Ning R, Zeng B, Li Y. Molecular evolution of PTEN pseudogenes in mammals. PLoS One. 2016;11(12): e0167851.
49. Deuker MM, Lewis KN, Ingaramo M, Kimmel J, Buffenstein R, Settleman J. Unprovoked Stabilization and Nuclear Accumulation of the Naked Mole-Rat p53 Protein. Sci Rep. 2020;10(1): 6966.
50. Heemst DV. Insulin, IGF-1 and longevity. Aging Dis. 2010;1(2): 147-157.
51. Cohen E, Dillin A. The insulin paradox: Aging, proteotoxicity and neurodegeneration. Nat Rev Neurosci. 2008;9(10): 759-767.
52. Lee WS, Kim J. Insulin-like growth factor-1 signaling in cardiac aging. Biochim Biophys Acta - Mol Basis Dis. 2018;1864(5): 1931-1938.
53. Sahm A, Bens M, Szafranski K, Holtze S, Groth M, Gorlach M, et al. Long-lived rodents reveal signatures of positive selection in genes associated with lifespan. PLoS Genet. 2018;14(3): e1007272.
54. Brohus M, Gorbunova V, Faulkes CG, Overgaard MT, Conover CA. The insulin-like growth factor system in the long-lived naked mole-rat. PLoS One. 2015;10(12): e0145587.
55. Fontana L, Partridge L. Promoting health and longevity through diet: From model organisms to humans. Cell. 2015;26(161): 106-118.
56. Segall P. Long term tryptophan restriction and aging in the rat. Aktuelle Gerontol. 1977;7(10): 535-538.

57. Sidransky H. Dietary tryptophan and aging. Amino Acids. 1997;13(2): 91-103.

58. Orentreich N, Matias JR, DeFelice A, Zimmerman JA. Low methionine ingestion by rats extends life span. J Nutr. 1993;123(2): 269-274.

59. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. Aging Cell. 2005;4(3): 119-125.

60. Mota-Martorell N, Jové M, Berdún R, Pamplona R. Plasma methionine metabolic profile is associated with longevity in mammals. Commun Biol. 2021;4(1): 725.

61. Viltard M, Durand S, Pérez-Lanzón M, Aprahamian F, Lefevre D, Leroy C, et al. The metabolomic signature of extreme longevity: Naked mole rats versus mice. Aging (Albany NY). 2019;11(14): 4783-4800.

62. Lewis KN, Rubinstein ND, Buffenstein R. A window into extreme longevity; the circulating metabolomic signature of the naked mole-rat, a mammal that shows negligible senescence. GeroScience. 2018;40(2): 105-121.

63. Pearson KJ, Lewis KN, Price NL, Chang JW, Perez E, et al. Nrf2 mediates cancer protection but not prolongevity induced by caloric restriction. Proc Natl Acad Sci U S A 7. 2018;105(7): 2325-2330.

64. Fontana L, Klein S, Holloszy JO. Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. Age (Omaha). 2010;32(1): 97-108.

65. Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci. 2010;31(2): 89-98.

66. Richardson NE, Konon EN, Schuster HS, Mitchell AT, Boyle C, Rodgers AC, et al. Lifelong restriction of dietary branched-chain amino acids has sex-specific benefits for frailty and life span in mice. Nat Aging. 2021;1(1): 73-86.

67. Valerio A, Antona GD, Nisoli E. Branched-chain amino acids, mitochondrial biogenesis, and healthspan: An evolutionary perspective. Aging (Albany NY). 2011;3(5): 464-478.

68. Buffenstein R, Park T, Hanes M, Artwohl JE. Naked Mole Rat. In: The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. 2012: 1055-1074.

69. Wu Z, Song L, Liu SQ, Huang D. Independent and additive effects of glutamic acid and methionine on yeast longevity. PLoS One. 2013;8(11): e79319.

70. Edwards C, Canfield J, Copes N, Brito A, Rehan M, et al. Mechanisms of amino acid-mediated lifespan extension in Caenorhabditis elegans. BMC Genet. 2015;16(1): 8.

71. Viltard M, Durand S, Pérez-Lanzón M, Aprahamian F, Lefevre D, Leroy F, et al. The metabolomic signature of extreme longevity: naked mole rats versus mice. Aging (Albany NY). 2019;11(14): 4783-4800.

72. Faulkes CG, Eykyn TR, Aksentijevic D. Cardiac metabolomic profile of the naked mole-rat—glycogen to the rescue. Biol Lett. 2019;15(11): 2019070.

73. Mocchegiani E, Costarelli L, Giacconi R, Cipriano C, Muti E, Rink L, et al. Zinc Homeostasis in Aging: Two Elusive Faces of the Same "Metal." Rejuvenation Res. 2006;9(2): 351-354.

74. Fabris N, Mocchegiani E. Zinc, human diseases and aging. Aging (Milano). 1995;7(2): 77-93.

75. Birkenmeier G, Müller R, Huse K, Forberg J, Gläser C, Hedrich H, et al. Human α2-macroglobulin: genotype–phenotype relation. Exp Neurol. 2003;184(1): 153-161.

76. Yu C, Li Y, Holmes A, Szafranski K, Faulkes CG, Coen CW, et al. RNA sequencing reveals differential expression of mitochondrial and oxidation reduction genes in the long-lived naked mole-rat when compared to mice. PLoS One. 2011;6(11): e26729.

77. Thieme R, Kurz S, Kolb M, Debebe T, Holtze S, Morhart M, et al. Analysis of alpha-2 macroglobulin from the long-lived and cancer-resistant naked mole-rat and human plasma. PLoS One. 2015;10(6): e0130470.

78. Kurz S, Thieme R, Amberg R, Groth M, Jahnke HG, Pieroh P, et al. The anti-tumorigenic activity of A2M—A lesson from the naked mole-rat. PLoS One. 2017;12(12): e0189514.

79. Park TJ, Reznick J, Peterson BL, Blass G, Omerbašić D, Bennett NC, et al. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science. 2017;356(6335): 307-311.

80. Gould S. Ontogeny and Phylogeny. 1985.

81. Mcmahon DP, Hayward A. Why grow up? A perspective on insect strategies to avoid metamorphosis. Ecol Entomol. 2016;41(5): 505-515.

82. Foster MS. Delayed maturation, neoteny, and social system differences in two manakins of the genus chiroxiphia. Evolution. 1987;41(3): 547-558.

83. Dawson A. Neoteny and the thyroid in ratites. Rev Reprod. 1996;1(2): 78-81.

84. De Groef B, Grommen SVH, Darras VM. Forever young: Endocrinology of paedomorphosis in the Mexican axolotl (Ambystoma mexicanum). Gen Comp Endocrinol. 2018;266: 194-201.

85. Filippi E, Gargini V, Brancaleoni M, Felici P. First observation of partial neoteny in Salamandrina perspicillata. Nat Hist Sci. 2020;7(2).

86. Swingle WW. Experiments on the metamorphosis of neotenous amphibians. J Exp Zool. 1922;36(4): 397-421.

87. Safi R, Bertrand S, Marchand O, Duffraisse M, De Luze A, Vanacker J-M, et al. The Axolotl (Ambystoma mexicanum), a Neotenic Amphibian, Expresses Functional Thyroid Hormone Receptors. Endocrinology. 2004;145(2): 760-772.

88. Morafka DJ, Spangenberg EK, Lance VA. Neonatology of reptiles. Herpetol Monogr. 2000;14:353-370.

89. Bufill E, Agustí J, Blesa R. Human neoteny revisited: The case of synaptic plasticity. Am J Hum Biol. 2011;23(6): 729-739.

90. Somel M, Franz H, Yan Z, Lorenc A, Guo S, Giger T, et al. Transcriptional neoteny in the human brain. Proc Natl Acad Sci U S A. 2009;106(14): 5743-5748.

91. Skulachev VP, Holtze S, Vyssokikh MY, Bakeeva LE, Skulachev MV, Markov AV, et al. Neoteny, prolongation of youth: From naked mole rats to "naked apes" (humans). Physiol Rev. 2017;97(2): 699-720.

92. Buffenstein R, Lewis KN, Gibney PA, Narayan V, Grimes KM, Smith M, et al. Probing pedomorphy and prolonged lifespan in naked mole-rats and dwarf mice. Physiology. 2020;35(2): 96-111.

93. Loeb J, Northrop JH. Is There a Temperature Coefficient for the Duration of Life? Proc Natl Acad Sci U S A. 1916;2(8): 456-457.

94. Rikke BA, Johnson TE. Lower body temperature as a potential mechanism of life extension in homeotherms. Exp Gerontol. 2004;39(6): 927-930.

95. Valenzano DR, Terzibasi E, Cattaneo A, Domenici L, Cellerino A. Temperature affects longevity and age-related locomotor and cognitive decay in the short-lived fish: Nothobranchius furzeri. Aging Cell. 2006;5(3): 275-278.

96. Hsu CY, Chiu YC. Ambient temperature influences aging in an annual fish (Nothobranchius rachovii). Aging Cell. 2009;8(6): 726-737.

97. Johnston RK, Snell TW. Moderately lower temperatures greatly extend the lifespan of Brachionus manjavacas (Rotifera): Thermodynamics or gene regulation? Exp Gerontol. 2016;78: 12-22.

98. Conti B, Sanchez-Alavez M, Winsky-Sommerer R, Morale MC, Lucero J, Brownell S, et al. Transgenic mice with a reduced core body

temperature have an increased life span. Science. 2006;314(5800): 825-828.

99. Lane MA, Baer DJ, Rumpler WV, Weindruch R, Ingram DK, Tilmont EM, et al. Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-aging mechanism in rodents. Proc Natl Acad Sci U S A. 1996;93(9): 4159-4164.

100. Carrillo AE, Flouris AD. Caloric restriction and longevity: Effects of reduced body temperature. Ageing Res Rev. 2011;10(1): 153-162.

101. Guijas C, Montenegro-Burke JR, Cintron-Colon R, Domingo-Almenara X, Sanchez-Alavez M, Aguirre CA, et al. Metabolic adaptation to calorie restriction. Sci Signal. 2020;13(648): eabb2490.

102. Heilbronn LK, De Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, Rood J, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: A randomized controlled trial. J Am Med Assoc. 295(13): 1539-1548.

103. McNab BK. On Estimating Thermal Conductance in Endotherms. Physiol Zool. 1980;53(2): 145-156.

104. Buffenstein R, Yahav S. Is the naked mole-rat Hererocephalus glaber an endothermic yet poikilothermic mammal? J Therm Biol. 1991;16(4): 227-232.

105. Keil G, Cummings E, De Magalhães JP. Being cool: how body temperature influences ageing and longevity. Biogerontology. 2015;16(4): 383-397.