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Revelations About Aging and Disease from Unconventional Vertebrate Model Organisms

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Abstract

Aging is a major risk factor for multiple diseases. Understanding the underlying mechanisms of aging would help to delay and prevent age-associated diseases. Short-lived model organisms have been extensively used to study the mechanisms of aging. However, these short-lived species may be missing the longevity mechanisms that are needed to extend the lifespan of an already long-lived species such as humans. Unconventional long-lived animal species are an excellent resource to uncover novel mechanisms of longevity and disease resistance. Here, we review mechanisms that evolved in nonmodel vertebrate species to counteract age-associated diseases. Some antiaging mechanisms are conserved across species; however, various nonmodel species also evolved unique mechanisms to delay aging and prevent disease. This variety of antiaging mechanisms has evolved due to the remarkably diverse habitats and behaviors of these species. We propose that exploring a wider range of unconventional vertebrates will provide important resources to study antiaging mechanisms that are potentially applicable to humans.

1. INTRODUCTION

Aging is a persistent functional decline in fitness that occurs in most organisms over time (100, 140). In humans, the process of aging is often associated with multiple diseases, including cancer, cardiovascular disease, neurodegeneration, diabetes, osteoarthritis (OA), and chronic inflammation (118). Traditionally, studies on the mechanisms of aging and age-associated diseases have been conducted using model animals, including nematodes (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), zebrafish (*Danio rerio*), and mice (*Mus musculus*). Model animals have been used for research due to their accessibility and convenience. Their genomes are sequenced and well annotated, they have uniform genotypes and phenotypes due to their inbred nature, and they have short lifespans and fast life cycles. These characteristics make them a great tool for studies involving drug treatments and gene manipulation.

Extensive attempts have been made to increase mouse lifespan. Inhibiting the mechanistic target of rapamycin (mTOR) pathway by genetically knocking out the *S6K* gene increased mouse lifespan by 9%, while rapamycin treatment increased lifespan by 9%–14% (70, 151). Transgenic overexpression of a sirtuin protein, Sirt6, increased lifespan in mice by up to 27% (84, 139). Clearance of senescent cells ($p16^{Ink4a}$-positive cells) increased only the median but not the maximum lifespan of mice (12). These increments of lifespan, however, are not remotely comparable to the lifespan differences across species of mammals. In mammals, the maximum lifespans of different species vary from about 2 years in Mueller's giant Sunda rats (*Sundamys muelleri*) (120) to 211 years in bowhead whales (*Balaena mysticetus*) (167). Maximum lifespan correlates positively with body mass (19); therefore, larger mammals tend to be long lived. However, there are many outliers to this rule, including mouse-sized animals that are very long lived. The naked mole rat (*Heterocephalus glaber*) has a maximum lifespan of over 37 years (23, 24). Multiple species of bats have maximum lifespans of up to 30–40 years (168). Remarkably, many nonmodel animals are also shown to be resistant to multiple age-associated diseases, which further contribute to their longevity. These facts suggest that different species have evolved novel longevity mechanisms that are absent in short-lived model animals. Here, we review the mechanisms of longevity and disease resistance observed in a variety of unconventional model vertebrates and discuss what can be learned from them for understanding and addressing aging and age-associated diseases in humans.

2. CANCER

Cancer is one of the major age-associated diseases. In humans, although cancer can occur in young individuals, the incidence of cancer increases steeply at older age (67, 109). The epidemiological studies showing an exponential, instead of linear, increase in cancer incidence with age suggest that multiple mutations rather than a single mutation are required to develop cancer (66, 104, 136, 141). Indeed, experimental studies showed that at least two mutations (genetic hits) are required to malignantly transform mouse fibroblasts, while five mutations are required to transform human fibroblasts (93, 134). The number of hits required for malignant transformation varies across species, with larger and longer-lived animals needing a higher number of oncogenic hits (176). Additionally, in long-lived species, it takes much longer for cancer to develop. Mice develop cancer in their second year of life (99), while in humans, cancer affects mostly people above 60 years of age (158). However, several species of wild animals are known to be extremely resistant to cancer, including the naked mole rat, bind mole rat, elephant, and bowhead whale (**Figure 1**). Importantly, these species adopt distinct strategies to prevent cancer.

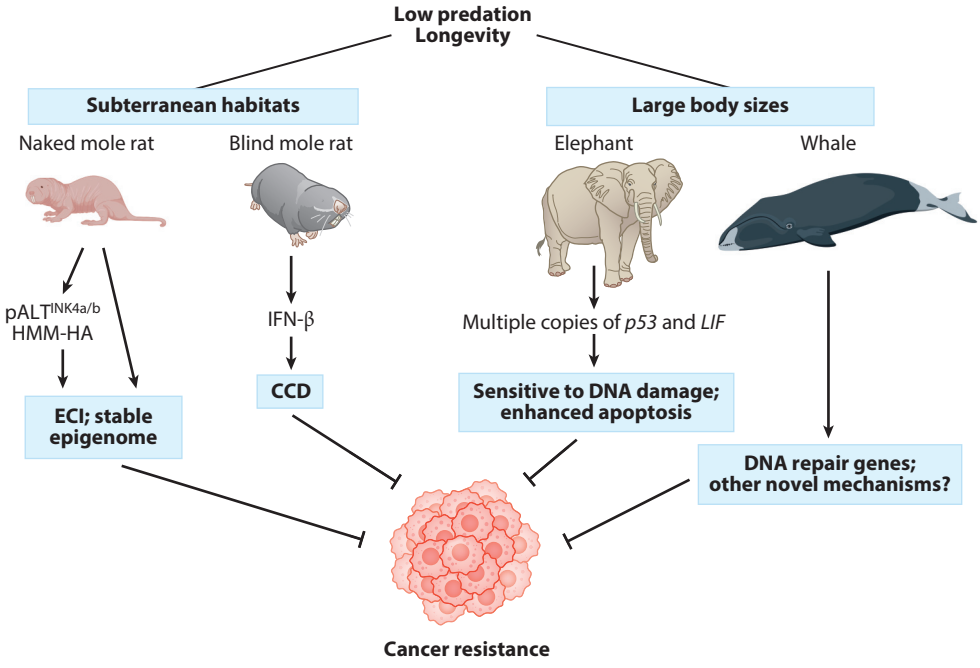

Figure 1

Distinct cancer resistance mechanisms of the naked mole rat, blind mole rat, elephant, and whale. Naked mole rat cells undergo early contact inhibition (ECI) through high-molecular-mass hyaluronan (HMM-HA) and an additional INK4a/INK4b hybrid locus (pALT$^{INK4a/b}$). Blind mole rat cells undergo concerted cell death (CCD) triggered by interferon β (IFN-β). Elephants have multiple copies of *p53* and leukemia inhibitory factor (*LIF*) genes, facilitating enhanced apoptosis. Whale DNA repair genes have undergone positive selection. Other novel mechanisms for cancer resistance in whales are yet to be determined. Both naked mole rats and blind mole rats inhabit subterranean burrows, and elephants and whales have large body sizes: These characteristics make them relatively protected from nonhuman predators, permitting the selection for longevity and cancer resistance. Figure adapted from images created with BioRender.com.

2.1. Naked Mole Rats

The naked mole rat (*H. glaber*), which inhabits subterranean burrows in East Africa, is the longest-lived rodent species. A mouse-sized rodent, the naked mole rat has a maximum recorded lifespan of over 37 years (23, 24). Studies report that naked mole rats do not display aging phenotypes and age-associated diseases until very late in life, and their mortality does not increase with age, which defies the Gompertz law (23, 142). Most strikingly, naked mole rats are highly resistant to cancer (98). Out of thousands of individuals that have been monitored in research laboratories and zoo facilities, only seven cases of spontaneous neoplasia and one presumptive case have been reported by three groups to date (29, 37, 173).

Some of the secrets of naked mole rat cancer resistance were revealed by studying the behavior of naked mole rat culture cells. Primary adult naked mole rat fibroblasts grow considerably more slowly compared to mouse fibroblasts (154). Furthermore, naked mole rat fibroblasts display a unique phenotype that is termed early contact inhibition (ECI) (154). Contact inhibition is an important anticancer mechanism to prevent overproliferation (2). Normal cells stop proliferating when they reach confluence and form a monolayer in the culture dishes. Cancer cells, which have

lost contact inhibition, continue growing to form multilayered foci. Contact inhibition is mediated by the expression of the cyclin-dependent kinase (CDK) inhibitor $p27^{kip1}$ (p27), which interacts with the cyclin-CDK complex to induce G1 arrest (96, 127). Instead of becoming confluent, naked mole rat fibroblasts stop proliferating after loosely contacting each other, i.e., undergoing ECI (154). Different from normal contact inhibition, ECI of naked mole rat cells is triggered by the activation of another CDK inhibitor, $p16^{INK4a}$ (p16) (154). ECI adds an additional layer of control of cell proliferation to the naked mole rat. Interestingly, the gene locus of $p15^{INK4b}$, $p16^{INK4a}$, and alternate reading frame (ARF) in the naked mole rat codes an additional gene, which fuses $p15^{INK4b}$ exon 1 and $p16^{INK4a}$ exons 2 and 3. This novel gene, termed $pALT^{INK4a/b}$, can efficiently induce cell cycle arrest (175).

In the naked mole rat, the ECI is triggered by extracellular signals mediated by a unique high-molecular-mass hyaluronan (HMM-HA) (174). Hyaluronan is a linear polysaccharide and a major component of the extracellular matrix (179). The biological function of hyaluronan depends on its length. Longer molecules have antiproliferative and anti-inflammatory effects (89, 179), whereas short molecules are proinflammatory and facilitate proliferation and metastasis (130, 179). The hyaluronan secreted by naked mole rat cells has the molecular weight of 6–12 MDa compared to 0.5–3 MDa in mouse cells and 0.5–2 MDa in human cells (73, 174). The high molecular weight of naked mole rat HMM-HA is achieved by two mechanisms. The naked mole rat hyaluronan synthase 2 (*Has2*) gene has two unique asparagine-to-serine mutations that enhance the synthesis of hyaluronan. The hyaluronan-degrading enzymes, HAases, have a lower activity in naked mole rat cells and tissues (174). Naked mole rat HMM-HA plays important roles in inhibiting cell proliferation and suppressing tumorigenesis. Naked mole rat fibroblasts are resistant to transformation by $Hras^{G12V}$ and SV40 large T antigen (LT). Removing HMM-HA by either silencing Has2 or overexpressing HAase made naked mole rat cells more susceptible to oncogenic transformation (174). It is known that hyaluronan mediates extracellular signals by interacting with its major receptor, CD44, on the cell surface (89, 128, 130). The naked mole rat very-high-molecular-mass hyaluronan is shown to suppress CD44 protein–protein interactions, an effect opposite to its shorter counterpart (170). As a result, naked mole rat hyaluronan uniquely regulates CD44-dependent genes and protects cells from stress in a p53-dependent manner (170).

Researchers have hypothesized that naked mole rat HMM-HA evolved elastic skin that facilitates squeezing into underground burrows as an adaptive trait to their subterranean habitat. This trait could later have been co-opted to protect naked mole rats from cancer during their long lives. The anticancer effect of HMM-HA may thus have been a by-product of their subterranean life.

Other mechanisms also contribute to the cancer resistance of the naked mole rat. Cellular senescence is an important anticancer mechanism preventing damaged or premalignant cells from proliferating (30, 193). There are multiple types of cellular senescence, including replicative senescence (RS) (69, 106) induced by telomere shortening, oncogene-induced senescence (16, 39, 156), and stress-induced premature senescence (SIPS) (181, 182) triggered by DNA damage. More recently, programmed senescence was observed during embryonic development, which plays a critical role in tissue remodeling (113, 163). Cellular senescence contributes to aging and age-associated diseases, as clearance of senescent cells extends lifespan and healthspan in mice (11, 12, 166, 194). As small-sized rodents, naked mole rats constitutively express telomerase, and thus their cells do not undergo RS (152, 155). However, all three other types of senescence have been observed in the naked mole rat (201). Compared with mouse cells, naked mole rat fibroblasts require a higher dose of DNA damage to induce SIPS and are more resistant to DNA damage-induced apoptosis (201). Gene expression analysis demonstrated some unique changes in

gene expression in naked mole rat senescent cells, including the upregulation of lysosomal genes; oxidative stress response; changes in the extracellular matrix; and inhibition of transcription, spliceosome, and mitochondrial translation (201). These changes may contribute to the stress resistance of naked mole rat cells.

It was recently shown that upon oncogene challenge, naked mole rat cells are more resistant to transcriptomic changes induced by $HRAS^{G12V}$. Specifically, the Ras effector pathway, which is the phosphoinositide 3-kinase (PI3K)–AKT signaling pathway downstream of Ras, is inherently decreased in naked mole rat cells (200). This may be an evolutionary adaptation to resist oncogenic transformation in the naked mole rat.

Another potential anticancer mechanism of naked mole rat cells is that they are very resistant to induced pluripotent stem cell (iPSC) reprogramming by OSKM factors (*Oct4*, *Sox2*, *Klf4*, and *Myc*) (94, 111, 171). This characteristic may be attributable to the more stable epigenome in naked mole rats, which has higher levels of repressive H3K27 methylation marks and lower levels of activating H3K27 acetylation marks in the histone landscape (171). This more stable epigenome is likely to contribute to cancer resistance in naked mole rats as iPSC reprogramming shares similar properties with tumorigenesis (17, 165).

2.2. Blind Mole Rats

The blind mole rat (*Spalax ehrenbergi*) superspecies is a group of related subterranean rodent species that inhabit the Middle East, Eastern Europe, and Asia Minor (117). Blind mole rats spend their entire lives in subterranean burrows and thus have been extensively studied as a model of hypoxia tolerance (117). Strikingly, it was later revealed that blind mole rats are very long lived and extremely cancer resistant (62). Blind mole rats are phylogenetically closer to mice and rats than to naked mole rats (108), and their body size is similar to a rat. However, the maximum lifespan of blind mole rats in captivity has reached over 21 years (117). Thousands of blind mole rats have been captured and studied in the past 50 years, and not a single case of spontaneous cancer had been observed. Furthermore, a high-dose regimen of carcinogen DMBA/TPA, a model to induce skin cancer in mice, failed to induce cancer in blind mole rats, even with multiple attempts (62, 102). Therefore, blind mole rats are resistant to both spontaneous and induced tumorigenesis.

Blind mole rats adopt a distinct strategy from naked mole rats to prevent cancer. Blind mole rat fibroblasts grow faster in cell culture than naked mole rat cells and do not undergo early contact inhibition. Instead, the cells keep proliferating for 10 to 15 population doublings before they enter a growth arrest. Within a few days, the cells undergo necrotic cell death (62). This phenotype, termed concerted cell death (CCD), is associated with the secretion of interferon β (IFN-β) (62). The CCD mechanism senses overproliferation and eliminates premalignant cells. Genome analysis of the blind mole rat demonstrated duplications of the IFN gene pathway, which further supports this model (48).

Interestingly, the *Tp53* gene of blind mole rats carries an adaptive mutation of arginine to lysine on codon 172 (Arg-174 in humans), which weakened its transactivation toward proapoptotic target genes (8). This mutation is believed to contribute to the hypoxia tolerance of the blind mole rat by preventing excessive cell death induced by hypoxia. However, the weakened p53 would put the blind mole rat at risk of cancer. Therefore, it is speculated that the duplicated IFN pathway genes and their responsiveness to cell overproliferation act as a compensatory strategy. p53 has been shown to negatively regulate the expression of transposable elements (95, 188). Therefore, it is possible that the weak p53 in blind mole rats contributes to the derepression of transposable elements, which activates IFN through the transcription of repeats activates IFN (TRAIN) mechanism (48, 95).

2.3. Elephants

Elephants have large body sizes and a maximum lifespan of 65 years (1). The number of cell divisions throughout the life of an elephant is much larger than that of small animals, and the chance of mutation accumulation is higher, which predicts higher cancer risk. However, elephants are reported to have very low cancer incidence (1). This contradiction is referred to as Peto's paradox (126). As reported previously, somatic cells from large animals (body mass above 5 to 10 kg) limit telomerase expression and undergo replicative senescence after overproliferation (152, 153, 155). However, as implied by Peto's paradox, additional tumor suppressive mechanisms are required for elephants to counteract the high cancer risk. In recent studies, 19 additional copies of the *Tp53* gene were identified in the elephant genome (1, 164). These 19 copies are believed to be pseudogenes, and some of them are transcribed from transposable element–derived promoters, while 2 of their transcripts are translated in elephant fibroblasts (164). As a result, the elephant cells are more sensitive to DNA damage; a lower dose of DNA damage is required to induce p53-dependent apoptosis (1, 164). As there are no DNA-binding, tetramerization, or nuclear localization domains in these retrogenes, their products are not likely to function as transcription factors. Instead, these additional Tp53 products dimerize with the canonical p53 proteins to protect them from MDM2-dependent ubiquitination (164).

In addition to duplicated *p53* genes, multiple copies of another gene, the leukemia inhibitory factor (*LIF*), were also discovered in the elephant genome (183). One transcript of a duplicate *LIF* gene (*LIF6*) in elephants is upregulated by p53 in response to DNA damage, contributing to the enhanced DNA damage response in elephants. Because the *LIF6* gene contains a p53 responsive element, researchers have speculated that elephant *LIF6* re-evolved into a functional target gene of p53 from a pseudogene (183). Collectively, these gene duplications provide additional tumor suppressors to mitigate cancer risk for elephants. An enhanced apoptosis in response to DNA damage helps ensure the integrity of the genome without causing problematic cell loss for the large-sized elephants.

2.4. Whales

Whales are the largest mammals on earth, with a body weight of up to 100 tons. They are also the longest-lived mammals. The maximum lifespan of the bowhead whale reaches 211 years (167), and considering both their lifespan and exceptionally large body mass, cancer incidence in whales is extremely low. Interestingly, whales did not evolve similar anticancer mechanisms to those of elephants. Genomic analysis did not identify duplications of the *p53* gene in whales (55, 195). Instead, several genes associated with aging and cancer were identified that carried bowhead whale–specific mutations, including excision repair cross-complementing rodent repair deficiency, complementation group 1 (*ERCC1*), histone deacetylase 1 (*HDAC1*), and *HDAC2* (86). *ERCC1* is involved in DNA repair, and *HDAC1* and *HDAC2* are associated with age-related epigenetic modification (59, 138). Furthermore, several genes underwent duplication during the evolution of bowhead whales. Proliferating cell nuclear antigen (*PCNA*), participating in DNA repair, is duplicated, and both copies are expressed in several bowhead whale tissues. Late endosomal/lysosomal adaptor, MAPK and MTOR activator 1 (*LAMTOR1*), which is involved in the mTOR pathway, has an additional copy with lower but detectable expression in heart and retina (86). Several other genes associated with mitosis, cancer, and stress response had also undergone duplication, including 26S proteasome non-ATPase regulatory subunit 4 (*PSMD4*), ubiquitin carboxyl-terminal hydrolase L3 (*UCHL3*), cAMP-regulated phosphoprotein 19 (*ARPP19*), stomatin-like 2 (*STOML2*), heat shock factor binding protein 1 (*HSBP1*), spermine synthase (*SMS*), and suppression of tumorigenicity 13 (*ST13*) (86).

Transcriptome studies also demonstrated bowhead whale–specific changes of gene expression. Insulin signaling genes are differentially expressed in the bowhead whale, including reduced expression of the growth factor receptor-bound protein 14 (*Grb14*) gene and elevated expression of the *Cited2* gene. The expression pattern of these genes mimics the effect of calorie restriction in mice, potentially contributing to the longevity of bowhead whales (150). In gray whales, several genes involved in senescence and autophagy were among the most expressed genes, including cellular repressor of E1A-stimulated genes 1 (*CREG1*) and genes coding for CAAX box proteins (180). Although the data about gray whale cancer resistance are absent, similar genes were found highly expressed in bowhead and minke whales (180). Meanwhile, highly expressed genes in DNA maintenance and repair, ubiquitination, and apoptosis were observed in several whale species (bowhead, gray, and minke whales) and in naked mole rats (180).

In summary, large-sized animals like elephants and whales have evolved additional tumor suppressor mechanisms to compensate for the high risk of mutations due to their large body size, but different species adopt distinct strategies coincident with their own adaptive evolution.

3. CARDIOVASCULAR DISEASE

In humans, cardiovascular diseases remain the number one cause of death in developed countries (137). The risk of cardiovascular diseases is associated with age, with an especially high risk in populations over 65 years old (38, 79, 119). Multiple aging-related genes and pathways are associated with cardiovascular health, including insulin/IGF-1, TOR, AMPK, LKB1, and Sirtuins (119). Several wild animals possess uniquely protective mechanisms against cardiovascular disease that evolved as an adaptation to their unique behaviors and environments (**Figure 2**).

3.1. Hibernating Animals: Bears and Ground Squirrels

One of the major cardiovascular health issues in human patients is a hibernating myocardium, which refers to the dysfunction of a resting left ventricle (LV) due to chronically reduced coronary blood flow or repetitive ischemic episodes (40, 41, 133). Structural degeneration was observed in patients with hibernating myocardium, characterized by reduced expression of protein and messenger RNA (mRNA), as well as disorganized contractile and cytoskeletal proteins, coupled with fibrosis and cell apoptosis (44). If blood flow to the myocardium is restored, it often takes weeks to months for the contractile apparatus to reform (88). Patients with hibernating myocardium are at risk for arrhythmias (28). In the wild, many hibernating animal species endure low metabolic rates and body temperatures, associated with the limited oxygen supply to their cardiovascular system during hibernation, showing characteristics comparable to those of patients with hibernating myocardium, yet they recover smoothly from hibernation to their active state. Their adaptive mechanisms to hibernation provide important insights into human cardiovascular health (18).

Brown bears (*Ursus arctos*) hibernate six months every year. During hibernation, a brown bear's cardiovascular system undergoes adaptive mechanisms to the low metabolic rate, including reduced heart rate and the decreased systolic and diastolic pressures of the LV. These changes are not associated with cardiac atrophy (81). Similarly, in grizzly bears (*Ursus arctos horribilis*), the LV volume:mass ratio increases during hibernation. The total left atrial emptying fraction was reduced, and the atrial contraction blood flow velocities and atrial contraction ejection fraction were decreased during hibernation (115). Proteomic and transcriptomic study of hibernating grizzly bears revealed increased nonessential amino acids in muscle. In contrast to atrophied muscles, hibernating muscles display differentially regulated genes, including pyruvate dehydrogenase kinase 4 (*Pdk4*) and serpin family F member 1 (*Serpinf1*), showing trophic effects beyond hibernating animals (112). In American black bears (*Ursus americanus*), 24 genes were found to be

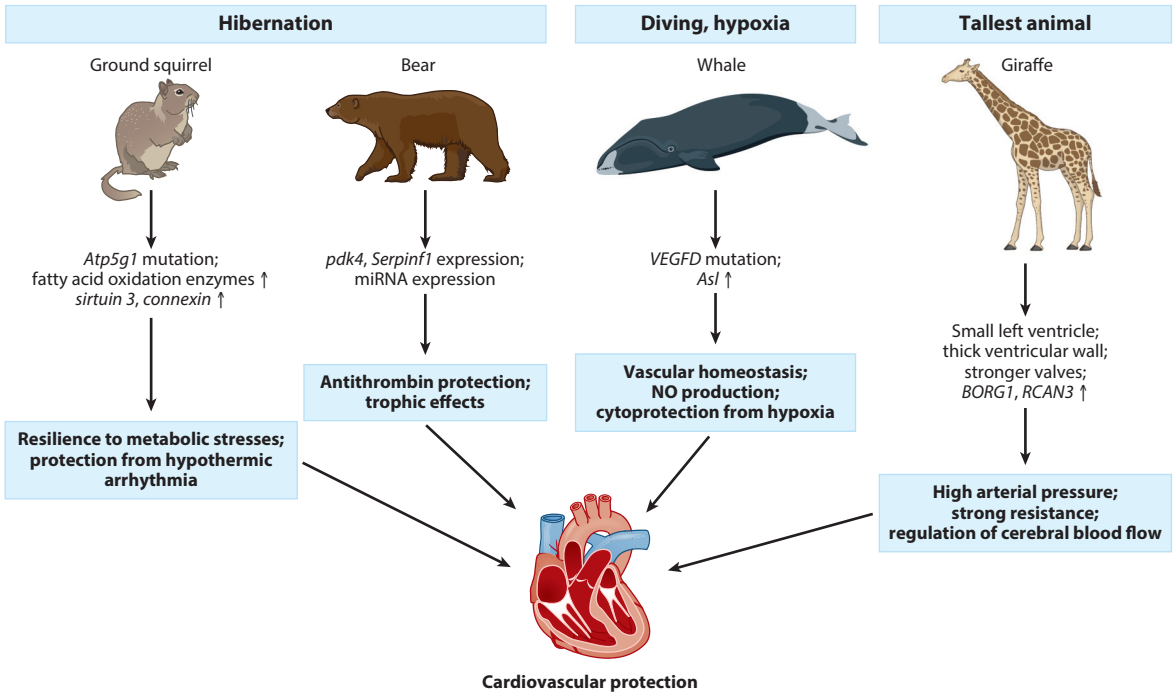

Figure 2

Cardiovascular protection mechanisms of the ground squirrel, bear, whale, and giraffe. The ground squirrel and bear evolved cardioprotective mechanisms, adapting to hibernation. These protections are achieved by altered sequences or expression of genes involved in metabolism, cell respiration, amino acid synthesis, and cell–cell communication. Whales adapt to hypoxic environments during diving in deep water and carry mutations in genes coding for *VEGFD* and for upregulated expression of the *Asl* gene responsible for NO production, protecting cardiovascular function. As the tallest animal, the giraffe has a small left ventricle and thick ventricular wall, providing higher arterial pressure to maintain cerebral blood flow. Giraffes also developed stronger valves to resist the high blood pressure. This may be partly due to the adaptively regulated expression of genes that regulate blood pressure or cardiovascular function, including *BORG1* and *RCAN3*. Abbreviations: *Asl*, argininosuccinate lyase; miRNA, microRNA; NO, nitric oxide; *pdk4*, pyruvate dehydrogenase kinase 4; *RCAN3*, regulator of calcineurin 3; *Serpinf1*, serpin family F member 1; *VEGFD*, vascular endothelial growth factor D.

differentially expressed during hibernation in both liver and heart (50). These genes are involved in lipid catabolism and protein biosynthesis, which enhances protein synthesis at hypothermic temperatures (50). Moreover, 15 microRNAs (miRNAs) were also differentially expressed in the plasma of hibernating black bears. Three of these miRNAs (miR-141-3p, miR-200a-3p, and miR-200c-3p) were predicted to target the serpin family C member 1 (*SERPINC1*) gene, which may contribute to antithrombin protection (49). Some changes of gene expression, including genes involved in fatty acid β-oxidation, carbohydrate synthesis, lipid biosynthesis, carbohydrate catabolism, cellular respiration, and detoxification pathways, are shared between hibernating bears and small hibernators (50).

Compared to bears, the much smaller hibernating ground squirrels display a more acute hypometabolic state during hibernation. During the nonresponsive hibernating state, the body temperature of ground squirrels drops from 37°C to between 3 and 5°C, compared to 33°C in bears (116). Cardiac output during hibernation is sharply reduced in ground squirrels by 97% compared to a 75% reduction in bears (116). Uniquely, the hibernation of ground squirrels is associated with periodic warming and arousals, resulting in fluctuating O_2 requirements (116, 135). Well-adapted

to this fluctuation, the ground squirrel serves as a natural model to understand the protection against ischemia/reperfusion injury in human patients.

Hibernating arctic ground squirrels (*Urocitellus parryii*) displayed significantly reduced plasma levels of troponin I, myocardial apoptosis, and LV contractile dysfunction (131). Most proteins involved in mitochondrial energy transduction were downregulated in hibernating arctic ground squirrels. In contrast, fatty acid oxidation enzymes and sirtuin 3 were upregulated (131). The upregulation of sirtuin 3 suggests the importance of posttranslational modifications in cardiovascular protection in hibernating mammals (131). The arctic ground squirrel brain was shown to be resistant to cardiac arrest induced injury during euthermia (32). A Pro-32-Leu mutation of Atp5g1 was identified in arctic ground squirrels that contributes to resilience to metabolic stresses (160). Extremely low body temperature may cause fatal arrhythmia. Ground squirrels bypass it by regulating Ca^{2+} homeostasis in cardiomyocytes (43). The voltage shift of Ca^{2+} current (ICa) at a low temperature is compensated by a higher depolarization rate and a longer duration of action potential (97, 116). To protect from hypothermic arrhythmia, connexin43 and connexin45 are upregulated in hibernating ground squirrels, protecting against dispersion of depolarization (51).

3.2. Whales and Hypoxia

In addition to their longevity and cancer resistance, whales are also well adapted to diving and underwater environments, enduring periods of insufficient oxygen supply. The hypoxia-sensitive brain and heart of whales tolerate low oxygen conditions while diving. A unique amino acid substitution in the c-fos-induced growth factor (*Figf*) gene was identified in bowhead whales (150). The *Figf* gene codes for vascular endothelial growth factor D (VEGFD), which plays a role in vascular homeostasis (143). It was speculated that this mutation potentially contributes to the maintenance of vascular health in bowhead whales (150). Gene expression analysis showed a 4.4-fold higher expression of the argininosuccinate lyase (*Asl*) gene in whales (150). Expression of the *Asl* gene is essential for the production of nitric oxide, which confers cytoprotection to tissues during hypoxia and may help preserve cardiac function in diving mammals (80, 150). However, as this differential expression analysis was based on only one bowhead whale heart and one minke whale heart (150), more thorough study is required to solidify the conclusion.

3.3. Giraffes and Cerebral Blood Flow

Blood supply to the brain may be compromised by age-related decline of cardiovascular function through impaired cerebral blood flow (CBF) (35). Acute reduction of CBF can cause loss of consciousness. Therefore, the regulation of CBF is of great importance. Multiple factors are known determinants of CBF, including neurovascular coupling, arterial blood pressure, cardiac output (CO), and autonomic neural activity (172). Most of these factors show an age-dependent decline. For example, the CBF/CO ratio index (CCRI) is negatively correlated with age (192).

The giraffe is a perfect model to study the regulation of CBF. Giraffes are the tallest animals on earth. The positional change of a giraffe head between ground level and standing upright is the largest of all animals, yet loss of consciousness never occurs because they evolved mechanisms to provide adequate blood flow (110). The rapid changes in the relative position of the brain to the heart require a well-adapted maintenance of cardiovascular homeostasis. With a normal-sized heart relative to their body size, giraffes naturally have a blood pressure twice that of humans (6, 161). Several physiological and anatomical characteristics of the giraffe cardiovascular system potentially contribute to this adaptation. The giraffe heart has a small LV and thick ventricular wall, which allow the generation of high arterial pressure (161). Adapting to the high blood pressure, the aortic valve of giraffes is stronger and stiffer than that of its bovine counterparts (6). This

is likely due to the giraffe valve's higher content of collagen and elastin, which make it more resistant to the high-pressure forces (6). Another risk is the potential for high pressure in the brain when giraffes lower their heads. This is avoided by the changing blood pressures governing transcapillary exchange, precapillary vasoconstriction, and low permeability of capillaries to plasma proteins (68). CBF is related to cerebral perfusion pressure (CPP). In giraffes, an increased CPP in the standing upright position was observed to protect from loss of consciousness. In the head-down position, the viscous resistance in the extracranial circulation decreases more than it does in the intracranial circulation, and CBF is diverted to the jugular veins (110).

Genome sequencing of the giraffe compared with that of the okapi, the closest relative of giraffes but of much shorter stature, revealed the adaptive evolution of eight genes that regulate blood pressure or cardiovascular function in giraffes (3). Among these genes, *BORG1* and *RCAN3* are highly expressed in the heart, potentially contributing to cell shape and cardiac muscle contraction, respectively. Additionally, several metabolic genes related to cardiovascular functions showed multiple signs of adaptation (3).

4. NEURODEGENERATIVE DISEASES: DEGUS AS A NATURAL MODEL

Aging is the main risk factor for neurodegenerative diseases, a major type of which is Alzheimer's disease (AD). AD was first described as extracellular amyloid plaques and intracellular neurofibrillary tangles in the brain, composed of abnormally folded amyloid-β42 (Aβ42) and tau proteins (190). As an age-associated disease, AD affects over 40 million people worldwide (47). Despite decades of research, no curative intervention is available. Current studies use a great number of mouse models for AD. Nearly 200 transgenic rodent models for AD are available, most of which are based on mutations linked to Aβ protein misprocessing. Recent models also incorporate the mutation of tau proteins (114). These mouse models mimic the familial AD but do not model the sporadic AD, which represents >97% of all AD cases (114). The generation of sporadic AD models has been attempted by incorporating mutations of *APOE* and *TREM2*, observed in sporadic AD, but these models did not cover many risk factors related to lifestyle, including diabetes, hypercholesterolemia, and stress (54).

The degu (*Octodon degus*), a South American rodent, has been described as a natural sporadic AD model due to its AD-like neuropathology (20, 75). Degus are highly social, thus resembling humans. Unlike other rodents, in their social interactions, degus rely largely on visual and vocal communications (22, 31, 132). They have even demonstrated the ability to use tools (121). However, during aging, degus experience cognitive decline associated with memory loss (7, 36). Many degus spontaneously develop AD-like pathologies with symptoms similar to human AD patients. For example, the cognitive decline of aged degus is correlated with high levels of Aβ (76). This is possibly due to a highly similar sequence of Aβ in degus and humans, with only one amino acid difference (Arg13His). Other rodents, like mice and rats, which do not develop AD-like pathology, have three amino acids that differ from those of humans in their Aβ peptides (75, 76). *ApoE* is the most frequently identified genetic risk factor for sporadic AD. The *ApoE* sequences in humans and degus have a higher similarity than those in humans and rats (145). This may explain why the degu is a good model for sporadic AD. Affected degus also share other symptoms found in human patients, including activated inflammation factors. Similar to the brains of human patients, proinflammatory cytokine interleukin-6 (IL-6), tumor necrosis factor α (TNFα), IFN-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were elevated in AD-like degu brains (36, 77). Therefore, degus are an excellent model to study AD and may be highly valuable for preclinical trials for therapy and interventions.

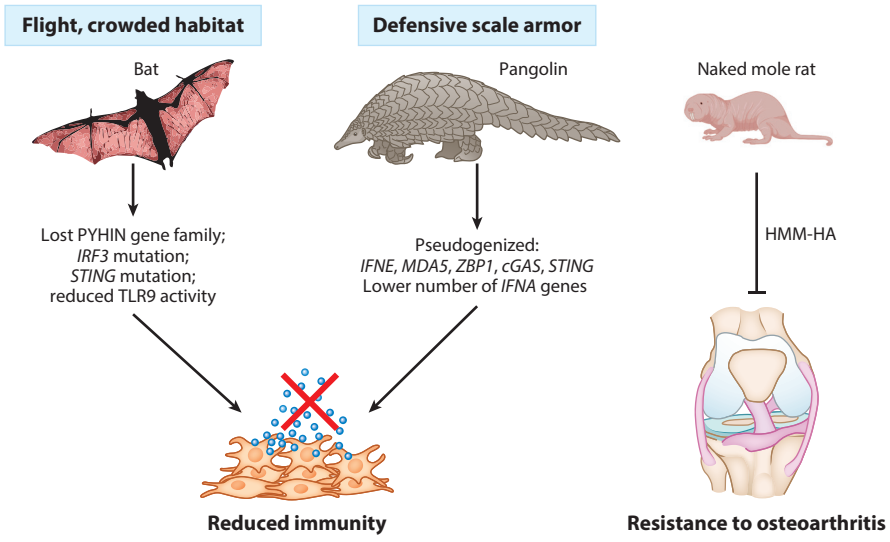

Figure 3

Resistance to inflammatory diseases in the bat, pangolin, and naked mole rat. Both bats and pangolins evolved tolerance to viruses and reduced inflammatory response by mutations or pseudogenization of RNA and DNA innate immune sensors. The driving forces that shape immune responses in bats are believed to be the ability to fly and their crowded habitats. Pangolins have defensive keratinized scale armor, which provides additional protection from skin injuries and infection. The reduced inflammatory response in pangolins may have coevolved with the formation of scale armor. Naked mole rats are extremely resistant to osteoarthritis, possibly through the anti-inflammatory function of HMM-HA. Abbreviation: HMM-HA, high-molecular-mass hyaluronan. Figure adapted from images created with BioRender.com.

5. INFLAMMAGING AND INFLAMMATORY DISEASES

Immune response is important for protecting organisms from infection with viruses or bacteria; however, dysregulated immune response can be damaging to the host tissues and cells. This is a health concern particularly for aged populations. Inflammation is a driver of multiple age-associated diseases, including cancer, cardiovascular disease, neurodegenerative diseases, diabetes, and OA. This persistent and progressive increase in the proinflammatory status with aging is termed inflammaging (56). Many age-associated factors contribute to inflammaging, including cellular senescence, viral infections, microbiome bacteria, and self-products of cell damage such as cytoplasmic nucleic acids (sterile inflammation) (34, 57, 159). Bats, pangolins, and naked mole rats have been shown to resist inflammatory diseases by different mechanisms (**Figure 3**).

5.1. Dampened Inflammatory Response in Bats and Pangolins

The bat is a perfect model in which to study inflammatory disease resistance and longevity. Many species of bats have an extraordinarily long lifespan relative to their body size. For instance, the little brown bat, Brandt's bat, mouse-eared bat, and Indian flying fox have maximum lifespans of 30–40 years (64). Bats are also resistant to cancers; very few cancers have been identified in bats (64). Most strikingly, bats are very tolerant to different kinds of viruses, including Ebola, rabies, and coronaviruses. Often, bats coexist with viruses without displaying signs of disease or pathology.

The mechanisms of virus tolerance in bats have been extensively studied. Several studies indicate that bats have enhanced RNA-sensing and dampened DNA-sensing mechanisms. A novel phosphorylation site, Ser-185, was identified in the IFN regulatory factor 3 (*IRF3*) gene

in multiple bats species, which significantly improved antiviral protection through RNA sensing (15). Bats also constitutively express IFN-α, contributing to antiviral activity and resistance to DNA damage (202).

To conquer the potentially excessive immune response, multiple immune pathways are attenuated in bats. Bat immune cells have dampened NLRP3 inflammasome (4), the overactivation of which is associated with inflammatory states and age-related diseases (196). Interestingly, viral double-stranded RNA (dsRNA)-induced IFN-β in bat cells failed to activate TNFα (14). This is due to a potential repressor on the TNF promoter in bats, which is a strategy of bats to suppress excessive immune response (64). In addition, DNA sensing is remarkably dampened in bats. The PYHIN gene family, which includes cytoplasmic DNA sensors AIM2 and IFI16, are missing in 10 bat species (5, 198). The major cytoplasmic DNA sensing pathway, the cGAS-STING pathway, is dampened in bats by a mutation in STING, resulting in the loss of the conserved S358 (191). The TLR9 receptor, which is activated by unmethylated CpG-containing DNA, evolved under positive selection in bats and reduced its activation (14, 46). Recently, a genome-wide study of bats revealed selection and loss of NF-κB regulators and expansion of antiviral *APOBEC3* genes (78).

Bats show an enhanced autophagy in response to Australian bat lyssavirus infection (91). This acts as a compensation of the immune system to clear damaged cells; meanwhile, autophagy also contributes to longevity (144). Other prolongevity features discovered in bats include mutations of GH and IGF1 receptors (149), positive selection on double-stranded break (DSB) repair genes (198), resistance to oxidative stress (146), higher heat-shock proteins (26), a stable microbiome composition (74), and tolerance to transposons (129).

It is believed that the dampened inflammatory response in bats may have evolved as an adaptation to flight (13, 83, 125, 198) and crowded habitats (64). The ability to fly is one of the longevity-favoring features of bats, permitting escape from predators (9). Remarkably, dampened immune response may also serve as a longevity-promoting adaptation by reducing chronic inflammation, which is associated with aging in other species (64).

Similar to bats, pangolins are another group of species that are reservoirs of different viruses but do not themselves get sick. In addition to bats, pangolins were also identified as possible intermediate hosts of the recent SARS-CoV-2 coronavirus (92, 199). Several studies of the pangolin immune system revealed mechanisms that may contribute to their viral tolerance. Genome sequencing and analysis demonstrated that the *IFN-ε* gene was pseudogenized in all African and Asian pangolin species (27). The *IFN-ε* gene is expressed exclusively in epithelial cells and inner mucosa-protected tissues and serves an important role in protecting skin and mucosa from infection (33, 189). Frameshift and premature stop codons were identified in *IFN-ε* in pangolins (27). It was proposed that this mutation is associated with the evolution of keratinized scales in pangolins, which protect the skin from injuries and infection and possibly replace the function of *IFN-ε* (27). Other genes of the IFN family are intact in pangolins, but the number of *IFN-*α genes is lower in pangolins than in humans (27). As a result of the reduced IFN-mediated immunity, many genes involved in other immunity-related pathways have undergone positive selection (27).

Unlike bats, which have enhanced RNA sensing and reduced DNA sensing, pangolins seem to have dampened both RNA- and DNA-sensing pathways. The IFN-induced with helicase C domain 1 (*IFIH1*) gene, which codes for a cytoplasmic RNA sensor, MDA5, is inactivated by frameshift and premature stop mutations in exon 1 in three pangolin species (53). The Z-DNA-binding protein (*ZBP1*) gene, which recognizes both Z-DNA and Z-RNA, was also pseudogenized by multiple premature stop mutations (53). The loss of *IFIH1* and *ZBP1* in pangolins occurred shortly after their evolutionary divergence from other mammalian lineages (53). DNA sensors cGAS and its interactor STING are also inactivated by frameshift and premature stop mutations

(52). It will be important to experimentally confirm these genomic findings and identify potential compensatory pathways that allow pangolins to remain healthy despite dampened immunity.

5.2. Resistance to Osteoarthritis in Naked Mole Rats

OA is a chronic, degenerative joint disease associated with cartilage degeneration and joint inflammation (105). Aging is the major factor causing OA. The number of OA patients is predicted to increase with the increasing elderly population. In addition to aging, traumatic injuries can also cause OA (45). The effects of current treatments of OA are limited (169). The long-lived naked mole rats provide a good model for better treatment of OA. The cartilage of naked mole rats was found to be stiffer than that of mice, and the naked mole rat chondrocytes are resistant to traumatic damage (169). Using a meniscal-ligamentous injury (MLI) model, researchers found that naked mole rats displayed much better recovery than mice and showed no signs of degenerative changes, suggesting that naked mole rats are extremely resistant to OA (169). Interestingly, HMM-HA is abundant in naked mole rat cartilage, suggesting its potential role in resistance to OA. This discovery encourages the use of HMM-HA in OA therapies.

6. ADAPTATIONS COUNTERACTING THE HALLMARKS OF AGING

Evolutionary adaptations that slow the rate of aging may increase resistance to multiple age-related diseases. Researchers have proposed that aging is a result of the accumulation of unrepaired cellular and molecular damage (87), which may eventually cause nutrient sensing dysregulation, genomic instability, loss of proteostasis, and stem cell exhaustion, among others (118). These changes are closely correlated with aging and age-associated diseases and thus are referred to as the hallmarks of aging (100). Some wild species have evolved mechanisms that counteract the hallmarks of aging (**Figure 4**). Studying these nonmodel animals with diverse lifespans may reveal novel mechanisms critical for longevity.

6.1. DNA Repair and Lifespan: From Mice to Beavers

Genomic stability plays a pivotal role in longevity. DNA damage occurs every day. Without DNA repair, the accumulation of DNA damage may potentially cause mutations in critical genes like oncogenes and tumor suppressors. Researchers have proposed that DNA damage is a driving force of aging by causing genomic instability, cellular senescence, and apoptosis (186) and by destabilizing the epigenetic structure (63). Therefore, DNA repair is a key player in maintaining genomic stability. The role of DNA repair in aging is supported by multiple examples of evidence demonstrating that mutations in DNA repair genes result in premature aging phenotypes (71); however, it is harder to demonstrate that improved DNA repair would result in lifespan extension.

With comparative biology, it is possible to compare DNA repair capabilities of species with extreme lifespan differences. Comparisons of transcriptomes of humans, naked mole rats, and mice, which have maximum lifespans of 120, 30, and 3 years, respectively, showed higher expression of DNA repair genes in long-lived species (humans and naked mole rats) compared with short-lived mice (101). A functional study of DNA repair was more extensively performed, comparing 18 different rodent species (177). Skin and lung fibroblasts of all 18 rodent species were transfected with DNA repair reporter systems for two types of DNA DSB repair, homologous recombination and nonhomologous end joining. Both types of DSB repair showed strong positive correlation with the maximum lifespan of the species. The fibroblasts from longer-lived animals have better DSB repair than the cells from short-lived animals (177). SIRT6 is a histone deacetylase and mono-ADP-ribosylase enzyme involved in DNA repair and epigenome maintenance (103; reviewed

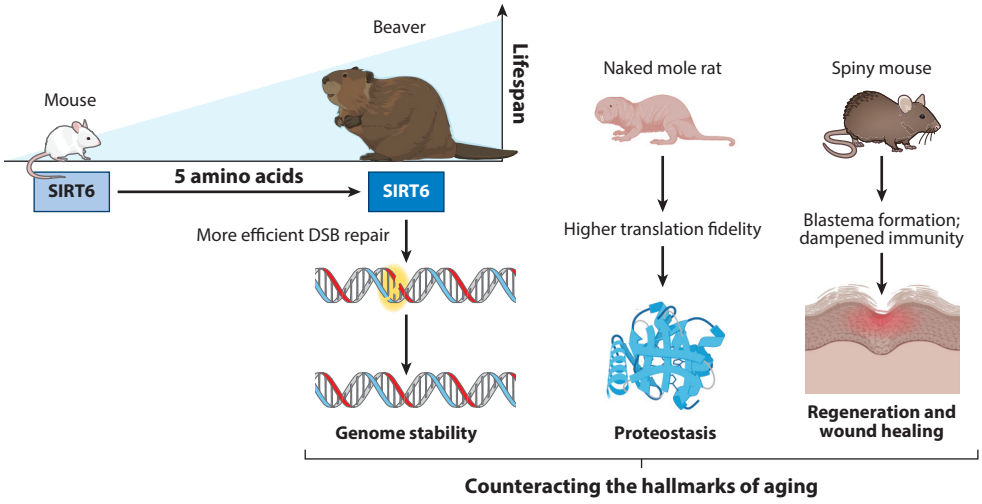

Figure 4

Mechanisms targeting the hallmarks of aging. SIRT6-mediated double-stranded break (DSB) repair positively correlates with maximum lifespan across rodent species, with the beaver having one of the highest DSB repair activities among rodents. Five amino acid substitutions in the SIRT6 gene determine the differential SIRT6 activity between the beaver and mouse. Stronger DSB repair ability contributes to genome stability. The naked mole rat has higher translational fidelity, contributing to improved proteostasis. The spiny mouse has the strongest regenerative ability in mammals, due to the formation of blastema in wounded tissues and a dampened immunity. Enhanced genome stability, proteostasis, and regenerative ability are all conserved mechanisms for longevity. These functions decline during aging and are considered aging hallmarks. Figure adapted from images created with BioRender.com.

in 25). The different DSB repair capabilities of the 18 rodent species depend largely on the different DSB repair activities of their *Sirt6* gene, with the beaver having one of the most active and mouse having the least active SIRT6 (177). Further dissecting the SIRT6 sequences revealed five amino acids at the C terminus that are fully responsible for the different enzymatic activities between the beaver and mouse. Mouse SIRT6 carrying so-called beaverized mutations resulted in more efficient DNA repair and increased lifespan, suggesting that SIRT6 activity is a determinant of lifespan (177). Therefore, protein features evolved in long-lived nonmodel animals provide important information for understanding aging and longevity.

6.2. High Translation Fidelity in Naked Mole Rats

The best way to address the accumulation of molecular damage, which drives aging, is to prevent it from happening in the first place. The error catastrophe theory of aging was proposed by Orgel (122–124). This theory proposed that translational fidelity plays an important role in aging. Although many in vitro studies challenged the error catastrophe theory, a theoretical study using molecular evolution simulation supported it by showing that mistranslation-induced protein misfolding acts as a strong selective pressure (42).

Using firefly luciferase reporters with various mutations that abrogate the luciferase, researchers showed that the naked mole rat cells have significantly higher translational fidelity than that of mouse cells (10). Coincidently, it was shown that the 28S ribosomal RNA (rRNA) of naked mole rats has a cleavage within the D6 region, resulting in two fragments of 2.5 kb and 3 kb (10). It was speculated that this cleaved 28S rRNA contributes to the higher translational fidelity of naked mole rats. Interestingly, the only other vertebrate known to have fragmented 28S rRNA is

the tuco-tuco, belonging to the genus of *Ctenomys* (107). Although phylogenetically distant from naked mole rats, *Ctenomys* shares similar subterranean habitats and social behavior (107). The maximum lifespan of *Ctenomys* in capacity is not determined; however, it has higher translation fidelity than many other rodents (85).

With the same luciferase reporter system, the translational fidelity of 17 rodent species with diverse lifespans was compared. The frequency of amino acid misincorporation at the first and second codon positions negatively correlated with maximum lifespan (85), suggesting that translational fidelity coevolves with longevity. As other long-lived rodent species compared in this study did not have the fragmented 28S rRNA, additional mechanisms must have played important roles in increasing the translational fidelity.

6.3. Enhanced Regeneration: Axolotls and Spiny Mice

The ability to heal wounds and recover from injury decreases with age (58, 60, 65). A slower healing process in the elderly results in increased morbidity and mortality. Furthermore, approaches to improve regeneration would be equally valuable for younger trauma victims.

The axolotl (*Ambystoma mexicanum*) has been used as a model to study regeneration due to its remarkable capability for limb regeneration (82, 184). During limb regeneration, cartilage-derived blastema cells harbor positional identity to ensure that the limb regrows properly (90). Multiple mutations of axolotl p53 were identified, which may contribute to the regulation of limb regeneration (185, 197). Interestingly, one of the mutations of axolotl p53 (Arg174Lys) was also observed in the blind mole rat (8). However, axolotl is not a mammal, and some of the regenerative mechanisms discovered may be difficult to translate or may pose a cancer risk to humans.

The African spiny mouse, *Acomys*, is the only mammal known to possess dramatically enhanced regenerative ability. Spiny mice have evolved a trait to escape from predators, termed autotomy (148). The skin of spiny mice can easily tear with very low tension. Afterwards, the skin quickly regrows with no scar formation and with regenerated hair follicles (148). The remarkable regenerative ability of spiny mice also applies to ear wound healing, with complete regeneration of hair follicles, sebaceous glands, dermis, and cartilage, resembling the structure of the axolotl blastema during limb regeneration (90, 148). Other than skin and ear wounds, other tissues are also highly regenerative in spiny mice, including skeletal muscle, heart, spinal cord, and kidney (147). It is speculated that the regenerative ability of spiny mice benefits from a dampened immune response following injury, expressing lower or absent inflammatory cytokines (21). Other characteristics of spiny mice fibroblasts also contribute to enhanced regeneration. Spiny mouse fibroblasts generate lower contractile forces (162) and produce a more porous collagen network (148). Further studies of vertebrates with enhanced regenerative abilities will provide important avenues to promote tissue regeneration in humans.

7. CONCLUSIONS

Aging is a major risk factor for multiple diseases. Understanding the mechanisms of aging will significantly contribute to lifespan extension and disease prevention in humans. Nature has provided numerous wild species with remarkable diversity. Their lifespans vary up to 100-fold (167), and from this variation novel antiaging mechanisms can be learned. Studies on model animals, from worms to mice, revealed important conserved pathways responsible for aging, including the insulin/IGF, mTOR, DNA repair, and Sirtuin protein family pathways (178). Some of these pathways are modified in long-lived wild species. Examples include the mutations of GH and IGF receptors and resistance to oxidative stress in bats (146, 149), positive selection on DSB repair in whales and bats (86, 198), and strong DNA repair capabilities in long-lived rodents including

beaver (101, 177). However, manipulating these conserved aging mechanisms in mice led to modest increases in lifespan (up to 10–15%), which cannot fully explain the large difference in lifespans between mammals. A possible reason is that naturally long-lived mammals have evolved multiple prolongevity mechanisms, providing a synergetic effect. Combining different mechanisms learned from unconventional model animals may be a promising way to further extend lifespan. This underlies the importance of comprehensive studies on nonmodel animals.

It has been proposed that species living in protected environments tend to live longer, although the causal relationship is controversial (19, 187). Whales and elephants have large body sizes, protecting them from nonhuman predators (19); naked mole rats and blind mole rats are exposed to far fewer predators by living in subterranean burrows (61); and bats' flight capability permits them to escape from predators (64, 72). With the low extrinsic death risk, these species have undergone selection for longevity. This prediction was further supported by the observation that arboreal mammals outlive their terrestrial counterparts (157).

Notably, although all these long-lived species seem to be selected for longevity due to protected environments, their longevity and disease-resistance mechanisms differ largely across species (**Table 1**). For example, naked mole rats live in subterranean burrows, where they rub their skin

Table 1 List of nonmodel mammals and their mechanisms and behaviors associated with longevity and disease

Age-associated disease	Species	Mechanisms	Behavioral and ecological adaptations
Cancer	Naked mole rat	High-molecular-mass hyaluronan (HMM-HA), early contact inhibition, unique INK4 locus, epigenome stability	Subterranean burrows, hypoxia, protected environment
	Blind mole rat	Interferon-mediated concerted cell death	Subterranean burrows, hypoxia, protected environment
	Elephant	Multiple *p53* and *LIF* copies	Large size, lack of nonhuman predators
	Whale	Whale-specific mutations in DNA repair genes	Large size, lack of nonhuman predators, deep water diving, cold tolerance
Cardiovascular disease	Bear	Protection and trophic effects by gene expression	Hibernation (responsive) with low metabolic rate
	Ground squirrel	Gene mutation and expression, protection from metabolic stresses and hypothermic arrhythmia	Hibernation (nonresponsive, periodic) with low metabolic rate
	Whale	Genes protecting from hypoxia	Deep water diving, cold tolerance
	Giraffe	Strong arterial pressure and resistance, regulation of cerebral blood flow	Tallest animal
Neurodegenerative disease	Degu	Alzheimer's disease–related genes similar to humans	Social organization
Inflammatory disease	Bat	Tolerance to viruses, reduced inflammation	Flight, crowded habitat
	Pangolin	Tolerance to viruses, reduced inflammation	Defensive scale armor
	Naked mole rat	Resistance to osteoarthritis, possibly through HMM-HA	Longevity
Counteracting hallmarks of aging	Beaver	Enhanced genome stability, high SIRT6-dependent DNA repair	Long-lived, large-sized, semiaquatic
	Naked mole rat	Enhanced proteostasis, higher translation fidelity	Longevity
	Spiny mice	Enhanced regeneration, blastema formation, dampened immunity	Skin autotomy and regeneration

against underground tunnels. The HMM-HA has likely evolved to provide flexible skin in adaptation to subterranean environments while also providing protection from cancer. Likewise, dampened inflammation in bats coevolved with their flight and crowded habitats while at the same time providing a longevity benefit by protecting bats from inflammaging. Therefore, exploration of a broad spectrum of unconventional model animals reveals numerous antiaging mechanisms that can be adopted to extend human healthspan and lifespan.

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