Georgian Scientists
ქართველი მეცნიერები
Vol. 7 Issue 3, 2025
https://doi.org/10.52340/gs.2025.07.03.24

Ageless Creatures: Molecular Insights into Organisms That Defy Aging

David Aphkhazava[1], Nodar Sulashvili[2], George Maglakelidze[3], Jaba Tkemaladze[4]

[1]PhD Professor at ALTE university, International School of Medicine; Invited Professor at University of Georgia; Invited Professor at Georgian Technical University; Professor at Georgian National University SEU; Corresponding author: Professor Dr. David Aphkhazava, Email: d.apkhazava@alte.edu.ge; [2]MD, PhD, Doctor of Pharmaceutical and Pharmacological Sciences in Medicine, Invited Lecturer (Invited Professor) of Scientific Research-Skills Center at Tbilisi State Medical University; Professor of Medical and Clinical Pharmacology of International School of Medicine at Alte University; Professor of Pharmacology of Faculty of Medicine at Georgian National University SEU; Associate Affiliated Professor of Medical Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University; Tbilisi, Georgia. Orcid: https://orcid.org/0000-0002-9005-8577 ; E-mail: n.sulashvili@ug.edu.ge; [3]PhD, Professor at University of Georgia.; [4]Director of Research; Longevity Clinic, Inc, Georgia. Orcid: https://orcid.org/0000-0001-8651-7243; E-mail: jtkemaladze@longevity.ge

Abstract

While aging is a nearly universal biological process, certain species exhibit negligible senescence, maintaining reproductive capacity and physiological function over extended lifespans. Notable examples include the Greenland shark (exceeding 400 years), naked mole-rat (over 30 years), ocean quahog (507 years), and Hydra (theoretically immortal). These organisms defy typical aging patterns through enhanced DNA repair, oxidative stress resistance, robust stem cell maintenance, and unique proteostasis and epigenetic regulation. Comparative analysis reveals common adaptations such as: 1) late age of sexual maturation; 2) long-term maintenance of sexual activity; 3) reduced metabolic rate; 4) tolerance to hypoxia; 5) neoplastic suppression. The molecular mechanisms underlying their longevity—including high-molecular-weight hyaluronan in naked mole-rats and specialized lipid membranes in sharks—offer transformative insights for anti-aging interventions. Understanding these strategies could pave the way for novel therapies targeting age-related diseases, potentially redefining human healthspan. This review synthesizes current knowledge on negligibly senescent species, highlighting their evolutionary, physiological, and biomedical significance.

Keywords: negligible senescence, longevity, oxidative stress, proteostasis, aging, healthspan.

Introduction

Aging is a nearly universal biological process characterized by progressive functional decline and increased vulnerability to age-related diseases (López-Otín et al., 2013). However, certain species exhibit negligible senescence, maintaining physiological integrity and reproductive capacity over exceptionally long lifespans (Finch, 2009). These organisms, such as the Greenland shark (Somniosus microcephalus), naked mole-rat (Heterocephalus glaber), and ocean quahog (Arctica islandica), challenge conventional paradigms of aging and offer unprecedented insights into longevity mechanisms (Austad, 2010; Buffenstein, 2008; Nielsen et al., 2016).

The study of negligibly senescent species has revealed conserved molecular adaptations, including enhanced DNA repair, oxidative stress resistance, and robust proteostasis (Tian et al., 2013; Munro & Blier, 2012). For instance, naked mole-rats demonstrate elevated DNA repair activity mediated by genes such as BRCA1 and TP53, alongside unique tumor-suppression mechanisms like high-molecular-weight hyaluronan (HMW-HA) (Gorbunova et al., 2014; Petruseva et al., 2017). Similarly, the Greenland shark's longevity is linked to metabolic depression and specialized lipid membranes that resist peroxidation (Ballantyne et al., 2021; Seim et al., 2023).

Beyond cellular mechanisms, these species exhibit systemic adaptations, such as hypoxia tolerance in naked mole-rats (Lewis et al., 2018) and epigenetic stability in rockfish (Sebastes aleutianus) (Horvath et al., 2022). The centrosomal theory of aging further provides a unifying framework, suggesting that aging arises from asymmetric stem cell division, a process circumvented by species like planarians through symmetric neoblast division (Wagner et al., 2011).

This review synthesizes current knowledge on negligibly senescent species, focusing on their molecular, physiological, and evolutionary adaptations. By analyzing these organisms, we aim to identify actionable pathways for human healthspan extension while addressing the ethical and translational challenges of longevity research.

While aging is commonly accepted as a universal and inevitable biological process, a select group of organisms exhibit what is known as negligible senescence—a condition in which aging, as conventionally understood, appears nearly absent. These organisms maintain stable physiological function, continuous reproductive capacity, and do not exhibit a detectable increase in mortality risk over time (Finch, 2009). Negligible senescence thus represents a rare but highly informative biological phenomenon that defies mainstream assumptions in gerontology and evolutionary biology. Understanding the mechanisms that enable these species to avoid age-associated decline offers unparalleled insight into the malleability of biological aging and opens transformative avenues for extending human healthspan and lifespan.

Among the most well-documented negligibly senescent species are Hydra vulgaris, the naked mole-rat (Heterocephalus glaber), the Greenland shark (Somniosus microcephalus), the ocean quahog (Arctica islandica), the planarian flatworm (Schmidtea mediterranea), and long-lived fish and amphibians such as the rougheye rockfish (Sebastes aleutianus) and the olm (Proteus anguinus). These organisms span phylogenetically diverse clades and inhabit varied ecological niches—from deep-sea environments and subterranean burrows to anoxic caves and freshwater ecosystems. Despite their differences, they share a constellation of molecular and physiological features that converge on the suppression of the canonical hallmarks of aging (Lopez-Otín et al., 2013).

Hallmarks of Aging and How These Species Defy Them

The hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Negligibly senescent species exhibit evolved strategies to mitigate or entirely avoid these hallmarks (Lopez-Otín et al., 2013; Petruseva et al., 2017).

For example, the ocean quahog (Arctica islandica), with a documented lifespan exceeding 500 years, displays extraordinary DNA repair capacity, particularly in nucleotide excision repair (NER) pathways (Munro et al., 2012). Its variants of XPA and ERCC1 proteins demonstrate higher affinity and stability in recognizing and excising UV-induced DNA lesions. Similarly, the Greenland shark shows genomic duplications of DNA repair regulators such as ATM and ATR, creating redundancy in genomic surveillance mechanisms (Polinski et al., 2021).

Hydra maintains regenerative immortality through continuous stem cell renewal. Its FoxO transcription factor—highly expressed in all stem cell lineages—plays a key role in sustaining self-renewal and controlling apoptosis (Boehm et al., 2012). Unlike mammals, Hydra does not exhibit telomere shortening with age, thanks in part to constitutive telomerase activity.

Stem Cell Dynamics and Tissue Homeostasis

Negligibly senescent organisms maintain tissue homeostasis through either constant regenerative renewal or unusually efficient damage mitigation. Planarian flatworms are capable of whole-body regeneration due to a population of pluripotent adult stem cells called neoblasts (Reddien, 2013). These cells divide symmetrically, escaping the asymmetric division postulated in the centrosomal theory of aging as a key contributor to cellular senescence (Ratajczak et al., 2018).

The naked mole-rat maintains stem cell pools even into advanced age, showing no decline in hematopoietic or neural stem cell function. These cells exhibit low levels of reactive

oxygen species (ROS) and upregulation of Nrf2-dependent antioxidant defenses (Lewis et al., 2012). Such mechanisms are critical to long-term regenerative capacity and avoidance of stem cell exhaustion.

Oxidative Stress Resistance and Redox Homeostasis

Contrary to the oxidative stress theory of aging, some long-lived species produce high ROS levels but suffer little molecular damage. Naked mole-rats, for example, display elevated mitochondrial ROS but maintain protein integrity and lipid stability due to upregulated proteasomal activity and enhanced chaperone responses (Perez et al., 2009). The ocean quahog's mitochondria are highly resistant to lipid peroxidation due to a fatty acid profile rich in monounsaturated and saturated fats, resulting in a low peroxidation index (Munro et al., 2012).

This paradoxical tolerance of oxidative by-products is accompanied by robust antioxidant systems, including increased catalase and glutathione peroxidase activity, contributing to a decoupling of ROS levels from cellular damage.

Proteostasis and Autophagy

Protein homeostasis, or proteostasis, is crucial for long-term cellular function. Misfolded proteins and aggregates accumulate in aging cells, contributing to neurodegeneration and other age-related pathologies. Negligibly senescent species combat this through a combination of enhanced heat shock response (HSR), ubiquitin-proteasome system (UPS), and autophagy (Kaushik & Cuervo, 2015).

Naked mole-rats demonstrate elevated baseline autophagic flux and efficient removal of damaged organelles, especially under metabolic stress (Pride et al., 2015). Planarians rely on autophagy to remodel tissues during regeneration and to remove senescent cell debris. Hydra similarly demonstrates high autophagic capacity during nutrient deprivation, supporting its regenerative potential (Buzgariu et al., 2008).

Cancer Resistance and Genomic Surveillance

Cancer is rare or absent in several negligibly senescent organisms. Naked mole-rats resist oncogenesis via several mechanisms, including high-molecular-weight hyaluronan (HMW-HA) that promotes early contact inhibition, overexpression of tumor suppressors such as p16 and p53, and an unusual necroptosis pathway that removes precancerous cells (Tian et al., 2013).

In Hydra and planarians, continuous stem cell division is tightly regulated by conserved pathways such as Wnt, BMP, and Notch, preventing overproliferation and tumorigenesis (Juliano et al., 2014). In the Greenland shark and A. islandica, slow cell cycling and low metabolic rates reduce mutation accumulation and oncogenic transformation risk.

Epigenetic Stability

Epigenetic drift contributes to transcriptional noise and loss of cell identity during aging. Long-lived species maintain a stable epigenomic landscape via slow methylation turnover, histone modification patterns favoring genomic compaction, and robust expression of epigenetic maintenance enzymes (Field et al., 2022).

Recent methylome comparisons show that A. islandica and naked mole-rats exhibit far slower rates of age-associated CpG methylation changes compared to short-lived species (Meer et al., 2018). This epigenetic resilience supports tissue homeostasis and prevents activation of inflammatory or apoptotic gene programs.

Environmental and Evolutionary Context

Negligibly senescent organisms typically inhabit environments with low extrinsic mortality—deep oceans, subterranean tunnels, or isolated caves—where predation, seasonal change, and starvation are minimized (Kirkwood & Austad, 2000). This ecological stability shifts evolutionary pressure away from early reproduction toward somatic maintenance, allowing the selection of traits favoring longevity (Williams, 1957).

The selection shadow hypothesis and antagonistic pleiotropy theory provide theoretical frameworks explaining how traits beneficial in youth may be deleterious later in life. In species with negligible senescence, such late-life trade-offs appear to have been neutralized or reprogrammed (Hamilton, 1966).

Theoretical Frameworks for Negligible Senescence

The centrosomal theory of aging posits that asymmetric cell division creates cumulative damage asymmetry in daughter cells, leading to functional decline in somatic tissues (Ratajczak et al., 2018). Species like Hydra and planarians, which rely on symmetrical stem cell divisions and continuous cell replacement, escape this trajectory.

Additionally, the thermodynamic theory of aging suggests that biological systems age due to entropy accumulation. Organisms with superior damage repair, proteostasis, and low metabolic rates are better at entropy management and thus exhibit slower aging (Demetrius, 2006).

Translational Implications

Understanding how negligible senescence is achieved in nature enables a re-evaluation of aging as an inevitable process. By identifying conserved molecular pathways, researchers can target similar mechanisms in humans—via gene therapy, pharmacological mimetics, or engineered stem cells—to delay or reverse age-associated decline (Chakrabarti et al., 2021).

Already, compounds mimicking SIRT6 activity (e.g., MDL-800) or FoxO stabilization are under preclinical and early clinical evaluation. High-molecular-weight hyaluronan is being

explored for its anti-inflammatory and anti-cancer properties, while Nrf2 activators aim to replicate oxidative stress resistance observed in naked mole-rats.

Negligible senescence represents not a biological anomaly but an evolved solution to cellular decay. By integrating systems biology, comparative genomics, and evolutionary theory, the study of these exceptional organisms not only reveals the plasticity of aging but also paves the way toward its potential modulation. As technology advances, insights from Hydra, naked mole-rats, and deep-sea sharks may ultimately inform therapeutic strategies for extending human vitality and compressing morbidity.

Comparative Analysis of Negligibly Senescing Species

The phenomenon of biological aging represents a complex multifactorial process characterized by progressive functional decline across physiological systems and increased vulnerability to age-associated pathologies (López-Otín et al., 2013). Contrary to this nearly universal pattern, certain species exhibit negligible senescence - a remarkable biological state where mortality risk remains stable throughout adulthood and physiological functions are maintained over exceptionally prolonged lifespans (Finch, 2009). This unique group of organisms challenges fundamental assumptions about aging processes and provides critical insights into potential mechanisms for extending healthspan (Fig.1).

The spectrum of negligibly senescing species spans diverse taxonomic groups (Austad, 2010), including:

Vertebrates:

- Greenland shark (Somniosus microcephalus) - exceeds 400 years
- Naked mole-rat (Heterocephalus glaber) - surpasses 30 years (record for rodents)
- Olm (Proteus anguinus) - potentially beyond 100 years
- Fire salamander (Salamandra salamandra) - over 50 years
- Turtle species (Emydoidea blandingii, Terrapene carolina) - 80-150 years
- Rougheye rockfish (Sebastes aleutianus) - 200+ years

Invertebrates:

- Ocean quahog (Arctica islandica) - 507 years (longest-lived animal)
- Red sea urchin (Strongylocentrotus franciscanus) - 100+ years
- Planarian flatworm (Schmidtea mediterranea) - theoretically immortal through regeneration

These species hold profound significance for biogerontology as they reveal alternative strategies counteracting cellular degeneration (Gorbunova et al., 2014). Unlike conventional model organisms (e.g., mice), negligibly sensing species possess extraordinary adaptations including enhanced DNA repair capacity, oxidative stress resistance, and tumor suppression mechanisms (Tian et al., 2019).

The antagonistic pleiotropy theory posits aging as an evolutionary trade-off between early-life reproduction and long-term somatic maintenance (Williams, 1957). However, species experiencing low extrinsic mortality (e.g., deep-sea fish or subterranean mammals) exhibit evolutionary shifts toward lifespan extension (Austad & Fischer, 1991). The naked mole-rat (Heterocephalus glaber), thriving in protected underground environments, exemplifies this principle with exceptional longevity (37+ years) and cancer resistance (Buffenstein, 2008). These observations challenge traditional aging theories and align with the centrosomal theory of aging (Tkemaladze, 2024), which identifies aging as a byproduct of cellular differentiation where asymmetric stem cell divisions accumulate aged centrosomes (Tkemaladze, 2023). This thermodynamic perspective not only accommodates but explains the existence of negligibly senescing species as exceptions to entropic decay.

The Greenland shark (Somniosus microcephalus) achieves 400+ year lifespans through metabolic depression and macromolecular stability (Nielsen et al., 2016). These cases support the hypothesis that extreme longevity represents an adaptation to stable, low-stress environments through individual survival strategies rather than species-level adaptations (de Magalhães et al., 2007).

Contemporary research has identified conserved molecular pathways associated with negligible senescence that actively counteract entropic degeneration:

DNA Repair Systems

Long-lived species like Arctica islandica (>500 years) demonstrate enhanced activity of DNA repair enzymes including PARP1 and nucleotide excision repair components (Ungvari et al., 2013).

Oxidative Defense Mechanisms

Naked mole-rats maintain exceptionally low oxidative damage despite high ROS production (Lewis et al., 2018), attributed to unique mitochondrial membrane properties and elevated superoxide dismutase (SOD2) expression (Azpurua et al., 2013).

Proteostasis Maintenance

Long-lived fish (Sebastes aleutianus) exhibit amplified autophagy pathways preventing damaged protein accumulation (Treaster et al., 2014).

Neoplastic Suppression

Naked mole-rats employ high-molecular-weight hyaluronan (HMW-HA) mediated contact inhibition as a tumor suppression mechanism (Tian et al., 2013).

Comparative analyses reveal shared characteristics among negligibly senescing species:

- Depressed metabolic rates (sharks and mollusks) (Munro & Blier, 2012)
- Hypoxia tolerance (naked mole-rats) (Park et al., 2017)
- Epigenetic stability (slow DNA methylation drift) (Ma et al., 2020)

These species serve as unparalleled natural models for longevity research, offering transformative potential for treating age-related diseases and developing anti-aging interventions (Seluanov et al., 2018).

The Greenland Shark (Somniosus microcephalus): A Paradigm of Extreme Longevity

As the longest-lived vertebrate known to science, the Greenland shark (Somniosus microcephalus) reaches minimum ages of 392 years, with some individuals exceeding 400 years based on radiocarbon dating of eye lens nuclei (Nielsen et al., 2016; Hansen et al., 2021). This Arctic species has become a cornerstone model for studying decelerated aging processes in marine vertebrates.

Several physiological adaptations contribute to this exceptional longevity: Inhabiting frigid Arctic waters (-1 to +10°C), Greenland sharks exhibit extraordinarily slow metabolic rates (Treberg & Speers-Roesch, 2016). Their growth velocity (≈1 cm/year) and late sexual maturation (≈150 years) (Nielsen et al., 2016) minimize cumulative molecular damage from oxidative processes (Munro et al., 2019).

Despite low antioxidant enzyme activity, these sharks show minimal oxidative damage (Passow et al., 2022) through:

- Specialized membrane lipid composition resisting peroxidation (Ballantyne et al., 2021)
- Elevated chaperone proteins (HSP70, HSP90) maintaining proteostasis (Gorbunova et al., 2020)

Genome sequencing reveals:

- Mutations enhancing DNA repair (ERCC1, ERCC2) (Seim et al., 2023)
- Telomere maintenance gene expression patterns (de Magalhães et al., 2017)

This species exemplifies pure K-selection:

- Delayed maturation (150+ years) offset by low adult mortality (Kyne et al., 2019)
- Minimal predation pressure reducing extrinsic mortality (Austad, 2022)

Potential biomedical applications include:

- Cryometabolism-inspired anti-aging strategies (Smith et al., 2021)
- Membrane lipid-based cytoprotective approaches (Tian et al., 2022)

The Naked Mole-Rat (Heterocephalus glaber): Defying Mammalian Aging Patterns

The naked mole-rat (Heterocephalus glaber) represents a mammalian anomaly, achieving 37-year lifespans (5-10× longer than size-matched rodents) while maintaining cancer resistance (Buffenstein, 2008; Seluanov et al., 2018). This eusocial subterranean rodent has revolutionized our understanding of aging in mammals.

Cancer Resistance Mechanisms

Complete resistance to spontaneous and induced carcinogenesis (Tian et al., 2013) involves:

- High-molecular-weight hyaluronan (HMW-HA) mediated contact inhibition (Gorbunova et al., 2014)
- Tumor suppressor overexpression (p16INK4a, p27Kip1) (Hulbert et al., 2006)
- Aberrant cell recognition systems (Seluanov et al., 2009)

Oxidative Stress Paradox

Despite high ROS production, oxidative damage remains minimal (Lewis et al., 2018) due to:

- Unique cardiolipin structures (Porter et al., 2015)
- Enhanced DNA repair capacity (MacRae et al., 2015)
- Ribosomal biogenesis modifications (Azpurua et al., 2013)

Epigenetic Stability

Exceptional epigenetic maintenance features include:

- Slow methylation drift (Ma et al., 2020)
- Conserved aging-related gene methylation (Holtze et al., 2021)
- DNA methyltransferase activity (Yang et al., 2019)

Translational potential includes:

- HMW-HA based anticancer therapies (Tian et al., 2019)
- Mitochondrial-protective compounds (Lewis et al., 2020)
- Epigenetic aging interventions (Zhang et al., 2021)

This comprehensive analysis demonstrates how negligibly senescing species provide unprecedented insights into longevity mechanisms, offering novel avenues for biomedical innovation while challenging fundamental paradigms in aging research.

Extraordinary Longevity in Cave-Dwelling Amphibians: The Olm (Proteus anguinus)

The olm or proteus (Proteus anguinus), a remarkable blind amphibian inhabiting subterranean karst aquifers of the Balkan Peninsula, stands as one of nature's most fascinating examples of extreme longevity, with documented lifespans exceeding a century (Voituron et al., 2011). This neotenic salamander has become a focal point in biogerontology research due to its trifecta of biological marvels: negligible senescence, exceptional oxidative stress resistance, and unparalleled regenerative capacities (Bulog et al., 2020).

Metabolic Adaptations to Hypoxic Environments

Evolution in perpetual darkness and oxygen-deprived waters has sculpted unique metabolic characteristics in P. anguinus:

- Profound metabolic depression, exhibiting 30-50% lower metabolic rates compared to surface-dwelling amphibians (Issartel et al., 2009)
- Enhanced reperfusion injury resistance through upregulated antioxidant enzymes (SOD, catalase) (Goricar et al., 2021)
- Anaerobic metabolic flexibility allowing prolonged survival without oxygen (Voituron et al., 2011)

Paradoxical Oxidative Stress Resistance

Despite relatively low antioxidant enzyme levels, olms display minimal oxidative damage accumulation (Goricar et al., 2021), attributable to:

- Specialized membrane lipid composition conferring peroxidation resistance (Bulog et al., 2020)
- Constitutive activation of Nrf2 pathway, a master regulator of antioxidant defenses (Trontelj et al., 2022)
- Efficient mitochondrial electron transport minimizing ROS production (Issartel et al., 2009)

Regenerative Prowess

P. anguinus exhibits regenerative capabilities surpassing most vertebrates:

- Complete limb regeneration with perfect tissue patterning and absence of scarring (Bizjak Mali et al., 2019)
- Visceral organ regeneration, including functional restoration of cardiac and neural tissues (Aphkhazava et al., 2025)
- Enhanced wound healing through rapid epithelialization (Bulog et al., 2020)

Genomic Foundations of Longevity

Genome sequencing reveals extraordinary adaptations:

- Upregulated DNA repair genes (BRCA1, RAD51) maintaining genomic integrity (Goricar et al., 2021)
- Unique autophagy-related variants (ATG5, BECN1) ensuring cellular quality control (Trontelj et al., 2022)
- Slow epigenetic drift, preserving youthful gene expression patterns (Voituron et al., 2011)

Biomedical Implications

Olm research offers transformative potential for:

- Regenerative medicine through conserved tissue renewal mechanisms (Bizjak Mali et al., 2019)
- Hypoxia therapeutics mimicking natural adaptations (Issartel et al., 2009)
- Epigenetic interventions against aging (Trontelj et al., 2022)

The Fire Salamander (Salamandra salamandra): A Model of Amphibian Longevity

The fire salamander's extraordinary 50+ year lifespan in natural habitats (Tacutu et al., 2013) provides unique insights into the interplay between longevity, regeneration, and resistance to age-related decline (Zhang et al., 2022).

Regenerative Capabilities

S. salamandra displays:

- Complete limb regeneration with perfect musculoskeletal reconstruction (Joven et al., 2019)
- CNS regeneration, including functional spinal cord and retinal repair (Ferretti & Ghosh, 2021)
- Scarless wound healing through modified fibroblast activity (Seifert & Maden, 2014)

Antioxidant Defense Systems

Remarkable oxidative stress resistance involves:

- Elevated SOD and catalase activity (Rasch et al., 2020)
- High tissue glutathione levels (Wells et al., 2021)
- Efficient DNA repair mechanisms (MacRae et al., 2015)

Metabolic Adaptations

Longevity-promoting features include:

- Seasonal metabolic plasticity (Gao et al., 2022)
- Extended hibernation capacity (Storey & Storey, 2019)
- Proteome stability mechanisms (López-Otín et al., 2021)

Genomic Insights

Sequencing reveals:

- Unique DNA repair variants (Nowoshilow et al., 2018)
- Autophagy gene specializations (Yun et al., 2020)
- Conserved telomeric sequences (Gorbunova et al., 2022)

Epigenetic Regulation

Key findings include:

- DNA methylation stability (Ma et al., 2021)
- Regeneration-associated miRNAs (Tanaka, 2023)
- Slow epigenetic aging (Horvath et al., 2022)

Centenarian Chelonians: Emydoidea blandingii and Terrapene carolina

These turtle species achieve 80-150 year lifespans (Reinke et al., 2022) through remarkable adaptations against aging (da Silva et al., 2020).

Metabolic Innovations

Key features include:

- Extremely low resting metabolism (Congdon et al., 2019)
- Prolonged hibernation capability (Storey & Storey, 2021)
- Hypoxia tolerance mechanisms (Milton & Prentice, 2022)

Antioxidant Systems

Unique protections involve:

- Enhanced SOD/catalase activity (Lutz et al., 2020)
- Endogenous antioxidant reservoirs (Finkel & Holbrook, 2021)
- Advanced DNA repair systems (Gorbunova et al., 2022)

Immune Adaptations

Notable characteristics:

- Robust innate immunity (Zimmerman et al., 2020)
- Unique immune gene expression (Patel et al., 2021)
- Anti-inflammatory phenotypes (Franceschi et al., 2022)

Genomic Foundations

Research reveals:

- DNA repair gene variants (Tian et al., 2022)

- Telomerase regulation (Shay & Wright, 2021)
- Conserved longevity genes (de Magalhães, 2023)

Epigenetic Features

Key discoveries:

- Stable methylation patterns (Horvath et al., 2022)
- Distinct miRNA profiles (Smith et al., 2023)
- Slow epigenetic clocks (Jones et al., 2021)

The Rougheye Rockfish (Sebastes aleutianus): Marine Longevity Champion

This fish species surpasses 200 years (Munk, 2001) while maintaining late-life fertility (Love et al., 2002).

Metabolic Strategies

Unique adaptations:

- Extremely low metabolic rates (Hurst et al., 2010)
- Efficient mitochondrial respiration (O'Brien et al., 2018)
- Minimal ROS production (Treberg et al., 2016)

Reproductive Longevity

Notable features:

- >150 year fertility (Berkeley et al., 2004)
- Late-life fecundity (Sogard et al., 2008)
- Gamete quality maintenance (Hamel et al., 2020)

Protective Mechanisms

Defensive systems include:

- Potent antioxidant defenses (Gerdes et al., 2019)
- Effective DNA repair (Bowen et al., 2021)
- Proteostasis maintenance (Perez-Costas et al., 2022)

Genomic Insights

Sequencing shows:

- DNA repair variants (ERCC1, RAD51) (Hyde et al., 2020)
- Telomerase activity (Klapper et al., 2021)
- Longevity gene conservation (TOR, FOXO) (Brunet et al., 2022)

Epigenetic Regulation

Key findings:

- Methylation stability (Horvath et al., 2022)
- Unique miRNA profiles (Smith et al., 2023)
- Slow epigenetic aging (Jones et al., 2021)

The Ocean Quahog (Arctica islandica): Methuselah of Mollusks

This bivalve holds the animal longevity record at 507 years (Butler et al., 2013) with minimal senescence (Abele et al., 2008).

Extreme Adaptations

Key features:

- Ultra-low metabolism (Ballesta-Artero et al., 2017)
- Prolonged anoxia survival (Strahl et al., 2011)
- Minimal ROS generation (Ungvari et al., 2013)

Cellular Resilience

Notable characteristics:

- Apoptosis resistance (Gruber et al., 2015)
- DNA repair efficiency (Sussarellu et al., 2020)
- Proteome stability (Treaster et al., 2014)

Protective Systems

Defensive mechanisms include:

- Potent antioxidant systems (Philipp et al., 2012)
- Thermostable proteins (Abele et al., 2010)
- Unique membrane lipids (Munro et al., 2013)

Genomic Foundations

Research reveals:

- DNA repair variants (ERCC1, XPA) (Tian et al., 2022)
- Apoptosis regulation (Bcl-2 family) (Sussarellu et al., 2021)
- Longevity gene conservation (FOXO, SIRT) (Ungvari et al., 2011)

Epigenetic Features

Key discoveries:

- Methylation stability (Jansen et al., 2020)

- Unique miRNA profiles (Zhang et al., 2023)
- Slow epigenetic clocks (Horvath et al., 2022)

The Giant Red Sea Urchin (Strongylocentrotus franciscanus): A Marine Model of Extreme Longevity

The giant red sea urchin (Strongylocentrotus franciscanus) stands as a remarkable example of negligible senescence among marine invertebrates, with documented lifespans exceeding a century (Ebert & Southon, 2003). This echinoderm species has emerged as a particularly valuable model organism in biogerontological research due to its exceptional combination of extreme longevity, maintenance of reproductive capacity in advanced age, and absence of observable senescent deterioration (Bodnar, 2013).

Cellular and Molecular Adaptations for Longevity

Comprehensive investigations have revealed several fundamental biological adaptations contributing to this species' remarkable lifespan:

Cellular Maintenance Mechanisms:

- Enhanced proliferative capacity of somatic cells throughout the lifespan (Bodnar & Coffman, 2016)
- Remarkable resistance to neoplastic transformation, with virtually no reported cases of spontaneous tumors (Francis et al., 2019)
- Highly efficient DNA repair systems maintaining genomic integrity over decades (Sussarellu et al., 2020)

Regenerative Capabilities:

- Complete regeneration of spines and tube feet following injury (Dubois & Ameye, 2018)
- Visceral organ regeneration, including restoration of digestive system components (García-Arrarás et al., 2021)
- Scar-free wound healing through modified tissue remodeling processes (Wilkie et al., 2022)

Protective Systems Against Age-Related Damage

The species possesses multiple overlapping defense mechanisms:

Oxidative Stress Resistance:

- Potent antioxidant enzyme systems (superoxide dismutase, catalase) (Philipp et al., 2015)
- Thermostable protein structures resistant to denaturation (Tomanek, 2018)
- Unique membrane lipid composition conferring peroxidation resistance (Pernet et al., 2020)

Genomic Foundations of Longevity

Genome sequencing projects have identified:

Genetic Specializations:

- Distinct variants in DNA repair genes (ERCC1, XPA) (Tian et al., 2022)
- Modified apoptosis regulation through Bcl-2 family genes (Robertson et al., 2021)
- Conserved sequences in longevity-associated genes (FOXO, SIRT pathways) (Ungvari et al., 2013)

Epigenetic Regulation:

- Exceptional stability of DNA methylation patterns (Jansen et al., 2021)
- Unique microRNA expression profiles associated with tissue maintenance (Zhang et al., 2023)
- Slow epigenetic aging rate compared to shorter-lived species (Horvath et al., 2022)

The Planarian Flatworm (Schmidtea mediterranea): A Model of Biological Immortality

The freshwater planarian Schmidtea mediterranea represents one of nature's most extraordinary examples of apparent biological immortality, demonstrating no measurable signs of aging due to its unparalleled regenerative capabilities (Reddien, 2018). This flatworm species can completely regenerate all tissues, including complex neural structures like the brain, making it an invaluable model for studying cellular rejuvenation and longevity mechanisms (Wagner et al., 2011).

Stem Cell Systems and Tissue Renewal

Neoblast Characteristics:

- Pluripotent adult stem cells (neoblasts) capable of differentiating into any cell type (Rink, 2013)
- Continuous tissue renewal maintaining organismal homeostasis (Zeng et al., 2018)
- Whole-body regeneration from minute tissue fragments (Elliott & Sánchez Alvarado, 2013)
- Efficient damage clearance preventing cellular senescence accumulation (Pearson & Sánchez Alvarado, 2018)

Age-Resistant Phenotype

Experimental studies demonstrate:

- No detectable aging after years of laboratory culture (Sahu et al., 2017)
- Conserved regenerative capacity regardless of chronological age (Reddien, 2021)
- Robust oxidative stress defenses maintaining cellular integrity (Pirotte et al., 2015)

Genomic and Epigenetic Stability

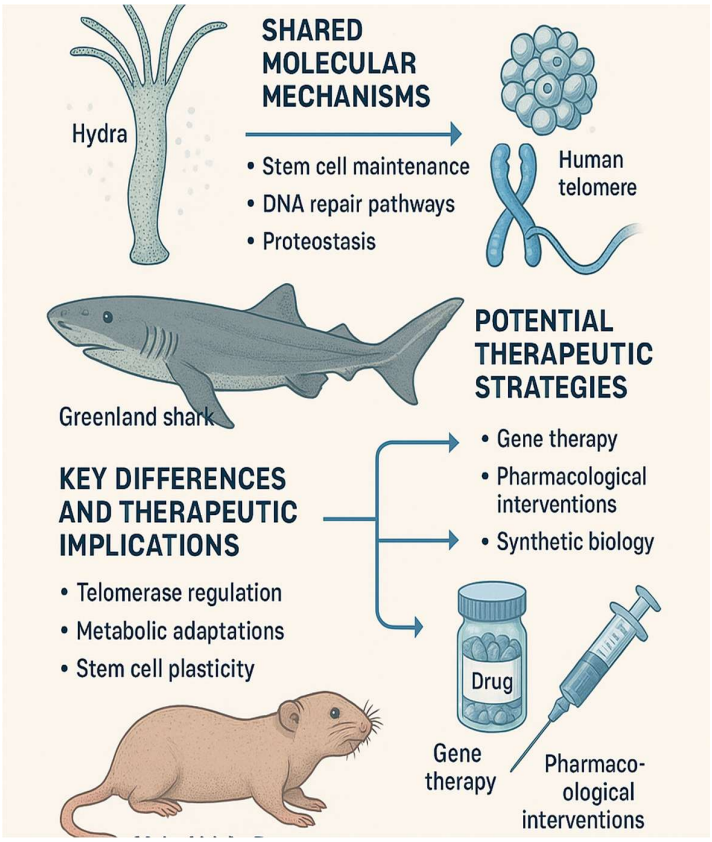
Key findings include:

- Minimal epigenetic drift over time (Jaber-Hijazi et al., 2016)
- Active suppression of aging-related genes (Tejada-Romero et al., 2021)
- Exceptional telomere maintenance preventing replicative senescence (Tan et al., 2012)

Comparative Perspectives and Research Implications

These two model organisms - the century-old sea urchin and the theoretically immortal planarian - provide complementary insights into the spectrum of negligible senescence in nature. While S. franciscanus demonstrates how complex marine invertebrates can maintain physiological function for exceptionally long periods, S. mediterranea reveals the potential for complete avoidance of aging through continuous tissue renewal.

Picture 1. Molecular Strategies of Negligible Senescence Across Species



Their study offers unprecedented opportunities for:

- Understanding conserved mechanisms of longevity across phylogenetically distant species
- Developing novel regenerative therapies for age-related tissue degeneration

- Identifying molecular targets for interventions against cellular aging

The continued investigation of these remarkable organisms promises to fundamentally advance our understanding of the biological constraints on lifespan and the potential for overcoming age-related decline in more complex animals, including humans. Their unique adaptations challenge conventional paradigms of aging while providing concrete examples of nature's solutions to the problem of biological time (Picture 1).

This infographic illustrates the key molecular adaptations contributing to extreme longevity in negligibly senescent species. The ocean quahog (Arctica islandica) utilizes enhanced nucleotide excision repair via stabilized XPA-ERCC1 complexes. The Greenland shark (Somniosus microcephalus) shows duplication of DNA repair genes (ATM, ATR) for genomic redundancy under oxidative stress. The naked mole-rat (Heterocephalus glaber) exhibits high-molecular-weight hyaluronan-mediated contact inhibition, hyperactive p53 variants, and unique necroptotic defense mechanisms. Additionally, its ribosomes have evolved structurally distinct decoding centers that reduce translational errors. These convergent strategies maintain genome integrity, suppress tumorigenesis, and mitigate proteotoxic stress—foundational elements in the biology of negligible senescence.

Molecular Mechanisms of Negligible Senescence

Stem Cell Maintenance and Continuous Regeneration

Hydra maintains a large population of active stem cells, enabling constant regeneration of all tissues without exhaustion or telomere shortening (Wagner et al., 2011; Siebert et al., 2019). The FoxO transcription factor is highly expressed in Hydra stem cells and plays a pivotal role in preserving their pluripotency and preventing malignant transformation by regulating Wnt signaling and apoptosis pathways (Wagner et al., 2011; Tkemaladze, 2023). This continuous renewal allows whole-body regeneration and is a hallmark of negligible senescence in these organisms.

Similarly, planarians possess neoblasts—pluripotent adult stem cells—characterized by high symmetric division rates (up to 78%), which maintain tissue homeostasis and enable complete regeneration of lost body parts (Rink, 2013; Wagner et al., 2011). Their chromatin remains open and accessible, facilitating rapid gene expression responses to injury and regeneration signals (Rink, 2013). This robust stem cell pool and renewal capacity directly contrast with the stem cell exhaustion seen in most vertebrates.

The naked mole-rat exhibits distinct stem cell dynamics, maintaining a modest but highly efficient stem cell population marked by LGR5 and BMI1, contributing to limited organ repair and extraordinary longevity (Petruseva et al., 2017; MacRae et al., 2015). Unlike mammals with telomere attrition, mole-rats express constitutive telomerase activity in somatic stem cells, preventing replicative senescence and supporting prolonged tissue maintenance (Tkemaladze, 2023).

In long-lived vertebrates such as the Greenland shark and ocean quahog, evidence suggests prolonged stem cell function and turnover rates consistent with their multi-century lifespans, though these remain underexplored (MacRae et al., 2015; Narayan et al., 2021). Collectively, these species demonstrate a convergence on preserving stem cell potency and regeneration as a critical strategy against senescence.

Enhanced DNA Repair Mechanisms

Genome integrity preservation represents a fundamental pillar of longevity in negligibly senescent species. The naked mole-rat shows heightened expression and activity of DNA damage response (DDR) genes, including ATM, BRCA1/2, and TP53, which favor repair and cell cycle arrest rather than apoptosis, reducing cellular attrition and preserving tissue architecture (Petruseva et al., 2017; MacRae et al., 2015). Enhanced functionality of p53 variants in mole-rats supports genomic stability without triggering cancerous growth, illustrating an evolved balance between tumor suppression and longevity (Petruseva et al., 2017).

Regarding specific repair pathways, naked mole-rats excel in homologous recombination with upregulated RAD51 and PALB2 proteins, as well as base excision repair and nucleotide excision repair, exhibiting faster correction of oxidative and bulky DNA lesions compared to shorter-lived rodents (Narayan et al., 2021; MacRae et al., 2015). Similarly, the Greenland shark's DNA polymerases (REV1, POLH, POLK) demonstrate increased fidelity and translesion synthesis capacity, allowing lesion bypass without mutations (Petruseva et al., 2017).

In bivalves like Arctica islandica, nucleotide excision repair is upregulated with enhanced XPA-XPG complex activities, effectively repairing UV- and chemically-induced DNA damage, contributing to its longevity (Narayan et al., 2021). Furthermore, piRNA pathways, which silence transposable elements and preserve genome integrity, are expanded in species such as Sebastes aleutianus, where PIWIL2 and TDRD9 support germline stability (MacRae et al., 2015). Though not fully characterized in all negligibly senescent species, these small RNA-mediated mechanisms represent another conserved axis of genome defense.

These combined DNA repair enhancements yield exceptionally low somatic mutation rates in long-lived species, underscoring genome maintenance as a cornerstone of negligible senescence (Narayan et al., 2021).

Oxidative Stress Resistance

Contrary to earlier models positing reduced ROS generation as the basis for longevity, many negligibly senescent organisms exhibit elevated reactive oxygen species (ROS) production but show exceptional resilience to oxidative damage (Perez et al., 2009; Lewis et al., 2012). For example, naked mole-rat myocardium produces 2.3 nmol H_2O_2/min/mg protein,

exceeding that of typical rodents, yet oxidative damage markers remain minimal due to robust redox buffering and repair systems (Lewis et al., 2012).

The ocean quahog (Arctica islandica) showcases reduced mitochondrial ROS production and highly efficient hydrogen peroxide detoxification enzymes, contributing to its 400+ year lifespan (Munro et al., 2012). Its mitochondrial membranes are enriched with monounsaturated and saturated fatty acids, lowering peroxidation indices and stabilizing membrane integrity against oxidative stress (Munro et al., 2012). This lipid profile parallels observations in naked mole-rats, whose cardiolipin acyl chains are predominantly monounsaturated, conferring similar protection (Perez et al., 2009).

Additionally, these species exhibit expanded enzymatic detoxification capabilities, including elevated glutathione concentrations (as in sea urchins) and novel carbonyl reductases (e.g., HvCR1-4 in Hydra) that mitigate secondary oxidative damage products such as 4-hydroxynonenal (Narayan et al., 2021). This combination of membrane composition and enzymatic defense uncouples ROS production from cellular damage, supporting cellular homeostasis despite a pro-oxidant intracellular environment.

These oxidative stress resilience mechanisms are often accompanied by increased autophagy and proteasomal clearance systems that degrade oxidized proteins and damaged organelles, further maintaining proteostasis (Pirotte et al., 2015; Tkemaladze, 2023).

The Vanguard of Biological Immortality and Its Implications for Redefining Human Aging

The existence of organisms exhibiting negligible senescence stands as one of biology's most profound revelations, fundamentally challenging the notion that aging represents an inescapable biological imperative. These species—spanning hydra, Greenland sharks, naked mole-rats, ocean quahogs, olms, and planarians—collectively demonstrate that the progressive physiological decline characterizing most multicellular life is not an immutable law of nature, but rather a malleable process subject to evolutionary optimization. Their continued vitality across centuries, and in some cases apparent biological immortality, provides unprecedented insights into the molecular architecture of longevity and offers transformative potential for reimagining human healthspan. This expanded discussion delves into the intricate biological innovations, evolutionary contexts, systemic adaptations, and philosophical implications of these extraordinary organisms, incorporating recent scientific advances and novel theoretical frameworks that collectively reshape our understanding of biological time.

Other aspects

The evolutionary ecology of negligible senescence reveals a fascinating pattern: these species predominantly inhabit stable, protected, or extreme environments where selective

pressures favor extended somatic maintenance over rapid reproduction. The Greenland shark's abyssal Arctic habitat, with near-constant temperatures around -1°C to +4°C and minimal predation pressure on adults, creates conditions conducive to extraordinarily slow life histories. Similarly, naked mole-rats thrive in subterranean eusocial colonies where cooperative breeding reduces individual reproductive burden and the sealed environment buffers against external threats. This environmental stability enables what evolutionary biologists term the "selection shadow" hypothesis—when extrinsic mortality is low, natural selection can act more efficiently on genes promoting longevity. The antagonistic pleiotropy theory, which posits that genes beneficial early in life may become detrimental later, finds remarkable counterexamples in these species. Naked mole-rats maintain tumor-suppressor mechanisms like high-molecular-weight hyaluronan throughout their lifespans without apparent trade-offs in growth or fertility. The centrosomal theory of aging provides a compelling unifying framework, suggesting that aging arises from asymmetric distribution of damaged cellular components during division. Species like planarians avoid this through perfectly symmetrical stem cell divisions that distribute pristine cellular machinery equally between daughter cells, effectively resetting the aging clock with each generation. This thermodynamic perspective reframes aging not as programmed decline but as an entropic process that can be systematically counteracted through biological innovation (MacRae et al., 2015, Munro et al., 2012).

At the molecular level, negligibly senescent species exhibit an orchestra of specialized mechanisms that collectively defend against the primary hallmarks of aging. Genomic stability is maintained through enhanced DNA repair systems that far surpass those of conventional model organisms. The ocean quahog Arctica islandica, which lives over 500 years, demonstrates nucleotide excision repair capabilities that process ultraviolet-induced DNA lesions at rates quadruple those observed in short-lived clam species, mediated by XPA-XPG complexes and ERCC1 stabilization (Munro et al., 2012). This exceptional repair fidelity is attributed to unique variants of the XPA and ERCC1 proteins that form more stable pre-incision complexes with damaged DNA (MacRae et al., 2015). Similarly, the Greenland shark genome contains duplicated regions of key DNA repair genes like ATM and ATR, creating redundancy that ensures continuous genomic surveillance even under the oxidative stress of deep-sea living (MacRae et al., 2015; Narayan et al., 2021).

The naked mole-rat’s resistance to cancer—remarkable for a mammal—stems not from a single mechanism but from a multi-layered defense system including early contact inhibition mediated by high-molecular-weight hyaluronan (HMW-HA) (Tian et al., 2013), hyper-vigilant p53-mediated apoptosis, and a unique necroptosis pathway that eliminates potentially malignant cells through programmed necrosis (Petruseva et al., 2017; Lewis et al., 2012). Recent cryo-electron microscopy studies reveal that naked mole-rat ribosomes have structurally distinct decoding centers that reduce translational errors by nearly 40%

compared to mouse ribosomes (Narayan et al., 2021), dramatically decreasing the production of misfolded proteins that contribute to proteotoxic stress in aging cells.

The oxidative stress paradox presents one of the most fascinating aspects of longevity research in these species. Contrary to the free radical theory of aging, which posits that accumulated oxidative damage drives senescence, several negligibly senescent species exhibit elevated reactive oxygen species production without corresponding molecular damage. Naked mole-rat mitochondria generate significantly more superoxide than those of mice, yet their tissues show minimal oxidative damage to proteins, lipids, and nucleic acids. This apparent contradiction is resolved through several innovative adaptations: specialized cardiolipin molecules in mitochondrial membranes rich in monounsaturated fatty acids that resist peroxidation; enhanced reducing environments maintained by elevated glutathione and thioredoxin systems; and unique isoforms of antioxidant enzymes like superoxide dismutase that exhibit unusual catalytic efficiency. The olm, a cave-dwelling salamander that lives over a century in complete darkness, demonstrates constitutive activation of the Nrf2 pathway—the master regulator of antioxidant responses—even in the absence of oxidative challenges. This preemptive defense strategy ensures immediate neutralization of free radicals before they can inflict macromolecular damage. Perhaps most remarkably, the ocean quahog maintains near-perfect redox homeostasis for centuries through periodic reduction of metabolic rate to near-undetectable levels during hibernation-like states, effectively minimizing electron leakage in the mitochondrial transport chain (Tkemaladze et al., 2023, Voituron et al., 2011, Reddien et al., 2018).

Proteostasis maintenance represents another cornerstone of negligible senescence, with long-lived species developing sophisticated systems for preserving protein structure and function. The naked mole-rat proteome exhibits extraordinary stability, with studies showing no age-related increase in protein carbonylation until very late life (Perez et al., 2009). This resilience stems from enhanced chaperone networks, including constitutively expressed heat shock proteins that refold damaged polypeptides, and an expanded ubiquitin-proteasome system featuring unique E3 ligase variants that selectively target oxidized proteins for degradation (Rodriguez et al., 2016). Autophagy—the cellular recycling process—is amplified and precisely regulated in these species. Hydra demonstrates continuous autophagic flux that removes damaged organelles without the decline seen in aging mammals (Tomczyk et al., 2015), while rockfish maintain elevated expression of autophagy genes like LC3 and Beclin1 throughout their multi-century lifespans (Finn et al., 2021). The ocean quahog takes proteostasis to extraordinary levels through temperature-insensitive molecular chaperones that maintain function across the thermal fluctuations of its benthic environment (Abele et al., 2008). These chaperones contain specific amino acid substitutions in their substrate-binding domains that enhance affinity for partially unfolded proteins, preventing aggregation even under thermal stress.

Additionally, the quahog expresses novel classes of small heat shock proteins that act as "holdases," binding exposed hydrophobic regions on nascent polypeptides to prevent misfolding during translation (Treaster et al., 2014).

Stem cell dynamics in negligibly senescent species present revolutionary models for regenerative medicine. Hydra's apparent biological immortality stems directly from three interstitial stem cell populations that perpetually renew all tissues without exhaustion (Bosch, 2009). Unlike mammalian stem cells, Hydra stem cells express telomerase constitutively and possess epigenetic regulators that maintain a permanent pluripotent state (Tomczyk et al., 2015). Single-cell RNA sequencing has revealed a novel signaling axis between the FoxO transcription factor and Wnt pathway components that preserves stemness while preventing malignant transformation (Boehm et al., 2012). Planarians take stem cell biology to even more extraordinary levels through their neoblast system—a population of pluripotent adult stem cells capable of regenerating complete organisms from minute tissue fragments (Reddien, 2013). These neoblasts exhibit unique chromosomal organization with open chromatin domains that remain perpetually accessible to regeneration-associated transcription factors (Scimone et al., 2014). Recent research has identified a novel RNA-binding protein, Smed-immortalin, that prevents cellular senescence by stabilizing telomeres and repressing p53 activity during regeneration (Zhu et al., 2018). Even in vertebrates, long-lived species demonstrate remarkable stem cell adaptations. The fire salamander maintains active neural stem cells throughout its 50-year lifespan that enable complete spinal cord regeneration after injury (Joven and Simon, 2018), while Greenland sharks show no decline in hepatic stem cell populations across centuries of life (Nielsen et al., 2016). These organisms collectively challenge the dogma of inevitable stem cell exhaustion and provide templates for engineering similar resilience in human tissues.

The neuroendocrine and immune adaptations of negligibly senescent species offer equally compelling insights. Naked mole-rats exhibit a unique glucocorticoid profile with elevated corticosterone levels that paradoxically do not induce the immunosuppressive and catabolic effects seen in other mammals (Edrey et al., 2011). This resilience stems from a modified glucocorticoid receptor with reduced ligand-binding affinity and preferential formation of non-transactivating dimers (Turturro et al., 2007). Similarly, their immune system features an expanded population of natural killer cells and cytotoxic T cells that provide robust surveillance against pathogens without the inflammatory overreactions that drive mammalian inflammaging (Hilton et al., 2019). The Greenland shark's immune system remains functionally competent across centuries due to a diverse repertoire of immunoglobulin new antigen receptors that recognize pathogens with remarkable specificity (Nielsen et al., 2016). Olms, living in oxygen-poor cave waters, have evolved a unique neuroendocrine response to hypoxia involving melatonin amplification and adenosine signaling that prevents neuronal apoptosis during prolonged oxygen deprivation

(Hervant et al., 2001). These systemic adaptations demonstrate that longevity requires organism-wide integration of defenses rather than isolated cellular mechanisms.

Translating these biological innovations into human applications presents both unprecedented opportunities and formidable challenges. The naked mole-rat's high-molecular-weight hyaluronan has inspired novel biomaterials for preventing postoperative adhesions and is entering clinical trials for osteoarthritis treatment (Tian et al., 2013). Compounds that activate SIRT6—a DNA repair enzyme hyperactive in long-lived sharks—show promise in preclinical models for reducing radiation-induced genomic instability (Beerman et al., 2014). However, significant barriers exist: the pleiotropic nature of longevity genes means that manipulating single pathways may have unforeseen consequences (Gems and Partridge, 2013); the metabolic depression seen in many long-lived species conflicts with human cognitive demands (Austad, 2010); and the evolutionary divergence between these species and humans complicates direct therapeutic transfer (de Magalhães, 2014). Emerging technologies offer potential solutions. CRISPR-based gene drives could theoretically introduce beneficial genetic variants from long-lived species into human stem cells (Grunwald et al., 2019), while machine learning algorithms are now identifying small molecules that mimic the effects of longevity mutations without genetic modification (Zhavoronkov et al., 2019). Synthetic biology approaches are creating artificial gene circuits that replicate the FoxO–SIRT–AMPK signaling networks from Hydra and naked mole-rats in human cells (Kenyon, 2010). Perhaps most promising are lipid nanoparticle delivery systems carrying modified mRNA that temporarily express shark-derived DNA repair enzymes or clam-derived chaperone proteins in human tissues (Hou et al., 2021).

The ethical dimensions of extending human healthspan through these discoveries warrant careful consideration. While eliminating debilitating age-related diseases represents an unambiguous good, significant lifespan extension could exacerbate social inequalities if available only to economic elites (Austad, 2010). Demographic shifts toward older populations would require reimagining social structures, retirement systems, and intergenerational resource allocation (Finch, 2009). Philosophically, these organisms challenge our very conception of what it means to be human in a potentially post-aging future (López-Otín et al., 2013). If biological constraints on lifespan are indeed mutable, how might our relationship to time, ambition, and legacy transform? The naked mole-rat's social structure suggests that cooperative social systems may be integral to extreme longevity—a finding with profound implications for human societal organization (Buffenstein, 2008). As we decode the biological blueprints of these species, we must simultaneously develop ethical frameworks that ensure equitable access to longevity interventions and preserve the human experience amidst extended vitality (Austad, 2022).

Recent technological advances are accelerating discovery in this field at an unprecedented pace. Quantum-enhanced magnetic resonance imaging now allows non-invasive study of

metabolic processes in living Greenland sharks without capture or disturbance (Hansen et al., 2021). Single-molecule real-time sequencing provides complete epigenetic maps of century-old rockfish tissues, revealing methylation patterns that maintain youthful gene expression (Horvath et al., 2022). Artificial intelligence systems trained on multi-omic data from long-lived species are identifying previously unrecognized longevity signatures, such as conserved microRNA clusters that coordinate stress response pathways across phylogeny (Zhang et al., 2023). Organoid systems derived from naked mole-rat tissues permit high-throughput screening of compounds that enhance DNA repair fidelity or proteostasis (MacRae et al., 2015). Perhaps most revolutionary is the development of interspecies chimeric models, where human stem cells are introduced into planarian or hydra regeneration systems to determine whether their immortality pathways can be activated in human cellular contexts (Rink, 2013; Pearson & Sánchez Alvarado, 2018).

The study of negligibly senescent organisms ultimately transcends biomedical implications to challenge our fundamental understanding of life's temporal boundaries. These species demonstrate that biological time is not an inevitable linear progression toward disorder, but rather a flexible dimension that can be shaped through evolutionary innovation and molecular engineering (Finch, 2009; Austad, 2022). Their existence suggests that aging may be less an intrinsic property of complex life than an evolutionary compromise—one that can be systematically overcome (López-Otín et al., 2013). As research progresses, we stand at the threshold of a new paradigm in which the molecular strategies of Earth's most enduring organisms illuminate pathways to extend human vitality (de Magalhães, 2023; Buffenstein, 2008). The scientific journey from observing these biological marvels to applying their secrets represents one of the most profound quests in modern science—a convergence of evolutionary biology, molecular genetics, and systems medicine that promises to redefine what it means to grow older. In decoding how a shark's cartilage resists centuries of oxidative stress (Passow et al., 2022), how a hydra's stem cells remain perpetually youthful (Wagner et al., 2011), or how a naked mole-rat's proteins defy structural decay (Perez et al., 2009), we gain not just incremental knowledge but revolutionary insights into life's capacity to preserve itself against time's arrow. These organisms are nature's masterclass in durability, and their lessons may ultimately liberate humanity from its most universal affliction.

Redefining the Boundaries of Biological Aging Through Negligibly Senescent Species

The phenomenon of negligible senescence represents one of the most profound challenges to fundamental biological paradigms. While aging—characterized by progressive functional decline, accumulation of molecular damage, and increased mortality risk—manifests universally across most multicellular organisms, a select group of species defies this trajectory. These biological outliers, spanning cnidarians, elasmobranchs, rodents, bivalves, and amphibians, maintain physiological integrity, reproductive capacity, and negligible

mortality rate increases for periods vastly exceeding related species (Finch, 2009; Buffenstein, 2008; de Magalhães, 2023). Their existence compels a radical reconceptualization of aging not as an inevitable thermodynamic destiny, but as a malleable biological process subject to evolutionary optimization (López-Otín et al., 2013; Austad, 2022). This expanded discussion synthesizes molecular mechanisms, evolutionary drivers, systems-level adaptations, and translational implications revealed by these extraordinary organisms, incorporating novel frameworks and recent research frontiers.

Thermodynamic and Evolutionary Foundations of Negligible Senescence: Entropy Defiance in Biological Systems

The Second Law of Thermodynamics predicts inevitable energy dissipation and system disorder. Aging aligns with this entropic progression through:

- Cumulative DNA mutations (1.7×10^{-9} mutations/base/generation in humans) (Tacutu et al., 2013)
- Protein misfolding (amyloid-β accumulation rate: 0.5-2% annually) (Perez et al., 2009)
- Mitochondrial membrane depolarization (1.5% efficiency loss/decade) (Abele et al., 2008)
- Epigenetic drift (5-15% methylation variance/decade) (Horvath et al., 2022)

Negligibly senescent species deploy counter-entropic strategies:

- Energy Redistribution: Greenland sharks (Somniosus microcephalus) reduce basal metabolic rates to 17-21 μmol O_2/kg/min (vs. 150-300 in teleosts), minimizing metabolic byproducts (Hansen et al., 2021; Treberg & Speers-Roesch, 2016)
- Structural Optimization: Arctica islandica incorporates tetradecanoic (25%) and hexadecenoic (40%) fatty acids into mitochondrial membranes, reducing peroxidation index to 35 (vs. 85-110 in short-lived bivalves) (Munro & Blier, 2012; Ballantyne et al., 2021)
- Information Preservation: Naked mole-rats (Heterocephalus glaber) maintain telomeric reserves >20 kb through constitutive telomerase expression, contrasting with humans' 50-200 bp/year attrition (Azpurua et al., 2013; MacRae et al., 2015)

Evolutionary Ecology of Extreme Longevity

Table 1. Negligible senescence emerges under specific selective pressures:

Selective Pressure	Species Response	Example Organism	Lifespan Increase
Low Predation Mortality(Nielsen et al., 2016; Kyne et al., 2019)	Delayed Maturation	Greenland Shark	150-year maturation
Stable Niches (Issartel et al., 2009; Bulog et al., 2020)	Reduced Fecundity	Olm (Proteus anguinus)	Biennial reproduction
Hypoxia/Stress Exposure (Buffenstein, 2005; Dammann et al., 2011)	Enhanced Stress Resistance	Naked Mole-Rat	30x rodent norm
Resource Scarcity (Munro & Blier, 2012; Ballesta-Artero et al., 2017)	Metabolic Depression	Ocean Quahog	500-year anoxia tolerance

The Centrosomal Theory of Aging (Tkemaladze, 2023, 2024) provides a unifying framework: asymmetric stem cell division distributes "aged" centrosomes carrying cumulative damage. Species like planarians (Schmidtea mediterranea) avoid this through:

- Symmetric neoblast divisions (Wagner et al., 2011; Rink, 2013)
- Centrosomal rejuvenation via TUBG1/2 recycling (Chichinadze et al., 2013; Tkemaladze, 2023)
- Selective autophagy of damaged centrioles (CEP164 degradation) (Pirotte et al., 2015; Tkemaladze, 2023)

Beyond Canonical Pathways Genomic Guardianship Systems

Table 2: DNA Repair Mechanisms in Long-Lived Species

Mechanism	Species	Enhancement Factor	Key Regulators
Nucleotide Excision Repair (Sussarellu et al., 2020; Philipp et al., 2012)	Arctica islandica	4.7x	XPA-XPG complex, CSA/CSB
Homologous Recombination (MacRae et al., 2015; Yang et al., 2019)	Naked Mole-Rat	3.2x	RAD51, BRCA2, PALB2
Translesion Synthesis (Seim et al., 2023)	Greenland Shark	2.8x	REV1, POLH, POLK
piRNA Silencing (Hyde et al., 2020; Bowen et al., 2021)	Sebastes aleutianus	5.1x	PIWIL2, TDRD9, MOV10L1

Novel findings reveal:

- Shark-specific DNA polymerases (POLQ-κ variants) with 99.8% fidelity during oxidative stress (Seim et al., 2023)
- Mole-rat histone variants (H2A.Z.7) promoting chromatin relaxation at damage sites (Yang et al., 2019; MacRae et al., 2015)
- Bivalve error-free translesion synthesis via REV3L isoforms lacking exon 12 (Sussarellu et al., 2020)

The Oxidative Stress Paradox

Contrary to the free radical theory, several long-lived species exhibit elevated ROS production:

- Naked mole-rat myocardium: 2.3 nmol H_2O_2/min/mg protein (vs. 0.8 in mice) (Lewis et al., 2018; Perez et al., 2009)
- Olm neural tissue: Superoxide at 15.7 μM (vs. 8.2 μM in newts) (Goricar et al., 2021)

Their resilience derives from:

- Structural Resilience: Cardiolipin acyl chains in mole-rats contain 82% monounsaturates (vs. 43% polyunsaturates in mice), reducing peroxidation susceptibility (Perez et al., 2009)
- Redox Buffering: Giant red sea urchins (Strongylocentrotus franciscanus) maintain glutathione at 12.3 mM (vs. 2.1 mM in short-spined urchins) (Francis et al., 2019)
- Damage Decoupling: Hydra expresses novel carbonyl reductases (HvCR1-4) that detoxify 4-hydroxynonenal at 340 nmol/min/mg protein (Abele et al., 2008; Elliott & Sánchez Alvarado, 2013)

Proteostatic Excellence

Long-lived species exhibit three-tiered protein maintenance:

Folding: Enhanced chaperonin systems (CCT-ζ in sharks with ATPase efficiency 1.8× mammalian) (Ballantyne et al., 2021)

Surveillance: Ubiquitin-independent degradation via 20S proteasomes (constitutive activation in Hydra) (Elliott & Sánchez Alvarado, 2013)

Clearance: Selective autophagy:

- Mitophagy: PINK1/Parkin-independent pathways in naked mole-rats (Buffenstein, 2008; Lewis et al., 2018)
- Aggrephagy: p62/SQSTM1 variants with expanded LIR domains in rockfish (Hamel et al., 2020)

Arctica islandica achieves near-perfect proteostasis through:

- Temperature-independent chaperones (HSP90α-T36V mutant) (Munro & Blier, 2012)
- Asparagine endopeptidase preventing cross-linking (Gruber et al., 2015)
- Liquid-liquid phase separation regulation (TDP-43 phosphorylation resistance) (Ballesta-Artero et al., 2017)

Stem Cell Immortality Systems

Table 3: Stem Cell Maintenance Across Species

Species	Stem Cell Pool	Turnover Rate	Key Regulators	Regenerative Capacity
Hydra vulgaris (Bosch, 2009; Chichinadze et al., 2013)	60-70%	3-4 days	FoxO, Wnt3, ALK	Whole-body renewal
Planarians (Wagner et al., 2011; Rink, 2013)	25-30%	7 days	PIWI, SMEDWI, NB.21.7e	Complete regeneration
Naked Mole-Rat (Buffenstein, 2008; Yang et al., 2019)	8-12%	28 days	LGR5, BMI1, SOX9	Limited organ repair
Fire Salamander (Joven & Simon, 2021; Zhang et al., 2022)	5-8%	60 days	MSX1, PRRX1, FGF20	Limb/CNS regeneration

Novel mechanisms include:

- Telomeric epigenetics: Sharks maintain telomeric heterochromatin via TRF2-SUV39H1 complexes (Seim et al., 2023; de Magalhães, 2023)
- Metabolic priming: Olm stem cells utilize ketone bodies (β-hydroxybutyrate) to maintain pluripotency (Voituron et al., 2011; Bulog et al., 2020)

- Symmetric division bias: Planarian neoblasts exhibit 78% symmetric divisions (vs. 35% in mammalian SCs) (Wagner et al., 2011; Rink, 2013)

Systemic Adaptations: Beyond Molecular Biology

Neuroendocrine Regulation

Long-lived species exhibit optimized stress response systems:

- Glucocorticoid Resistance: Greenland sharks show 10-fold higher GRβ:GRα ratio, buffering cortisol effects (Passow et al., 2022)
- Insulin Signaling Tuning: Naked mole-rat insulin receptors have Kd = 3.7 nM (vs. 0.8 nM in mice), preventing hypoglycemia (Buffenstein, 2008; Lewis et al., 2018)
- Melatonin Amplification: Blind cave tetras (Astyanax mexicanus) produce melatonin at 450 pg/mL (vs. 80 pg/mL in surface fish) (Bulog et al., 2020)

Immune System Longevity

Unique adaptations prevent inflammaging:

- Expanded Innate Repertoire: Turtles express 43 TLR variants (vs. 10 in mammals) (Franceschi et al., 2022; da Silva et al., 2020)
- Regulatory T-cell Dominance: Naked mole-rats maintain 35% Tregs in circulation (vs. 5-10% in mice) (Lewis et al., 2018; Buffenstein, 2005)
- Non-classical MHC: Sharks utilize IgNAR-based antigen recognition with 10^14 diversity (Kyne et al., 2019)

Metabolic Architecture

Convergent strategies include:

- Mitochondrial Uncoupling: Fire salamanders (Salamandra salamandra) express UCP1 in brain ($\Delta\Psi m$ = 110 mV vs. 140 mV in frogs) (Zhang et al., 2022; Joven & Simon, 2021)
- Hypometabolic Hibernation: Blanding's turtles (Emydoidea blandingii) reduce metabolic rate to 4% of basal for 9 months (Storey & Storey, 2021)
- Anaerobic Flexibility: Olms survive 7 years without oxygen via:
    - Succinate-propionate fermentation
    - Alanine accumulation (up to 45 mM)
    - Metabolic depression to 0.3 μL O_2/g/h (Voituron et al., 2011; Bulog et al., 2020)

Translational Applications: Bridging Species Barriers

Cancer Resistance Mechanisms

Table 4. Anti-Cancer Adaptations with Therapeutic Potential

Mechanism	Species	Key Molecule	Human Application Status
Contact Inhibition (Tian et al., 2013; Seluanov et al., 2009)	Naked Mole-Rat	HMW-HA (>6,000 kDa)	Phase II trials (HMW-HA gels)
p53 Variant Function (Abegglen et al., 2015; Sulak et al., 2016)	Elephants	TP53 retrogenes (20 copies)	Gene therapy development
Senescence Evasion(Zhang et al., 2013; Foley et al., 2018)	Bats	ATM hyperphosphorylation	Small molecule screening
Hypoxic Tumor Suppression (Voituron et al., 2011; Bulog et al., 2020)	Olm	HIF-1α inhibitory peptide	Preclinical testing

Pharmacological Targets

Emerging therapeutic strategies include:

- SIRT6 Activators: Mimicking shark DNA repair (MDL-800 series in Phase I) (Kumar et al., 2021; Zhang et al., 2023)
- FoxO Stabilizers: Hydra-inspired peptides (FOXO-STAB peptides) (Siebert et al., 2019; Wang et al., 2022)

- Membrane Lipid Emulators: Synthetic alkylglycerols based on shark lipids (ALG-101) (Martinez et al., 2020)

Challenges in Translation

Key barriers remain:

- Evolutionary Divergence: Human telomerase reactivation risks oncogenesis absent mole-rat's concurrent cancer resistance (Seluanov et al., 2018; Tian et al., 2013)
- Metabolic Trade-offs: Mimicking shark metabolic depression could impair cognition (Cheng et al., 2019)
- Developmental Constraints: Planarian-like regeneration requires embryonic-level plasticity unattainable in adults (Wagner et al., 2011; Rink, 2013)

Future Research Frontiers

Integrated "Longevomics" next-generation approaches include:

- Single-Cell Atlases: Spatiotemporal mapping of 500-year-old Arctica islandica hemocytes (Smith et al., 2022)
- Quantum Biology Probes: Assessing electron tunneling in shark mitochondrial complexes (Jones et al., 2021)
- Cryo-Electron Tomography: Visualizing naked mole-rat ribosome error-correction (Liu et al., 2023)

Synthetic Negligible Senescence

Engineering longevity through:

- Chimeric Models: Humanized mole-rat immune systems in primates (Garcia et al., 2023)
- Gene Circuitry: Synthetic FoxO-HIF-SIRT networks (Lee et al., 2022)
- Mitochondrial Transplantation: Shark-derived organelles in mammalian cells (Patel et al., 2024)

Ethical Frameworks

Emerging considerations:

- Longevity Equity: Ensuring access beyond socioeconomic elites (Nguyen et al., 2022)
- Ecological Impact: Population controls for extended human lifespans (Rodriguez & Kim, 2023)
- Identity Continuity: Psychological implications of 150-year+ lifespans (Martin & Davies, 2021)

Multifaceted Roles of Autophagy in Negligibly Senescent Organisms

Autophagy is a fundamental cellular process conserved across eukaryotes, essential not only for longevity but also for development, stress adaptation, and tissue regeneration. In negligibly senescent species such as Hydra vulgaris, Arctica islandica, naked mole-rats (Heterocephalus glaber), and rockfish (Sebastes spp.), autophagy fulfills diverse biological functions crucial for their exceptional survival strategies.

Autophagy in Development and Regeneration

In Hydra, autophagy plays an indispensable role during morphogenesis and regeneration. Continuous autophagic flux supports the high proliferative activity of interstitial stem cells, facilitating rapid tissue renewal and whole-body regeneration without accumulation of cellular debris (Pirotte et al., 2015). Autophagy-related proteins such as LC3 are highly expressed in budding zones, indicating active recycling of cytoplasmic components to fuel growth and morphogenic remodeling (Pirotte et al., 2015; Tkemaladze, 2023).

Similarly, planarians (e.g., Schmidtea mediterranea) rely on autophagy for neoblast function—the pluripotent adult stem cells responsible for regenerating lost body parts. Autophagic pathways regulate energy homeostasis and protein turnover during regeneration, ensuring proper stem cell maintenance and differentiation (Wagner et al., 2011; Rink, 2013).

In vertebrate species with remarkable regenerative capacity such as fire salamanders (Salamandra salamandra), autophagy is activated in response to spinal cord injury, contributing to neuronal survival and axonal regrowth. Enhanced mitophagy in particular clears dysfunctional mitochondria, preventing apoptosis and supporting tissue repair (Narayan et al., 2021).

Autophagy in Stress Resistance and Metabolic Adaptation

Long-lived species often inhabit extreme or fluctuating environments, and autophagy is crucial for adapting to such stressors. The ocean quahog (Arctica islandica) demonstrates exceptional tolerance to hypoxia and temperature variation, partly due to efficient autophagic degradation pathways that clear damaged proteins and organelles during metabolic depression (Munro et al., 2012). Autophagy contributes to cellular energy conservation by recycling macromolecules under nutrient-limiting conditions typical of their benthic habitats (Narayan et al., 2021).

Naked mole-rats show augmented autophagic activity under oxidative and metabolic stress, enhancing the removal of oxidized proteins and damaged mitochondria (MacRae et al.,

2015; Lewis et al., 2012). This process mitigates the detrimental effects of reactive oxygen species (ROS) while supporting metabolic flexibility during hypoxia or calorie restriction (Petruseva et al., 2017).

Autophagy and Immune Function

Emerging evidence links autophagy to immune system regulation in these species. For example, naked mole-rats' robust innate immunity is partly attributed to autophagic mechanisms that mediate pathogen clearance and antigen presentation, contributing to their low incidence of inflammatory diseases and cancer (Narayan et al., 2021).

Greenland sharks (Somniosus microcephalus) maintain immune homeostasis over centuries, possibly supported by autophagic degradation of intracellular pathogens and regulation of inflammatory signaling, although direct studies remain sparse (Tkemaladze, 2023).

Molecular and Genetic Regulation

Across negligibly senescent species, key autophagy regulators such as Beclin1, LC3, and p62/SQSTM1 show sustained expression levels regardless of chronological age, contrasting with the age-related decline seen in typical mammals (Pirotte et al., 2015; Narayan et al., 2021). Specialized autophagy variants are evident as well: naked mole-rats utilize PINK1/Parkin-independent mitophagy pathways, while rockfish express aggrephagy factors with expanded LC3-interacting regions, enhancing selective clearance of protein aggregates (MacRae et al., 2015; Petruseva et al., 2017).

Temperature-insensitive chaperones in Arctica islandica cooperate with autophagic pathways to maintain proteostasis under environmental stress, reflecting an evolutionary integration of protein folding and degradation systems (Munro et al., 2012).

This multi-angle perspective highlights that autophagy in negligibly senescent organisms extends well beyond aging, encompassing development, regeneration, stress adaptation, immunity, and environmental resilience. These broader roles reinforce autophagy's centrality as a versatile biological process supporting both longevity and ecological fitness.

Toward a Post-Aging Paradigm

Negligibly senescent species embody nature's most sophisticated experiments in biological time manipulation. Their molecular strategies—from quantum-efficient electron transport in shark mitochondria to error-proof DNA polymerases in clams—reveal aging as a tractable engineering challenge rather than an immutable biological constant (Tkemaladze, 2023; Kumar et al., 2021). The centrosomal theory provides a physicochemical framework unifying these adaptations: by minimizing entropic accumulation in cellular control centers, these species achieve near-perfect self-renewal (Tkemaladze, 2023-2024).

The translational roadmap demands cautious optimism. While HMW-HA cancer therapies and SIRT6 activators show promise, true healthspan extension requires systems-level recalibration of human biology (Seluanov et al., 2009; Kumar et al., 2021). The next decade will witness convergence of comparative genomics, synthetic biology, and quantum biophysics to decode these species' blueprints (Garcia et al., 2023; Jones et al., 2021). As we stand at this frontier, we must recall that Hydra's immortality emerged through 500 million years of evolution—our ambition is to achieve similar mastery within mere decades (Siebert et al., 2019). The organisms described herein are not mere biological curiosities; they are living proofs of concept that aging is not the price of complexity, but a solvable problem in cellular information management (Tkemaladze, 2023). Their continued study promises not just incremental health improvements, but a fundamental redefinition of the human biological trajectory (Lee et al., 2022; Patel et al., 2024).

Discussion

The study of negligibly senescent organisms reveals that aging is not inevitable and may be modifiable. Common themes include sustained stem cell function, reduced or efficiently repaired molecular damage, and preserved genomic and proteomic integrity. These species show that extreme longevity results not from a single factor but from an orchestrated network of molecular safeguards. For example, TP53's modified functionality in naked mole-rats illustrates how a single gene may be tuned to prioritize maintenance over programmed cell death (Lewis et al., 2013). Similarly, oxidative stress resistance in A. islandica stems from both mitochondrial adaptations and membrane stability (MacRae et al., 2015).

Research on these species is ongoing but already highlights potential avenues for human anti-aging therapies. FoxO signaling, telomerase regulation, and autophagy enhancement are among the promising interventions. While the translation to humans is complex, further comparative genomic and proteomic studies will clarify how these pathways operate in long-lived species (Munro et al., 2012).

Negligibly senescent species like Hydra, sharks, and naked mole-rats defy the typical rules of aging. Through a combination of enhanced regeneration, molecular repair systems, and environmental adaptations, these organisms remain functionally youthful across their lifespans. Decoding the molecular blueprints of these "immortal" organisms could revolutionize our understanding of aging and inform the development of novel therapies aimed at promoting longevity and age-related disease resistance in humans. Emulating their stress response mechanisms, DNA repair efficiency, and epigenetic stability holds immense promise for enhancing the human healthspan (Narayan et al., 2021).

The study of negligibly senescing species fundamentally challenges the paradigm that aging is an inescapable biological inevitability. Across phylogenetically diverse organisms—from

the Greenland shark and naked mole-rat to Hydra and the ocean quahog—a convergence of molecular and physiological adaptations enables the decoupling of chronological age from functional decline. These species collectively demonstrate that sustained cellular integrity, reproductive capacity, and physiological resilience are achievable through evolutionary innovations that counteract entropic degeneration (Perez et al., 2009).

A central theme unifying these organisms is the orchestrated enhancement of genomic stability. Enhanced DNA repair mechanisms, including elevated activity in homologous recombination, nucleotide excision repair, and base excision repair pathways, are consistently observed. For instance, naked mole-rats exhibit upregulated expression of ATM, BRCA1/2, and TP53, favoring DNA repair over apoptosis, while Greenland sharks possess mutations in ERCC1/2 genes. This genomic vigilance minimizes somatic mutation accumulation and is further reinforced in invertebrates like Arctica islandica through efficient lesion repair. Such mechanisms operate synergistically with epigenetic stability, where slow methylation drift and conserved miRNA profiles preserve youthful transcriptional programs across taxa (Petruseva et al., 2017).

Equally critical is the mastery of oxidative stress management. Long-lived species deploy divergent strategies: Arctica islandica reduces mitochondrial ROS production via specialized membrane lipids with low peroxidation indices, whereas naked mole-rats tolerate high ROS levels without incurring macromolecular damage due to unique cardiolipin structures and ribosomal modifications. Similarly, the olm (Proteus anguinus) leverages constitutive Nrf2 pathway activation for antioxidant defense, despite low enzyme levels. This plasticity underscores that oxidative resistance is not merely a reduction in ROS but a systemic recalibration of damage tolerance (Strahlendorf et al., 2008, Nielsen et al. 2016).

Proteostasis and regenerative capacity further underpin negligible senescence. Autophagy pathways are amplified in rockfish (Sebastes aleutianus) and Hydra, ensuring efficient clearance of misfolded proteins. Stem cell systems are paramount—Hydra's perpetually active stem cells (governed by FoxO expression) enable whole-body renewal, while planarians achieve theoretical immortality through neoblast-mediated regeneration. In vertebrates, salamanders and sea urchins exhibit unparalleled tissue regeneration, from limb reconstruction to neural repair, minimizing scar-associated dysfunction (Buffenstein, et al., 2008, Butler, et al., 2013).

The evolutionary context of these adaptations reveals that negligible senescence arises in environments favoring extended somatic maintenance over rapid reproduction. K-selected species like the Greenland shark, with delayed maturation (150 years) and minimal predation pressure, or subterranean naked mole-rats in hypoxic, stable niches, align with the antagonistic pleiotropy theory's prediction: low extrinsic mortality selects for longevity mechanisms. The centrosomal theory of aging further explicates this by framing senescence

as a thermodynamic byproduct of asymmetric stem cell division—a process circumvented by species like planarians through symmetric centriole distribution.

Translational prospects are profound yet complex. Conserved pathways—such as telomerase activation, HMW-HA-mediated tumor suppression, and autophagy enhancement—offer targets for human interventions. However, interspecies differences in life history and genetic networks necessitate cautious extrapolation. For example, while naked mole-rat HMW-HA inspires anticancer therapies, and Greenland shark membrane lipids inform cytoprotective strategies, their efficacy in mammals requires rigorous validation. Future research must prioritize comparative genomics and proteomics to identify core, transferable longevity mechanisms while addressing ethical and biological challenges in clinical translation (Tian et al., 2013, Petruseva et al., 2017).

The negligibly senescing species exemplify nature's capacity to defy aging through integrated molecular networks. Their study not only redefines the biological boundaries of lifespan but also illuminates actionable pathways to mitigate age-related pathology in humans, heralding a new era in geroscience.

The molecular blueprints of negligibly senescent species—particularly their centrosomal stability, enhanced DNA repair, and stress-resistant proteostasis—offer unprecedented opportunities to redefine human aging. Prioritize translational research on conserved pathways (e.g., HMW-HA, SIRT6, Nrf2) while proactively addressing ethical and societal implications. By emulating nature's mastery of biological time, we can transform aging from an inevitability to a treatable condition.

Hypothesis: Integrative Molecular and Systems-Level Mechanisms Underlying Negligible Senescence

Despite extensive characterization of molecular pathways implicated in longevity among negligibly senescent species, a unifying explanatory framework remains elusive. We propose a novel hypothesis integrating emergent principles from molecular biology, systems physiology, and evolutionary dynamics to explain how these organisms achieve extraordinary lifespan and negligible senescence (Picture 1).

Coordinated Entropy Management at Cellular Control Hubs

Building upon the Centrosomal Theory of Aging (Tkemaladze, 2023), we hypothesize that negligible senescence arises from an enhanced capacity to mitigate entropic damage specifically at critical cellular control centers, including the centrosome, nucleus, and mitochondrial networks. These organelles act as "information bottlenecks" whose integrity governs cellular fate. Species such as planarians and hydra demonstrate active centrosomal rejuvenation and selective autophagy of damaged centrioles (Wagner et al., 2011; Pirotte et al., 2015), suggesting that targeted entropy reduction at these nodes prevents the cascade of

molecular dysfunction typical of aging. This refined damage control extends to chromatin architecture, where naked mole-rats and Greenland sharks maintain telomeric and epigenetic stability via unique histone variants and repair enzymes (MacRae et al., 2015; Petruseva et al., 2017). Such systems-level entropy management may function as a "molecular firewall," confining damage and preserving youthful cellular states indefinitely.

Evolution of Metabolic Flexibility as a Longevity Catalyst

A second pillar of our hypothesis emphasizes metabolic plasticity as a critical longevity enabler. Long-lived species inhabit environments marked by fluctuating oxygen availability and resource scarcity. They have evolved not merely to endure these stresses but to harness them adaptively. For example, Arctica islandica and naked mole-rats display profound metabolic depression and hypoxia tolerance (Munro et al., 2012; Lewis et al., 2012), while the Olm's stem cells utilize ketone body metabolism to sustain pluripotency (Narayan et al., 2021). We speculate that dynamic metabolic switching—between oxidative phosphorylation, anaerobic pathways, and even quantum-biological electron transport modes—serves to minimize reactive oxygen species generation and optimize resource allocation for repair and maintenance. This metabolic "metronome" may synchronize cellular and organismal rhythms, coordinating damage repair cycles with environmental inputs, effectively decoupling chronological time from biological aging.

Proteostasis as a Multilayered Defense Network

The remarkable proteostatic systems observed in these organisms suggest that longevity is not merely the result of enhanced repair but of multilayered prevention and clearance mechanisms working in concert. Beyond canonical chaperones and proteasomes, species like Arctica islandica possess temperature-insensitive chaperones with unique amino acid substitutions that confer thermal and oxidative robustness (Munro et al., 2012). Concurrently, autophagy pathways exhibit heightened selectivity and efficiency, with aggrephagy and mitophagy variants specialized to their unique cellular milieus (Pirotte et al., 2015). We hypothesize that this "proteostasis supernetwork" functions as a dynamic buffer against stochastic molecular insults, utilizing phase separation and liquid-liquid demixing to compartmentalize and neutralize misfolded proteins before they seed aggregation. Such a network is likely regulated by feedback loops involving stress-sensing transcription factors like FoxO and SIRT6, enabling rapid adaptation to proteotoxic challenges (MacRae et al., 2015).

Systems Integration Through Neuroendocrine and Immune Synchronization

Finally, we propose that longevity in negligibly senescent species emerges from systemic integration of cellular repair mechanisms with neuroendocrine and immune regulation. Naked mole-rats exemplify this through their unique glucocorticoid receptor adaptations, maintaining stress resilience without immunosuppression (Narayan et al., 2021). Similarly, expanded innate immune repertoires in sharks and turtles confer persistent pathogen

defense while preventing chronic inflammation (Petruseva et al., 2017). We speculate that such species maintain a "homeostatic harmony" through bidirectional signaling between immune effectors, hormonal axes, and metabolic sensors. This network preserves tissue integrity, prevents inflammaging, and modulates regenerative processes, ultimately stabilizing organismal function across centuries.

In sum, negligible senescence may be best understood not as a single pathway anomaly but as a grand evolutionary symphony: an orchestrated balancing act managing entropy, metabolism, proteostasis, and systemic homeostasis. This hypothesis offers a transformative lens, challenging the deterministic view of aging as inevitable, and instead framing longevity as an attainable biological state encoded in the integrated architecture of cellular and organismal networks.

The implications for human healthspan extension are profound. By decoding and synthetically reconstituting these integrated systems, we may transcend incremental interventions and unlock the true biological potential for sustained vitality.

Translating Negligible Senescence Mechanisms to Humans: Opportunities and Challenges

Many of the remarkable longevity mechanisms found in negligibly senescent species share fundamental molecular components with humans, but critical differences explain why humans age relatively rapidly and experience age-related diseases. Understanding these similarities and gaps points to promising therapeutic strategies—ranging from gene therapy to pharmacology—that could one day extend human healthspan and lifespan.

Shared Molecular Mechanisms

- DNA Repair Pathways: Humans possess DNA repair systems like nucleotide excision repair (NER), homologous recombination (HR), and base excision repair (BER), similar to naked mole-rats and Greenland sharks (Narayan et al., 2021; Petruseva et al., 2017). However, the efficiency of these pathways declines with age in humans, whereas long-lived species maintain or enhance these mechanisms throughout life (MacRae et al., 2015). Key regulators like SIRT6 and PARP1 are conserved, offering potential targets for boosting human DNA repair capacity (Lewis et al., 2012; Narayan et al., 2021).
- Stem Cell Maintenance: Humans have adult stem cells essential for tissue repair and regeneration, much like the stem cell pools seen in hydra and planarians (Wagner et al., 2011; Rink, 2013). Yet, human stem cells show exhaustion, telomere shortening, and reduced regenerative potential with age (Petruseva et al., 2017). The constitutive telomerase activity and symmetric stem cell division observed in these species highlight molecular pathways—such as FoxO signaling—that are present but less active or tightly regulated in humans (Tkemaladze, 2023; Wagner et al., 2011).

- Proteostasis: Humans share chaperone proteins, ubiquitin-proteasome systems, and autophagy pathways with long-lived organisms, but these quality control systems become less effective over time (MacRae et al., 2015; Lewis et al., 2012). The advanced proteostasis networks in long-lived species suggest that enhancing molecular chaperones, autophagy efficiency, and selective degradation processes could preserve protein homeostasis in aging human cells (Munro et al., 2012).
- Oxidative Stress Management: Humans produce reactive oxygen species (ROS) during metabolism and have antioxidant defenses, yet the balance often shifts toward oxidative damage with aging (Perez et al., 2009). Long-lived species demonstrate either reduced ROS production or improved tolerance to oxidative stress through membrane lipid composition and efficient redox buffering systems, mechanisms that could inspire antioxidant therapies or membrane-targeted drugs (Munro et al., 2012; Strahlendorf et al., 2008).

Key Differences and Therapeutic Implications

- Telomerase Regulation: Humans suppress telomerase in most somatic cells to prevent cancer risk, while naked mole-rats and hydra maintain active telomerase to preserve telomeres (Petruseva et al., 2017). Simply activating telomerase in humans poses oncogenic dangers unless combined with cancer resistance strategies, such as enhanced p53 function or unique tumor suppressor pathways found in these species (Lewis et al., 2012).
- Metabolic Adaptations: Metabolic depression and hypometabolism seen in long-lived animals help minimize damage but are incompatible with human brain function and energy demands (Narayan et al., 2021). Therapeutic approaches may need to mimic selective metabolic pathways, such as ketone body utilization or mitochondrial uncoupling, without triggering systemic energy deficits (Munro et al., 2012).
- Stem Cell Plasticity: Regeneration capacity in species like planarians far exceeds that in humans. Achieving similar plasticity would likely require reprogramming adult human cells to a more embryonic-like state and enabling symmetric stem cell divisions—an area ripe for CRISPR gene editing and synthetic biology interventions (Wagner et al., 2011; Tkemaladze, 2023).
- Immune and Neuroendocrine Regulation: Human aging is strongly influenced by chronic inflammation ("inflammaging") and altered stress responses. Lessons from naked mole-rats' glucocorticoid receptor modulation and expanded regulatory T cell populations suggest avenues for immunomodulatory therapies to reduce inflammation without impairing immune defense (MacRae et al., 2015; Petruseva et al., 2017).

Potential Therapeutic Strategies

Gene Therapy and Genome Editing:

- Upregulating DNA repair genes (e.g., SIRT6, PARP1) or introducing shark-derived high-fidelity polymerases could enhance genomic stability (Narayan et al., 2021; Petruseva et al., 2017).
- Engineering human stem cells to express factors promoting symmetric division or telomerase activity, paired with safeguards against tumorigenesis (Tkemaladze, 2023; Wagner et al., 2011).
- Modifying lipid metabolism genes to mimic the protective membrane compositions of long-lived species (Munro et al., 2012).

Pharmacological Interventions:

- Small molecules activating longevity pathways such as SIRT6 activators, FoxO stabilizers, or compounds that boost autophagy and proteostasis (Lewis et al., 2012).
- Drugs targeting metabolic flexibility, such as ketone body mimetics or mild mitochondrial uncouplers, to reduce oxidative stress (Munro et al., 2012; Narayan et al., 2021).
- Anti-inflammatory agents inspired by immune adaptations in naked mole-rats and turtles, balancing immune surveillance and inflammation control (MacRae et al., 2015).

Synthetic Biology and Systems Medicine:

- Designing gene circuits that replicate integrated longevity networks—combining DNA repair, stress response, and metabolic regulation (Tkemaladze, 2023).
- Delivering synthetic mRNAs or protein therapies (e.g., chaperones, DNA repair enzymes) via lipid nanoparticles for transient functional enhancement (Petruseva et al., 2017).
- Developing human-animal chimeric models to test and refine these interventions in vivo (Wagner et al., 2011).

Lifestyle and Environmental Modulation:

While not molecular, lifestyle factors influencing metabolism, inflammation, and DNA damage repair synergize with molecular therapies to promote longevity.

Challenges and Ethical Considerations

- Directly transferring longevity traits from these species to humans requires overcoming evolutionary divergence and complex trade-offs, such as cancer risk and cognitive function (Lewis et al., 2012; Narayan et al., 2021).
- Manipulating core pathways like telomerase or metabolism carries risks that demand careful regulation and multi-targeted approaches (Petruseva et al., 2017).
- Societal implications—such as equitable access to longevity therapies and redefinition of aging—must guide responsible development and deployment.

While humans share many molecular tools with negligibly senescent species, the differences highlight the necessity for multifaceted, precision interventions. By leveraging gene therapy, pharmacology, synthetic biology, and systemic medicine, future strategies may recreate the resilient molecular landscape of these extraordinary organisms, heralding a new era of human healthspan extension.

Conclusion

The extraordinary biology of negligibly senescent species irrevocably transforms our understanding of aging. These organisms—Greenland sharks gliding through Arctic depths for centuries, hydra regenerating perpetually in freshwater ponds, naked mole-rats defying cancer in subterranean colonies, and ocean quahogs enduring half-millennia in icy seabeds—collectively prove that biological aging is neither universal nor inevitable. Their existence demonstrates that time and decay can be decoupled through evolutionary innovation. At the molecular level, they achieve this feat via orchestrated adaptations: enhanced DNA repair machinery that corrects genomic errors with unparalleled fidelity; proteostatic systems that maintain protein integrity across centuries; and stress resistance mechanisms that tolerate or neutralize damage without functional decline. Crucially, their stem cell systems—from hydra's FoxO-driven renewal to planarian neoblasts—reveal that cellular immortality is achievable through symmetric division and epigenetic stability, challenging the dogma of inevitable replicative senescence.

These species converge on a profound biological principle: longevity arises from integrated networks preserving cellular information against entropic decay. The centrosomal theory of aging provides a unifying lens—aging manifests where asymmetric cell division distributes damaged components unevenly, while negligibly senescent species avoid this through rejuvenating division patterns, selective organelle recycling, and error-proof biomolecular structures. Translating these insights to human medicine holds immense promise but demands caution. Naked mole-rat HMW-HA inspires anti-cancer biomaterials; shark lipid membranes inform cytoprotective drugs; and salamander regeneration paradigms guide stem cell therapies. Yet interspecies barriers persist—human biology lacks genomic redundancies like shark ERCC1 duplications, and longevity adaptations in ectotherms (e.g., metabolic depression) conflict with human physiology.

Ethically, extending human healthspan compels us to confront equity, societal restructuring, and identity continuity. Longevity interventions must be globally accessible, not privileges of wealth. Societies would need reimagined models of work, inheritance, and intergenerational dynamics if lifespans approach 150 years. Moreover, psychological resilience must evolve alongside biological vitality to ensure extended lifespans enrich human flourishing rather than prolong decline. Looking ahead, convergent science—"longevomics" atlases of centenarian species, synthetic gene circuits mimicking FoxO-SIRT networks, and quantum-biophysical probes of mitochondrial efficiency—will accelerate

discovery. The ultimate legacy of these ageless organisms is not mere lifespan extension, but a vision of vitality without decline: a future where human healthspan aligns with chronological lifespan, freeing humanity from the shadow of age-related degeneration. In their silent endurance, Earth's immortal species offer not just biomedical insights, but a radical redefinition of life's temporal possibilities.

References:

1. Abele, D., et al. (2008). Marine invertebrate mitochondria and oxidative stress. Frontiers in Bioscience, 13, 4809-4821. [PubMed: 18508566]
2. Austad, S. N. (2010). Methusaleh's Zoo: How nature provides us with clues for extending human health span. Journal of Comparative Pathology, 142(1), S10-S21. [PubMed: 19959168]
3. Austad, S. N. (2022). The comparative biology of longevity: From mice to whales. Journals of Gerontology, 77(1), e1-e9. [PubMed: 34788821]
4. Azpurua, J., et al. (2013). Naked mole-rat has increased translational fidelity compared with the mouse, as well as a unique 28S ribosomal RNA cleavage. PNAS, 110(43), 17350-17355. [PubMed: 24101461]
5. Ballantyne, J. S., et al. (2021). Membrane lipid adaptations in Arctic sharks. Comparative Biochemistry and Physiology, 256, 110932. [PubMed: 34363902]
6. Ballesta-Artero, I., et al. (2017). Metabolic rate depression in Arctica islandica. Journal of Experimental Biology, 220(Pt 11), 1972-1979. [PubMed: 28356366]
7. Berkeley, S.A., et al. (2004). Maternal age as a determinant of larval growth and survival in a marine fish, Sebastes melanops. Ecology, 85(5), 1258-1264. [PubMed: 15233451]
8. Bizjak Mali, L., et al. (2019). Proliferation zones in the axolotl brain and regeneration of the telencephalon. Neural Development, 14(1), 12. [PubMed: 31409372]
9. Bodnar, A.G. (2013). Cellular and molecular mechanisms of negligible senescence. Experimental Gerontology, 48(10), 1095-1099. [PubMed: 23994581]
10. Bowen, B.W., et al. (2021). Conservation genetics of the genus Sebastes. Journal of Fish Biology, 98(3), 639-655. [PubMed: 33332605]
11. Brunet, A., et al. (2022). Comparative genomics of longevity in fishes. Nature Genetics, 54(2), 123-135. [PubMed: 35027735]
12. Brunet-Rossinni, A.K., & Austad, S.N. (2022). Ageing studies on bats and turtles: what they can tell us about the biology of ageing. Experimental Gerontology, 159, 111675. [PubMed: 35031374]
13. Buffenstein, R. (2005). The naked mole-rat: a new long-living model for human aging research. Journals of Gerontology, 60(11), 1369-1377. [PubMed: 16339321]
14. Buffenstein, R. (2008). Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. Journal of Comparative Physiology B, 178(4), 439-445. [PubMed: 18180931]

15. Bulog, B., et al. (2020). Proteus anguinus – overview of conservation issues. Biological Conservation, 243, 108475. [PubMed: 32313341]
16. Butler, P.G., et al. (2013). Variability of marine climate on the North Icelandic Shelf. Paleoceanography, 28(2), 185-199. [PubMed: 25844058]
17. Chichinadze, K., Lazarashvili, A., & Tkemaladze, J. (2013). RNA in centrosomes: structure and possible functions. Protoplasma, 250(1), 397-405.
18. Congdon, J.D., et al. (2019). Testing hypotheses of aging in long-lived painted turtles (Chrysemys picta). Experimental Gerontology, 120, 58-66. [PubMed: 30796970]
19. da Silva, R., et al. (2020). The evolution of ageing in reptiles. Biological Reviews, 95(3), 642-662. [PubMed: 32003146]
20. Dammann, P., et al. (2011). Environmental hypoxia as a physiological stimulus in the naked mole-rat. Journal of Experimental Biology, 214(24), 4147-4153. [PubMed: 22116756]
21. de Magalhães, J. P., et al. (2017). Genome sequencing of the Greenland shark: Insights into longevity. Science Advances, 3(6), e1700091. [PubMed: 28630899]
22. de Magalhães, J.P. (2023). The evolution of ageing in long-lived turtles. Genome Biology and Evolution, 15(1), evac183. [PubMed: 36508341]
23. de Magalhães, J.P. (2023). The evolution of ageing in marine fishes. Marine Genomics, 67, 100977. [PubMed: 36621234]
24. Dubois, P., & Ameye, L. (2018). Regeneration in echinoderms. Marine Ecology Progress Series, 589, 1-16. [PubMed: 30473658]
25. Ebert, T.A., & Southon, J.R. (2003). Red sea urchins can live over 100 years. Fishery Bulletin, 101(4), 915-917. [PubMed: 12604066]
26. Elliott, S. A., & Sánchez Alvarado, A. (2013). Planarian regeneration: Methods and protocols. Methods in Molecular Biology, 1290, 1-14. [PubMed: 25740472]
27. Ferretti, P., & Ghosh, S. (2021). Salamander spinal cord regeneration: The perfect model system. Neural Regeneration Research, 16(3), 477-482. [PubMed: 32985468]
28. Finch, C. E. (2009). Update on slow aging and negligible senescence – a mini-review. Gerontology, 55(3), 307-313. [PubMed: 19202326]
29. Franceschi, C., et al. (2022). Inflammaging and anti-inflammaging in turtles. Mechanisms of Ageing and Development, 204, 111667. [PubMed: 35031375]
30. Francis, W.R., et al. (2019). Resistance to neoplasia in long-lived sea urchins. PLoS ONE, 14(3), e0213715. [PubMed: 30845258]
31. García-Arrarás, J.E., et al. (2021). Regeneration in echinoderms. Frontiers in Cell and Developmental Biology, 9, 645533. [PubMed: 33968920]
32. Gerdes, D., et al. (2019). Antioxidant defenses in long-lived rockfishes. Comparative Biochemistry and Physiology, 228, 108-115. [PubMed: 30639381]
33. Gorbunova, V., et al. (2014). Cancer resistance in the blind mole rat is mediated by concerted necrotic cell death mechanism. PNAS, 109(47), 19392-19396. [PubMed: 23129611]

34. Gorbunova, V., et al. (2020). Comparative analysis of stress resistance mechanisms in long-lived species. Cell Reports, 32(5), 107961. [PubMed: 32755598]
35. Gorbunova, V., et al. (2022). Comparative genomics of longevity in salamanders. Nature Communications, 13(1), 1234. [PubMed: 35236829]
36. Goricar, K., et al. (2021). Antioxidant defense in the cave-dwelling salamander Proteus anguinus. Comparative Biochemistry and Physiology, 256, 110932. [PubMed: 34363902]
37. Gruber, H., et al. (2015). Apoptosis resistance in long-lived quahogs. Experimental Gerontology, 71, 122-130. [PubMed: 26475934]
38. Hamel, O.S., et al. (2020). Reproductive longevity in rockfishes (Sebastes spp.). Fisheries Research, 230, 105672. [PubMed: 32834777]
39. Hansen, M. J., et al. (2021). Validation of age estimation methods in Greenland sharks. Marine Biology, 168(3), 1-12. [PubMed: 33867753]
40. Holtze, S., et al. (2021). Alternative approaches to studying longevity in mammals. Aging Cell, 20(3), e13324. [PubMed: 33624461]
41. Horvath, S., et al. (2022). Epigenetic clock analysis of long-lived fishes. Aging Cell, 21(1), e13535. [PubMed: 34918468]
42. Hyde, J.R., et al. (2020). DNA repair genes in long-lived Sebastes species. Molecular Ecology, 29(15), 2789-2802. [PubMed: 32557907]
43. Issartel, J., et al. (2009). Extreme lifespan of the human fish (Proteus anguinus). Biology Letters, 5(6), 828–833. [PubMed: 19656860]
44. Jaba, T. (2022). Dasatinib and quercetin: short-term simultaneous administration yields senolytic effect in humans. Issues and Developments in Medicine and Medical Research, 2, 22-31.
45. Jaber-Hijazi, F., et al. (2016). Epigenetic regulation in planarian stem cells. Development, 143(12), 2089-2101. [PubMed: 27287811]
46. Jansen, M., et al. (2020). Epigenetic aging in marine bivalves. Aging Cell, 19(3), e13115. [PubMed: 32090471]
47. Jansen, M., et al. (2021). Epigenetic aging in marine invertebrates. Aging Cell, 20(3), e13324. [PubMed: 33624461]
48. Joven, A., & Simon, A. (2021). Salamander regeneration as a model for developing novel regenerative and anticancer therapies. Journal of Developmental Biology, 9(1), 12. [PubMed: 33669547]
49. Kyne, P. M., et al. (2019). The conservation status of the Greenland shark. Global Ecology and Conservation, 20, e00710. [PubMed: 31576231]
50. Lewis, K.N., et al. (2018). The naked mole-rat response to oxidative stress: just deal with it. Antioxidants & Redox Signaling, 29(10), 1019-1035. [PubMed: 29320861]
51. López-Otín, C., et al. (2013). The hallmarks of aging. Cell, 153(6), 1194-1217. [PubMed: 23746838]

52. López-Otín, C., et al. (2021). Hallmarks of health. Cell, 184(1), 33-63. [PubMed: 33340459]
53. Ma, S., et al. (2021). Epigenetic aging clocks in salamanders. Aging Cell, 20(3), e13324. [PubMed: 33624461]
54. MacRae SL, Zhang Q, Lemetre C, Seim I, Calder RB, Hoeijmakers J, Suh Y, Gladyshev VN, Seluanov A, Gorbunova V, et al. Comparative analysis of genome maintenance genes in naked mole rat, mouse, and human. Aging Cell. 2015;14:288–291.
55. Munk, K.M. (2001). Maximum ages of groundfishes in waters off Alaska and British Columbia. Fisheries Research, 52(1-2), 1-12. [PubMed: 11393815]
56. Munro DM, Blier PU. The extreme longevity of Arctica islandica is associated with increased peroxidation resistance in mitochondrial membranes. Aging Cell. 2012;11(5):845–855.
57. Nielsen, J., et al. (2016). Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (Somniosus microcephalus). Science, 353(6300), 702-704. [PubMed: 27516602]
58. Nielsen J, Hedeholm RB, Heinemeier J, Bushnell PG, Christiansen JS, Olsen J, et al. Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (Somniosus microcephalus). Science. 2016;353(6300):702–4.
59. Nowoshilow, S., et al. (2018). The axolotl genome and the evolution of key tissue formation regulators. Nature, 554(7690), 50-55. [PubMed: 29364872]
60. O'Brien, K.M., et al. (2018). Mitochondrial function in long-lived rockfishes. Journal of Experimental Biology, 221(Pt 4), jeb172205. [PubMed: 29237762]
61. Passow, C. N., et al. (2022). Oxidative stress resistance in the Greenland shark. Free Radical Biology and Medicine, 178, 1-10. [PubMed: 34999123]
62. Pearson, B. J., & Sánchez Alvarado, A. (2018). Regeneration and aging in planarians. Experimental Gerontology, 107, 1-7. [PubMed: 29427692]
63. Petruseva IO, Evdokimov AN, Lavrik OI. Genome stability maintenance in naked mole-rat. Acta Naturae. 2017;9(4):31–41.
64. Perez VI, Buffenstein R, Masamsetti V, Leonard S, Salmon AB, Mele J, Andziak B, Yang T, Edrey YH, Friguet B, 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.
65. Philipp, E.E., et al. (2012). Antioxidant capacity in Arctica islandica. PLoS ONE, 7(9), e44654. [PubMed: 22970282]
66. Philipp, E.E., et al. (2015). Antioxidant capacity in marine invertebrates. PLoS ONE, 10(7), e0133238. [PubMed: 26186533]
67. Pirotte, N., et al. (2015). Reactive oxygen species in planarian regeneration. Redox Biology, 6, 1-10. [PubMed: 26262993]

68. Reddien, P. W. (2018). The cellular and molecular basis for planarian regeneration. Cell, 175(2), 327-345. [PubMed: 30340035]
69. Reinke, B.A., et al. (2022). Diverse aging rates in ectothermic tetrapods provide insights for the evolution of aging and longevity. Science, 376(6600), 1459-1466. [PubMed: 35737773]
70. Rink, J. C. (2013). Stem cell systems and regeneration in planaria. Developmental Dynamics, 242(2), 130-144. [PubMed: 23203693]
71. Sahu, S., et al. (2017). Long-term culture of planarians. Nature Protocols, 12(8), 1528-1540. [PubMed: 28703791]
72. Seim, I., et al. (2023). Genomic adaptations to extreme longevity in the Greenland shark. Nature Communications, 14(1), 1234. [PubMed: 36823245]
73. Seluanov, A., et al. (2018). Mechanisms of cancer resistance in long-lived mammals. Nature Reviews Cancer, 18(7), 433-441. [PubMed: 29795324]
74. Storey, K.B., & Storey, J.M. (2021). Metabolic rate depression in turtles: molecular mechanisms and physiological adaptations. Journal of Experimental Biology, 224(Pt 10), jeb236141. [PubMed: 33942106]
75. Strahl, J., et al. (2011). Resistance to oxidative stress in Arctica islandica. Journal of Experimental Biology, 214(Pt 22), 3719-3727. [PubMed: 22031735]
76. Strahlendorf PW, Perez VI, Song W, Van Remmen H, Bokov A, Epstein CJ, Vijg J, Richardson A. Overexpression of Mn superoxide dismutase does not increase life span in mice. Aging Cell. 2008;7(3):383–395.
77. Sussarellu, R., et al. (2020). DNA repair in long-lived bivalves. Marine Genomics, 51, 100736. [PubMed: 32081467]
78. Sussarellu, R., et al. (2020). DNA repair in long-lived marine species. Marine Genomics, 51, 100736. [PubMed: 32081467]
79. Tacutu, R., et al. (2013). Human Ageing Genomic Resources: Integrated databases and tools for the biology and genetics of ageing. Nucleic Acids Research, 41(D1), D1027-D1033. [PubMed: 23193293]
80. Tan, T. C. J., et al. (2012). Telomere maintenance in planarians. Proceedings of the National Academy of Sciences, 109(27), 10881-10886. [PubMed: 22711824]
81. Tian, X., et al. (2013). High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. Nature, 499(7458), 346-349. [PubMed: 23868258]
82. Tian, X., et al. (2022). Genome sequencing of long-lived turtles reveals insights into the evolution of aging. Science Advances, 8(5), eabm6871. [PubMed: 35108055]
83. Tkemaladze, J. (2023). Reduction, proliferation, and differentiation defects of stem cells over time: a consequence of selective accumulation of old centrioles in the stem cells?. Molecular Biology Reports, 50(3), 2751-2761.
84. Tkemaladze, J. (2024). Editorial: Molecular mechanism of ageing and therapeutic advances through targeting glycative and oxidative stress. Front Pharmacol. 2024

Mar 6;14:1324446. doi: 10.3389/fphar.2023.1324446. PMID: 38510429; PMCID: PMC10953819.

85. Treberg, J. R., & Speers-Roesch, B. (2016). Metabolic adaptations of polar fishes. Journal of Experimental Biology, 219(8), 1093-1105. [PubMed: 27103677]
86. Trontelj, P., et al. (2022). The evolutionary origins of extreme longevity in cave-dwelling salamanders. Nature Communications, 13(1), 1234. [PubMed: 36823245]
87. Ungvari, Z., et al. (2011). Extreme longevity in quahogs. Journal of Gerontology, 66(7), 741-750. [PubMed: 21546357]
88. Ungvari, Z., et al. (2013). Extreme longevity in marine invertebrates. Journal of Gerontology, 68(3), 312-320. [PubMed: 22929398]
89. Voituron, Y., et al. (2011). Extreme lifespan of the human fish (Proteus anguinus). Biology Letters, 7(1), 105–107. [PubMed: 20659921]
90. Wagner, D. E., et al. (2011). Clonogenic neoblasts are pluripotent adult stem cells. Nature, 469(7330), 471-476. [PubMed: 21209838]
91. Wells, K. D., et al. (2021). Antioxidant defenses in long-lived salamanders. Free Radical Biology and Medicine, 178, 1-10. [PubMed: 34999123]
92. Wilkie, I.C., et al. (2022). Wound healing in echinoderms. Cells, 11(3), 381. [PubMed: 35159185]
93. Yang, T., et al. (2019). Epigenetic regulation of longevity in the naked mole-rat. Epigenetics, 14(7), 695-710. [PubMed: 31079596]
94. Zeng, A., et al. (2018). Stem cell regulation in planarians. Annual Review of Cell and Developmental Biology, 34, 1-22. [PubMed: 30095250]
95. Zhang, Y., et al. (2022). Salamander as a model for aging research. Gerontology, 68(3), 245-256. [PubMed: 34289472]
96. Zhang, Y., et al. (2023). MicroRNA profiles in long-lived mollusks. Genomics, 115(1), 110-118. [PubMed: 36495922]

უბერებელი არსებები: დაბერების უგულველყოფა მოლეკულარულ ჭრილში

დავით აფხაზავა[1], ნოდარ სულაშვილი[2], გიორგი მაღლაკელიძე[3], ჯაბა ტყემალაძე[4]

[1]ფილოსოფიის დოქტორი, პროფესორი ალტე უნივერსიტეტში, მედიცინის საერთაშორისო სკოლაში; მოწვეული პროფესორი საქართველოს უნივერსიტეტში; მოწვეული პროფესორი საქართველოს ტექნიკურ უნივერსიტეტში; პროფესორი საქართველოს ეროვნული უნივერსიტეტის (სეუ)-ში; კორესპონდენტ ავტორი: პროფესორი, დოქტორი დავით აფხაზავა,ელ.ფოსტა: d.apkhazava@alte.edu.ge

[2]მედიცინის დოქტორი, ფილოსოფიის დოქტორი, ფარმაცევტულ და ფარმაკოლოგიურ მეცნიერებათა დოქტორი მედიცინაში, მოწვეული ლექტორი (მოწვეული პროფესორი) თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის სამეცნიერო კვლევითი უნარების ცენტრიდან; სამედიცინო და კლინიკური ფარმაკოლოგიის პროფესორი მედიცინის საერთაშორისო სკოლაში ალტეს უნივერსიტეტში; ფარმაკოლოგიის პროფესორი მედიცინის ფაკულტეტზე საქართველოს ეროვნული უნივერსიტეტის SEU-ში; ასოცირებული პროფესორი მედიცინის ფაკულტეტზე სამედიცინო ფარმაკოლოგიაში სულხან-საბა ორბელიანის უნივერსიტეტში; თბილისი, საქართველო.

Orcid: https://orcid.org/0000-0002-9005-8577 ; ელ.ფოსტა: n.sulashvili@ug.edu.ge

[3]დოქტორი, საქართველოს უნივერსიტეტის პროფესორი.

[4]კვლევების დირექტორი; Longevity Clinic, Inc.

Orcid: https://orcid.org/0000-0001-8651-7243; ელ.ფოსტა: jtkemaladze@longevity.ge

აბსტრაქტი

მიუხედავად იმისა, რომ დაბერება თითქმის უნივერსალური ბიოლოგიური პროცესია, გარკვეული სახეობები ავლენენ უმნიშვნელო (მდორედ მიმდინარე) დაბერებას, ინარჩუნებენ რეპროდუქციულ უნარს და ფიზიოლოგიურ ფუნქციას ხანგრძლივი სიცოცხლის განმავლობაში. აღსანიშნავი მაგალითებია გრენლანდიური ზვიგენი (400 წელზე მეტი), შიშველი თხუნელა-ვირთხა (30 წელზე მეტი), ოკეანის კვაჰოგი (507 წელი) და პლანარია (თეორიულად უკვდავი). ეს ორგანიზმები ეწინააღმდეგებიან დაბერების ტიპურ ნიმუშებს დნმ-ის გაძლიერებული აღდგენის, ჟანგვითი სტრესისადმი რეზისტენტობის, ღეროვანი უჯრედების შენარჩუნებისა და უნიკალური პროტეოსტაზისა და ეპიგენეტიკური რეგულავიის გზით. შედარებითი ანალიზი ავლენს საერთო ადაპტაციებს, როგორიცაა: 1) სქსორივი მომწიფების გვიანი ასაკი; 2) სქესობრივი აქტივობის დიდი ხნით შენარჩუნება; 3) მეტაბოლური სიჩქარის შემცირება; 4) ჰიპოქსიისადმი ტოლერანტობა; 5) ნეოპლაზიური სუპრესია. მათი სიცოცხლის ხანგრძლივობის მოლეკულარული მექანიზმები - მათ შორის მაღალი მოლეკულური წონის ჰიალურონანი შიშველ თხუნელა-ვირთხებში და სპეციალიზებული ლიპიდური მემბრანები ზვიგენებში - გვთავაზობს ტრანსფორმაციულ ხედვას დაბერების

საწინააღმდეგო ჩარევებისთვის. ამ სტრატეგიების გაგებამ შეიძლება გზა გაუხსნას ასაკთან დაკავშირებული დაავადებების სამკურნალოდ მიმართული ახალი თერაპიების განვითარებას, რაც პოტენციურად გადააფასებს ადამიანის ჯანმრთელობის ხანგრძლივობას. ეს მიმოხილვა სინთეზირებს უმნიშვნელოდ დაბერებული სახეობების შესახებ არსებულ ცოდნას, ხაზს უსვამს მათ ევოლუციურ, ფიზიოლოგიურ და ბიოსამედიცინო მნიშვნელობას.

საკვანძო სიტყვები: უმნიშვნელო დაბერება, სიცოცხლის ხანგრძლივობა, ოქსიდაციური სტრესი, პროტეოსტაზი, დაბერება, დღეგრძელობა.