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Insights from Animal Anti-Aging Mechanisms for Human Aging Therapy

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Abstract. Senescence is a ubiquitous but highly variable process that occurs in a variety of species, from short-lived rodents to centuries-long whales and clams. Comparative biology provides important insights into the molecular and cellular adaptations behind longevity. While humans face age-related genomic instability, telomere wear, mitochondrial dysfunction, and stem cell depletion, long-lived species such as whales, birds, naked mole rats, bats, and Greenland sharks exhibit unique adaptations that can mitigate these processes. These natural experiments shed light on therapeutic pathways to extend human healthspan, including anti-aging drugs, telomere therapy, epigenetic reprogramming, and caloric restriction mimics. This article reviews the characteristics of aging, explores the mechanisms of longevity at a very large scale, and evaluates their translational potential in human medicine. Combining evolutionary perspectives with biomedical research, it also reviews the common and differentiating mechanisms of aging across species and highlights how unique biological solutions can inspire innovative interventions in human medicine. We believe that combining evolutionary biology with clinical translation has the potential to fundamentally reshape the paradigm of aging research, providing a roadmap for advancing progress from disease management to staying alive throughout the human lifecycle and integrating evolutionary insights into biomedical research has the potential to fundamentally shift medicine from disease treatment to aging prevention.

Keywords: aging, longevity, whales, birds, anti-aging therapy

1. Introduction

Aging is one of the core challenges facing modern medicine. Aging is defined as a gradual decline in biological functions that can lead to chronic diseases such as cancer, cardiovascular disease, and neurodegenerative diseases [1]. By 2050, the global population aged 65 and above is expected to exceed 2 billion, putting unprecedented pressure on healthcare systems and economies [2]. Therefore, extending healthy life (life without serious diseases) has become a top priority in biomedicine.

However, the speed and severity of aging are not universal. Mice rarely live longer than three years, while bowhead whales (Balaena mysticetus) can live for more than two centuries without experiencing major pathological changes [3-5]. Although birds have a high metabolic rate, which increases oxidative stress, they generally live longer than mammals of similar size [6]. Greenland

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sharks (Somniosus microcephalus) live nearly 400 years [7], while naked mole rats (Heterocephalus glaber) have a low incidence of cancer despite living longer than rodents [8,9]. These examples show that natural selection produces several effective anti-aging mechanisms.

Traditional research has focused on short-lived model organisms such as yeast, nematodes, and mice because they are easy to experiment with. However, these systems can only capture limited aspects of aging. Unconventional longevity models reveal unique adaptations that directly address the characteristics of aging, offering complementary approaches to treatment development [10].

This article begins by reviewing the molecular mechanisms of aging, then exploring longevity strategies in various animal models, and finally discussing how these lessons can guide human treatment.

2. Cellular and molecular mechanisms of aging

2.1. Genomic instability and DNA damage

Genomic instability is a cornerstone of aging, driven by DNA replication errors, oxidative damage, and double-strand breaks [1]. Failure to repair this damage can lead to mutations that eventually lead to cancer and tissue dysfunction. In humans, DNA repair efficiency declines with age, leading to a higher mutational burden. However, long-lived species exhibit enhanced genomic stability. Bowhead whales possess unique duplications of genes involved in DNA repair and apoptosis, enhancing their resilience to genotoxic stress [3-5]. Naked mole rats also exhibit enhanced DNA repair pathway fidelity, which supports their resistance to cancer [8].

2.2. Telomere attrition

Telomeres shorten with each cell division, eventually triggering replicatic senescence [1]. While telomerase counteracts telomere wear, its expression is limited in most human somatic cells [11]. Birds are an exception: parrots and albatrosses exhibit very stable telomere dynamics despite the presence of high oxidative stress, suggesting an evolutionary adaptation to telomere maintenance [6,10]. These strategies may provide inspiration for therapies aimed at stabilizing telomeres in humans.

2.3. Epigenetic drift

Another hallmark of aging is epigenetic drift, the gradual loss of precision in DNA methylation and histone modification patterns [1]. Epigenetic clocks that measure changes in methylation can now predict chronological and biological age. Comparative studies have shown that long-lived mammals exhibit slower epigenetic drift [12], suggesting that epigenomic stability is a key determinant of longevity.

2.4. Protein homeostasis and mitochondrial dysfunction

Protein homeostasis, the maintenance of properly folded proteins, declines with age. Aggregation of misfolded proteins, leading to diseases such as Alzheimer's and Parkinson's [13]. Dysfunction is exacerbated by decreased autophagy and the ubiquitin-proteasome system.

Decreased mitochondrial function further accelerates aging. As we age, mitochondria produce too much reactive oxygen species (ROS) while producing less ATP, which damages DNA, proteins, and

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cell membranes. Long-lived species such as bats and birds maintain mitochondrial efficiency even under high metabolic demands, reducing ROS leakage [6,14].

2.5. Cellular senescence and stem cell depletion

Senescent cells accumulate and release pro-inflammatory signals with age, known as senescence-associated secretory phenotype (SASP). This chronic inflammation accelerates tissue degeneration [11]. At the same time, stem cells lose their regenerative potential. For example, in aging hematopoietic stem cells, DNA damage and clonal imbalances accumulate [15].

In contrast, species like whales and naked mole rats exhibit resilience in stem cell maintenance, delaying exhaustion and maintaining regenerative capacity over extended lifespans [3,8].

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3. Longevity mechanisms in non-traditional models

3.1. Birds: oxidative stress capacity

Birds offer a paradoxical pattern of longevity. Despite their high metabolic rates, many species, including crows, parrots, and albatrosses, outlive similarly sized mammals by decades. Birds exhibit less oxidative damage, more robust antioxidant enzyme activity, and efficient DNA repair mechanisms. For example, parrots maintain stable telomere lengths associated with reproductive strategies, suggesting that evolutionary life history trade-offs influence telomere dynamics [6,10,16].

3.2. Whales: tumor suppression and hypoxia tolerance

Bowhead whales embody the "Peto's paradox": despite their large size and large number of cells, they have a very low incidence of cancer. Genetic adaptations include replication of tumor suppressor genes and enhanced DNA repair pathways. Additionally, whales have evolved resistance to hypoxia in the Arctic environment, which may enhance their cellular resilience to stress [3-5]. These adaptations have made whales a leading model for studying cancer inhibition and tissue repair.

3.3. Bats: viral tolerance and DNA repair

Bats are an exception among mammals, with some species living over 30 years despite their small size. They exhibit strong DNA repair capabilities, robust interferon responses, and unique tolerance to viral infections [14]. These adaptations illustrate how immune modulation can extend longevity while balancing pathogen defenses.

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3.4. Naked mole rats: anti-cancer ability

Naked mole rats have a lifespan of 30 years, much longer than mice, and the incidence of cancer is negligible. They achieve this through unique tumor suppression pathways, including early exposure inhibition and modification of the p16 tumor suppression pathway [8]. Their adaptation to hypoxia and oxidative stress further supports their longevity [9].

3.5. Clams: negligible senescence

Arctic clam (Arctica islandica) aging is negligible, and the risk of death does not increase with age. It is able to maintain protein homeostasis and metabolic efficiency for centuries [13]. These findings suggest that aging is not a universal law, but an evolutionary consequence.

3.6. Greenland shark: extremely long-lived

The Greenland shark is estimated to live over 400 years, making it the longest-lived vertebrate. While the molecular basis for this is still being studied, some hypotheses include low metabolic rates, efficient protein homeostasis, and unique mitochondrial adaptations [7]. This example challenges the assumption that aging is inevitable.

4. Therapeutic implications for human

4.1. Senolytics: targeting senescent cells

While cellular senescence can prevent cancer in young adults, it contributes to chronic inflammation and tissue dysfunction in older adults through an age-associated secretory phenotype (SASP) [11]. Senolytic therapy aims to selectively eliminate these dysfunctional cells. For example, the combination of dasatinib and quercetin has been shown to be effective in eliminating senescent cells in mice, improving cardiovascular and lung function and increasing healthspan [11]. Clinical trials in patients with idiopathic pulmonary fibrosis have shown that anti-aging agents can relieve symptoms and improve physical function [9].

The discovery of long-lived animals also supports this approach. For example, naked mole rats reduced the accumulation of senescent cells compared to mice, suggesting that reducing SASP may be a key factor in its anti-cancer and life-prolonging properties [8]. By mimicking these natural strategies, anti-aging therapies can restore tissue homeostasis in humans.

4.2. Telomere stabilization and telomerase therapy

Telomere shortening limits cell proliferation and accelerates stem cell depletion [1]. While telomerase activation can extend the lifespan of mice, it also raises concerns about cancer risk due to its enhanced proliferative potential. However, telomeres in birds such as parrots and albatrosses remain relatively stable even under oxidative stress [6,10], proposing an evolutionary mechanism that balances telomere stability and tumor suppression.

Experimental telomerase gene therapy has been shown to restore tissue vitality, improve insulin sensitivity, and enhance neuromuscular coordination in aged mice without significantly increasing cancer incidence. If these strategies are combined with protective measures that suppress tumors, their application in humans may slow down age-related decline.

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4.3. Epigenetic reprogramming

Epigenetic drift disrupts gene expression programs, impairing stem cell renewal and tissue function. Long-lived species exhibit slower epigenetic changes, which are associated with increased lifespan [12]. In laboratory studies, partial reprogramming using Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) reversed some of the aging features and restored regenerative function in mice without inducing complete dedifferentiation [1].

This approach bears striking similarities to those observed in whales and naked mole rats, which maintain stem cell quiescence and resistance to epigenetic dysregulation in old age [3,8]. Therapies that mimic this epigenetic resilience can rejuvenate tissues while preserving their properties, offering potential interventions for age-related conditions such as neurodegeneration and frailty.

4.4. Mtor inhibition and calorie restriction mimicry

Inhibition of nutrient perception pathways is a recurring theme in longevity research. Comparative transcriptomic analysis of 41 mammalian species revealed that IGF-1 and mTOR signaling pathways are sustainably downregulated in long-lived species [9]. This echoes the results of calorie restriction studies, which suggest that increased lifespan is achieved by reducing growth signals and enhancing autophagy.

Rapamycin is an mTOR inhibitor that prolongs the lifespan of yeasts, nematodes, fruit flies, and mice. It can also improve immune function and reduce cancer incidence in mammalian models [1]. Calorie-restriction mimics such as resveratrol and metformin have shown similar promise, enhancing mitochondrial efficiency and stress recovery. These interventions echo the natural mechanisms of clams and whales, which rely on efficient energy metabolism and attenuated growth signals to sustain longevity [3,13].

4.5. NAD+ booster and mitochondrial health

Mitochondrial dysfunction accelerates with age, partly due to decreased levels of nicotinamide adenine dinucleotide (NAD+), a key cofactor in metabolism and DNA repair. Supplementation with NAD+ precursors, such as nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN), can improve mitochondrial health, enhance DNA repair, and extend lifespan in mice [1].

Bats and birds maintain mitochondrial function despite high metabolic demands, highlighting the potential to focus on mitochondrial health for longevity [6,14]. By restoring NAD+ levels, humans may be able to replicate the mitochondrial efficiency of these species, improving their ability to combat age-related metabolic decline.

4.6. Integrative therapy: towards a multimodal approach

There is no single treatment that can address all the characteristics of aging. However, studies of long-lived species have shown that resilience stems from a combination of mechanisms: DNA repair, protein homeostasis, telomere maintenance, and immune regulation. For humans, this means a multimodal treatment approach—combining anti-aging drugs, telomere stabilizers, epigenetic reprogramming, caloric restriction mimics, and mitochondrial enhancers.

This integration is similar to the natural convergence observed across species. Whales combine tumor suppression with DNA repair, birds combine antioxidant activity with telomere stability, and clams show little signs of aging while maintaining protein homeostasis. Conversion therapies may require similar system-level strategies that target multiple traits simultaneously.

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5. Discussion

Comparative biology emphasizes that aging is not inevitable but can be changed. Birds rely on oxidative defense, whales rely on tumor suppression, bats rely on immune resilience, and clams rely on protein homeostasis. Despite this diversity, commonalities exist: genomic stability, efficient repair, and metabolic optimization. These recurring mechanisms suggest an evolutionary "solution" to aging.

However, their application in humans requires caution. Telomerase activation, while having anti-aging potential, may also increase cancer risk. Anti-aging agents, while promising, may impair wound healing. The ethical question arises: Should life be extended if society exacerbates inequality or resource demands? These questions highlight the intertwining of ageing science with social policy and bioethics.

Yet, the integration of evolutionary insights into human medicine represents a paradigm shift. Treatment should not be treated in isolation for age-related diseases, but should be directed at aging itself—the basic driver of disease.

6. Conclusion

Studies of the biology of long-lived species have shown that the aging process, while pervasive, is neither fixed nor uniform. Rather, it represents a set of outcomes shaped by evolutionary pressures, ecological niches, and genetic innovations. Birds, whales, naked mole rats, bats, clams, and Greenland sharks all provide compelling evidence that aging can be slowed, resisted, or radically reshaped through various biological strategies. These adaptations range from enhanced DNA repair and cancer resistance to superior maintenance of mitochondrial function, protein homeostasis, and telomere integrity. Collectively, these organisms show that longevity is not a single trait, but rather a coordinated network of protective mechanisms that maintain health over extremely long time scales. These findings have far-reaching implications for human health. Translating natural adaptations into therapeutic strategies has the potential to change the current medical paradigm. Treatment should not treat age-related diseases as isolated diseases, but rather target the underlying biological drivers of aging itself. Interventions inspired by long-lived species include the development of anti-aging drugs that mimic caloric restriction, telomere-based therapies that stabilize chromosomal integrity, mitochondrial enhancers that maintain energy balance, and epigenetic reprogramming tools that restore youthful gene expression patterns. These strategies aim not only to extend lifespan but also to maximize healthspan—a lifespan free from chronic diseases and functional decline.

Equally important are the broader ethical, social, and translational challenges facing anti-aging research. The application of animal longevity research insights raises complex questions about accessibility, equity, and definition of healthy aging in different populations. In addition, the evolutionary trade-offs observed in long-lived species, such as slower reproduction or highly specialized ecological adaptations, may limit the direct application of certain mechanisms to humans. Therefore, careful consideration is needed to ensure that interventions from comparative biology remain safe, effective, and ethically sound. Despite these challenges, comparative biology offers a clear path forward for the future of human aging research. It emphasizes that biology has solved many of the aging challenges facing humanity, and by studying nature's most resilient species, researchers can discover the principles that guide therapeutic innovation. Beyond medical applications, this perspective redefines aging itself: no longer just an inevitable decline, but a transformative frontier in biology. Just as infectious diseases and malnutrition once determined

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human lifespan and can only be solved by science and medicine, the biology of aging now presents new challenges and opportunities for the 21st century.

Finally, research into the mechanisms of anti-aging in animals highlights a promising vision that aging can shift from a passive inevitability to a realm of proactive prevention and intervention. By combining evolutionary insights with modern biotechnology, medicine can go beyond treating age-related diseases and fundamentally alter the health trajectory of humans throughout their lifespan. In this way, the lessons learned from whales, birds, moles, sharks, and clams not only spark curiosity but also point the way to redefine what it means to age.

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