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THE EVOLUTION OF CANCER RESISTANCE AS AN INSPIRATION FOR MODERN ONCOLOGY – A REVIEW

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ABSTRACT

Background: Cancer is a leading cause of mortality worldwide and is associated with the accumulation of DNA damage, disruptions in cell cycle control, and loss of genomic stability. Statistical intuition suggests that large body size or long lifespan should increase cancer risk. However, empirical observations contradict this assumption. Species such as elephants, bowhead whales, and naked mole rats do not exhibit a proportionally higher incidence of cancer, a phenomenon known as Peto's paradox.
Aim: This study aimed to compare mechanisms of cancer resistance in selected mammalian species characterized by large body size or exceptional longevity, with particular emphasis on elephants, bowhead whales, and naked mole rats. The analysis focused on DNA repair pathways, cell cycle regulation, and tumor suppressor proteins, including p53 and CIRBP.
Materials and Methods: A literature review was conducted using the PubMed, ScienceDirect, Encyclopedia Britannica, Springer and the World Health Organization. The search included the terms "CIRBP," "Peto's paradox," "p53 protein," "DNA repair pathways," "Bowhead whale," "Cancer Resistance in Elephants," and "Naked Mole Rat." Only publications in English were included.
Conclusions: Comparative analysis revealed that evolution has led to diverse and effective mechanisms limiting carcinogenesis. Of particular significance is the identification of the CIRBP protein in the bowhead whale as a factor enhancing the efficiency of DNA repair, highlighting the translational potential of comparative oncology for cancer prevention and therapy.

KEYWORDS

CIRBP, Peto's Paradox, p53 Protein, DNA Repairs Pathways, Bowhead Whale, Naked Mole-Rat

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1. Introduction:

Cancer remains one of the most significant causes of mortality worldwide. According to the World Health Organization, nearly 10 million deaths were attributed to cancer in 2020, representing approximately one in six deaths globally. The term "cancer" encompasses a broad spectrum of diseases that may arise in virtually any tissue or organ. A hallmark of these conditions is the emergence of abnormal cells that proliferate uncontrollably, surpassing normal physiological boundaries (*World Health Organization*, 2025). Malignancies have the ability to metastasize, spreading from the primary site to distant organs and contributing to most cancer-related deaths (Garemilla et al., 2025).

The capacity of tumors to invade surrounding tissues and form distant metastases arises from the progressive accumulation of malignant characteristics. These features result from genetic and epigenetic alterations that disrupt essential cellular processes, including DNA damage detection and repair mechanisms, regulation of cell proliferation, and interactions with the immune system responsible for immune surveillance (Hanahan & Weinberg, 2011).

Some researchers have hypothesized that, if every cell has an equal chance of acquiring tumorigenic mutations, organisms with more cells and longer lifespans would theoretically be at higher risk of developing cancer. However, empirical evidence suggests otherwise, revealing the phenomenon known as Peto's paradox, whereby large, long-lived species do not exhibit proportionally higher rates of cancer compared to smaller, shorter-lived species (Caulin & Maley, 2011; Sun et al., 2025). This paradox indicates that such species have evolved additional mechanisms of cancer suppression, including enhanced DNA repair, increased tumor suppressor activity, and other cellular adaptations that maintain genomic stability (Maciak, 2022; Szasz, 2024).

Notable examples of species that illustrate Peto's paradox include elephants and bowhead whales. Despite their enormous body size and long lifespans, these animals exhibit remarkably low cancer incidence. In elephants, this resistance is primarily associated with the presence of multiple copies of the *TP53* gene,

which enhances the apoptotic elimination of damaged cells (Abegglen et al., 2015; Palefsky et al., 2025; Sulak et al., 2016). Bowhead whales (*Balaena mysticetus*), in contrast, appear to rely on mechanisms that improve genome protection and DNA repair efficiency (Firsanov et al., 2024, 2025).

In this work, we also highlight a smaller species that, although it does not represent a classical example of Peto's paradox, has likewise evolved impressive cancer resistance. The naked mole-rat (*Heterocephalus glaber*), a subterranean rodent, is characterized by exceptional longevity relative to other rodents and an extremely low incidence of both spontaneous and experimentally induced tumors (Shepard et al., 2025; Xia & Xu, 2023; Zhang et al., 2023). Its cancer resistance has been linked to high-molecular-mass hyaluronan, early contact inhibition, and strengthened regulation of the cell cycle, making it a valuable model for the study of natural anti-cancer mechanisms (Y. Chen et al., 2025; Lin et al., 2024; Shepard et al., 2025; Xia & Xu, 2023; Zhang et al., 2023).

Understanding the molecular foundations of cancer resistance across such diverse species provides important perspectives for oncology. Mechanisms observed in elephants, bowhead whales, and naked mole-rats — including enhanced DNA repair efficiency, strengthened tumor suppressor activity, and microenvironmental control of cell proliferation — may ultimately inspire new strategies for cancer prevention and therapeutic intervention in humans.

2. Peto's Paradox and the Evolution of Cancer Resistance

From a purely statistical perspective, if each cell in an organism has a similar likelihood of acquiring mutations that may lead to malignant transformation, then larger organisms—with correspondingly greater numbers of cells—would, in theory, be expected to face a higher risk of developing cancer (Caulin & Maley, 2011; Maciak, 2022). By the same reasoning, species that live longer should also theoretically face greater cancer risk, as their cells undergo a higher number of divisions over an prolonged lifespan (Szasz, 2024).

However, based on the work by Abegglen et al., an analysis of necropsy records from 36 mammalian species showed that cancer mortality does not rise with increasing body mass or prolonged lifespan, indicating that larger and longer-lived animals are not inherently more susceptible to cancer (Abegglen et al., 2015). One way to explain Peto's paradox is through the lens of evolution: species exposed to the selective pressures associated with cancer risk must develop strengthened cancer-suppression mechanisms to offset the disadvantages of having more cells and longer lifespans, or else face reduced fitness and potential extinction (Tollis et al., 2017).

3. Human DNA Repair Pathways

Human cells possess a range of mechanisms that protect the genome from damage. These operate at multiple levels, including DNA repair systems and surveillance checkpoints that continuously monitor genomic integrity and the functioning of individual repair pathways (Gartner & Engebrecht, 2021).

The core processes of DNA repair include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) (Waters & Spratt, 2024).

3.1. BER - Base Excision Repair

BER is responsible for the removal of minor base damage and single-strand breaks (Gohil et al., 2023). Key steps include the activity of DNA glycosylases, APE1, DNA polymerase beta, and DNA ligase, and also depend on histone variants that influence chromatin accessibility at damaged sites (Biechele-Speziale et al., 2022; Gohil et al., 2023). The deeper the damaged base is located within the nucleosome, the more difficult it is for BER enzymes to initiate repair and the slower the process proceeds (Biechele-Speziale et al., 2022). Disruption of the BER pathway leads to the accumulation of mutations and genomic instability, promoting cancer development (Sutton et al., 2024; Zhao et al., 2021).

3.2. NER - Nucleotide Excision Repair

NER addresses more extensive DNA damage. Short fragments containing modified nucleotides are detected and excised. Common substrates include thymine dimers induced by UV radiation and bulky adducts caused by environmental toxins (Gartner & Engebrecht, 2021).

3.3. MMR - Mismatch Repair

MMR plays a crucial role in maintaining replication fidelity. It detects mismatched nucleotides and insertion/deletion loops resulting from DNA polymerase errors. The pathway then initiates removal of the defective fragment and restores the correct sequence (Waters & Spratt, 2024).

3.4. HR - Homologous Recombination

HR is a highly accurate double-strand break repair pathway that uses a homologous DNA sequence as a template. It operates primarily during the S and G2 phases of the cell cycle, when sister chromatids are available (Wang et al., 2023).

3.5. NHEJ - Non-homologous End Joining

NHEJ is the most rapid pathway for repairing double-strand breaks. It involves recognition of DNA ends and their direct rejoining. Because the ends are not extensively processed before ligation, this pathway is error-prone. NHEJ does not require a homologous template and operates throughout the cell cycle (Wang et al., 2023).

4. Tumor Suppressor Proteins and Cell Cycle Control

Tumor suppressor proteins regulate the cell cycle, coordinate the response to DNA damage, and induce apoptosis when damage is severe. These mechanisms limit mutation accumulation and prevent malignant transformation (L. Chen et al., 2020; Hernández Borrero & El-Deiry, 2021).

4.1. p53 Protein

The p53 protein is encoded by the TP53 tumor suppressor gene and is referred to as the guardian of the genome (Efeyan & Serrano, 2007). It plays a key role in cellular homeostasis by integrating stress signals and controlling cell fate decisions (Aubrey et al., 2018). Upon DNA damage, p53 becomes stabilized and activated, functioning as a transcription factor that induces genes involved in cell cycle arrest (CDKN1A/p21), DNA repair (GADD45), and apoptosis (PUMA) (Hernández Borrero & El-Deiry, 2021).

Apoptosis triggered by p53 is mediated mainly through mitochondrial pathways, which constitutes a central aspect of its anticancer activity (Aubrey et al., 2018). Additionally, p53 modulates cellular metabolism by inhibiting glycolysis and stimulating oxidative phosphorylation, counteracting metabolic reprogramming characteristic of cancer cells (Simabuco et al., 2018).

4.2. Retinoblastoma Protein (pRb)

The retinoblastoma protein (pRb) is another key tumor suppressor. It regulates cell cycle progression by inhibiting E2F/DP transcription factors. In the presence of DNA damage, pRb prevents transition from G1 to S phase, ensuring that defective genes are not replicated (Kitajima & Takahashi, 2017; Yamasaki, 2003).

5. Telomeres and Chromosome End Protection

5.1. Telomere Structure

Telomeres are nucleoprotein structures located at chromosome ends and form a characteristic T-loop. The T-loop masks natural DNA termini from double-strand break detection systems, preventing unwanted fusion and degradation (Arnoult & Karlseder, 2015; Diotti & Loayza, 2011).

5.2. Telomerase (hTERT)

Telomerase is a reverse transcriptase that adds telomeric repeat sequences (TTAGGG) to chromosome ends, counteracting replicative shortening. It delays cellular senescence, particularly in highly proliferative cells (Smith et al., 2020).

5.3 Shelterin Complex

Shelterin is a multiprotein complex (TRF1, TRF2, POT1, RAP1, TIN2, and TPP1) bound to telomeric DNA. It protects chromosome ends from inappropriate activation of DNA damage responses and erroneous repair mechanisms (Diotti & Loayza, 2011). Shelterin supports T-loop formation and regulates telomerase access, indirectly affecting telomere length (Bandaria et al., 2016; Mir et al., 2020). By stabilizing telomeres, it reduces the risk of chromosome fusion, genomic instability, and tumorigenesis (Diotti & Loayza, 2011).

6. Mechanism of CIRBP Action in Response to DNA Damage

Cold-inducible RNA-binding protein (CIRBP) is an RNA-binding protein that plays an important role in the cellular stress response, including the response to DNA damage. Under genotoxic conditions, CIRBP contributes to the maintenance of genome stability by participating in the repair of DNA double-strand breaks (DSBs) and by regulating the expression of stress-response genes (J. K. Chen et al., 2018; Firsanov et al., 2025).

Following the formation of DSBs, one of the earliest activated enzymes is poly(ADP-ribose) polymerase-1 (PARP-1), which catalyzes the synthesis of poly(ADP-ribose) (PAR) at sites of DNA damage. PAR acts as a signaling platform that recruits DNA damage response proteins, including CIRBP. Through interactions with PAR and RNA, CIRBP is recruited directly to DSB sites, facilitating its localization to damaged chromatin and its incorporation into DNA repair complexes (J. K. Chen et al., 2018; Rana et al., 2024).

The presence of CIRBP promotes the association of key early DNA damage response factors, such as the MRN complex (Mre11–Rad50–NBS1) and the ATM kinase, which initiate damage signaling and activate DNA repair pathways (J. K. Chen et al., 2018; Rana et al., 2024). Consequently, CIRBP supports the activity of both major DSB repair mechanisms: homologous recombination (HR) and non-homologous end joining (NHEJ).

7. The Bowhead Whale (*Balaena mysticetus*) — A Model of Remarkable Cancer Resistance

7.1. Species Characteristics of the Bowhead Whale

The bowhead whale (*Balaena mysticetus*) is a very large baleen whale of the family Balaenidae, inhabiting Arctic waters. Adults can reach up to about 20 m in length and have extremely high body mass, making the bowhead one of the largest living marine mammals. The species is characterized by a massive body, the absence of a dorsal fin, and very long baleen plates that enable efficient filtration of plankton from seawater (Lagunas-Rangel, 2021).

Bowhead whales are also renowned for their exceptional longevity. Observations based on analyses of amino-acid racemization in the eye lens, together with other methods, suggest that some individuals can live for more than 200 years, making them the longest-lived mammals known to science (Tyshkovskiy et al., 2023). Despite their large body size, high cell number, and extreme lifespan, bowhead whales exhibit a low incidence of cancer, representing a striking example of Peto's paradox (Firsanov et al., 2024).

7.2. Mechanisms of Cancer Resistance in the Bowhead Whale

In the study conducted by Firsanov and colleagues (Firsanov et al., 2025), the authors examined mechanisms that may underlie the remarkably low cancer incidence in the bowhead whale, focusing specifically on DNA repair processes and the role of the protein CIRBP. The researchers demonstrated that fibroblasts of this species exhibit exceptionally efficient repair of DNA double-strand breaks, as well as lower mutation rates compared to other mammals, which substantially reduces the likelihood of accumulating changes that could lead to malignant transformation.

One of the key findings of the study was the discovery that CIRBP is present in the bowhead whale at remarkably high levels. Its elevated abundance significantly enhanced both major double-strand break repair pathways, NHEJ and HR. CIRBP also reduced the formation of micronuclei—markers of genomic instability—and supported the protection of DNA ends and their accurate rejoining. As a result, this protein contributed substantially to maintaining genomic stability and limiting the number of mutations arising from DNA damage. According to the authors, this highly effective genome-protection system, supported by CIRBP, may be a major factor underlying the low cancer incidence observed in the bowhead whale.

The researchers also showed that introducing bowhead whale CIRBP into human cells significantly improved the efficiency of DNA double-strand break repair, indicating a direct genome-protective effect across species. Moreover, overexpression of both human and bowhead whale CIRBP in *Drosophila melanogaster* led to a consistent extension of lifespan compared with controls and markedly improved survival following exposure to ionizing radiation, reflecting increased resistance to DNA damage *in vivo*.

Feature	Human CIRBP	Bowhead Whale CIRBP
Protein identity	Conserved RNA-binding protein	Conserved RNA-binding protein
Baseline expression level	Low to moderate	**Very high**
Induction by stress	Upregulated by cold and genotoxic stress	**Constitutively high, further responsive to stress**
Role in DNA repair	Participates in DSB repair and stress response	**Strongly enhances DSB repair efficiency and fidelity**
Effect on NHEJ and HR	Supports NHEJ and HR	**Significantly increases NHEJ and HR efficiency**
Genome stability	Standard mammalian genome maintenance	**Reduced mutations and chromosomal aberrations**
Functional consequence	Normal DNA damage response	**Associated with low mutation rates and cancer resistance**

Fig. 1. *Comparison of CIRBP in Humans and Bowhead Whales*

8. Cancer Resistance in Elephants

8.1 Characteristics of Elephants

Elephants are among the largest living land mammals. Their shoulder height ranges from approximately 3 to 4 meters, and body weight ranges from about 5.5 tons in Asian elephants to up to 8 tons in African savanna elephants. Elephants can live for 60–70 years (Shoshani, 2025).

Despite their exceptionally large body size and long lifespan—which would theoretically increase the risk of accumulating cancer-promoting mutations—epidemiological data indicate that cancer mortality in elephants is below 5%, compared with 11–25% in humans (Abegglen et al., 2015).

8.2 Mechanisms of Cancer Resistance in Elephants

One of the most important mechanisms underlying cancer resistance in elephants is the increased copy number of the tumor suppressor gene TP53. Genomic analyses have shown that African elephants possess approximately 20 copies of TP53, 19 of which are TP53 retrogenes (TP53RTGs). Several of these copies are actively transcribed and translated, contributing to an enhanced DNA damage response (Abegglen et al., 2015; Sulak et al., 2016).

In vitro experiments have demonstrated that TP53RTGs increase the sensitivity of elephant cells to genotoxic stress, leading to apoptosis at lower levels of DNA damage compared with closely related species (Sulak et al., 2016). Consistently, following exposure to ionizing radiation or chemotherapeutic agents, elephant lymphocytes exhibit significantly higher rates of apoptosis than human lymphocytes, suggesting a more efficient elimination of damaged cells (Abegglen et al., 2015).

Additionally, elephants possess unique variants of the MDM2 protein, a key regulator of p53 activity. Unlike human MDM2, elephant MDM2 variants can enhance p53 activation in response to DNA damage. This mechanism enables tighter control of cell proliferation and more effective removal of genetically compromised cells. Together with the expanded TP53RTG repertoire, these adaptations likely constitute a central foundation of elephants' remarkable resistance to cancer (Palefsky et al., 2025).

9. Cancer Resistance in Naked Mole-Rat

9.1. Species Characteristics of Naked Mole-Rat (*Heterocephalus glaber*)

The naked mole-rat (*Heterocephalus glaber*) is a subterranean rodent native to East Africa. This species is distinguished by its exceptional longevity, reaching 30–37 years, which is remarkably high for a rodent of its body size. Notably, naked mole-rats maintain physiological fitness throughout most of their lifespan and do not exhibit the typical age-related increase in cancer incidence.

Despite their small body size, naked mole-rats display an extraordinarily low incidence of both spontaneous and experimentally induced tumors (Shepard et al., 2025; Xia & Xu, 2023; Zhang et al., 2023)

9.2. Mechanisms of Cancer Resistance in Naked Mole-Rat

A central mechanism underlying cancer resistance in naked mole-rats is the presence of high-molecular-mass hyaluronan (HMM-HA), which promotes early contact inhibition and restricts excessive cell proliferation, forming an effective barrier against malignant transformation (Shepard et al., 2025; Xia & Xu, 2023; Zhang et al., 2023)

Their cells also exhibit strengthened activity of tumor-suppressive pathways such as p16^INK4a–RB and p27^Kip1, which enable robust G1 arrest even under oncogenic stimulation. As a result, naked mole-rat cells show a high resistance to experimental transformation and do not undergo easy immortalization.(Xia & Xu, 2023)

Additionally, both the tissue microenvironment and the immune system play critical roles in preventing the progression of mutated cells to malignant tumors (Hadi et al., 2021; Sanchez Sanchez et al., 2024).

On the genomic and epigenetic levels, naked mole-rats display increased genome stability, reduced somatic mutation rates, and unique regulation of long noncoding RNAs that modulate DNA repair, stress responses, and proliferation control (Lin et al., 2024; Zhang et al., 2023).

Furthermore, their cells are highly resistant to oxidative stress and hypoxia, and possess metabolic adaptations—such as efficient fructose utilization under low oxygen—that limit genomic instability and reduce the likelihood of malignant transformation (Y. Chen et al., 2025; Sanchez Sanchez et al., 2024)

10. Discussion

Some long-lived or large mammalian species exhibit remarkable resistance to cancer, which highlights the importance of understanding the evolutionary mechanisms underlying this phenomenon. Such knowledge may inspire novel approaches to cancer prevention and therapy in humans.

This work describes three model organisms: the bowhead whale, the elephant, and the naked mole-rat. These species have evolved highly effective yet distinct mechanisms of genome protection.

The bowhead whale represents one of the most extreme examples of natural cancer resistance. Despite its lifespan exceeding 200 years and its enormous number of cells, the species demonstrates exceptionally low cancer incidence. Studies by Firsanov et al. showed that bowhead whale fibroblasts repair DNA double-strand breaks with remarkable efficiency and accuracy, and they display lower mutation rates than fibroblasts of other mammals. A particularly significant discovery was the high expression of CIRBP, which enhances both NHEJ and HR pathways, reduces genomic instability, and stabilizes damaged DNA ends. These mechanisms may substantially limit cancer initiation in this species. Moreover, it has been shown that bowhead whale CIRBP improves DNA repair in human cells and significantly increases survival in Drosophila melanogaster, both under physiological conditions and after exposure to ionizing radiation. Overexpression of either human or bowhead whale CIRBP extended lifespan in flies and increased resistance to DNA damage in vivo, strongly supporting the role of CIRBP in promoting genomic stability and organismal longevity, and suggesting that this mechanism is at least partly evolutionarily conserved and potentially useful in medicine (Firsanov et al., 2024, 2025).

In elephants, the most important mechanism is the markedly increased number of TP53 gene copies, as well as unique variants of MDM2, which allow for more effective elimination of cells with damaged DNA. In practice, this means that elephant cells undergo apoptosis more frequently in response to DNA damage instead of attempting repair. Such a strategy minimizes the risk of survival of cells with oncogenic potential. A comparison of elephants and bowhead whales illustrates two different yet evolutionarily effective approaches to limiting carcinogenesis: one based on eliminating damaged cells and the other on exceptionally efficient genome repair (Abegglen et al., 2015; Palefsky et al., 2025; Sulak et al., 2016).

The naked mole-rat employs a combination of external and internal mechanisms. HMM-HA forms a unique extracellular matrix structure that imposes very early contact inhibition, significantly limiting uncontrolled proliferation. Enhanced activity of tumor-suppressive pathways such as p16^INK4a–RB and p27^Kip1 prevents cells from entering the S phase in response to oncogenic stimuli, raising the threshold for malignant transformation. Additionally, naked mole-rats display a stable genome, lower mutation rates, specific regulation of long non-coding RNAs, and resistance to oxidative stress and hypoxia. Collectively, these mechanisms create an environment highly unfavorable for cancer development (Y. Chen et al., 2025; Hadi et al., 2021; Lin et al., 2024; Sanchez Sanchez et al., 2024; Shepard et al., 2025; Xia & Xu, 2023; Zhang et al., 2023).

Despite clear differences among these species, a common theme emerges: cancer resistance arises from strengthened control over genomic integrity, improved responses to DNA damage, or an increased capacity to eliminate genetically defective cells. Understanding these mechanisms may have significant implications for medicine, particularly in the context of aging human populations, in which rising genomic instability is a key risk factor for cancer (Vijg & Suh, 2013).

11. Conclusions

A comparative analysis of cancer resistance mechanisms in the bowhead whale, the elephant, and the naked mole-rat demonstrates that evolution has produced diverse yet equally effective strategies for limiting carcinogenesis in species at elevated risk due to large body size or longevity. These species exhibit distinct but highly effective approaches, which may inspire new methods for cancer prevention and therapy in humans. These findings confirm the growing importance of comparative oncology as a field with considerable translational potential.

A particularly significant discovery is the identification of CIRBP in the bowhead whale as a key factor enhancing the efficiency and accuracy of DNA repair, thereby limiting genomic instability. The demonstration that overexpression of bowhead whale CIRBP improves DNA repair in human cells and increases resistance to damage and lifespan in Drosophila underscores its evolutionarily conserved nature and high translational potential. This discovery sheds new light on the relevance of comparative oncology and suggests that modulating DNA repair quality, rather than solely eliminating damaged cells, may represent a promising direction for developing novel strategies for cancer prevention and therapy in humans.

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Conceptualization: GK, KK
Methodology: AB
Software: Not applicable
Check: AK, RF, BT
Formal analysis: GK, KK
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Resources: AK, DG, BT
Data curation: AB, WW
Writing - rough preparation: GK, KK
Writing - review and editing: KK, AB, BT
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