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REVIEW

Analysis of Cancer-Resisting Evolutionary Adaptations in Wild Animals and Applications for Human Oncology

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Abstract

This literature review is to present a new direction in developing better treatment or preventive measures. The larger the body of an organism, the more numerous the cells, which theoretically lead to a higher risk of cancer. However, observational studies suggest the lack of correlation between body size and cancer risk, which is known as Peto's paradox. The corollary of Peto's paradox is that large organisms must be cancer-resistant. Further investigation of the anti-cancer mechanisms in each species could be potentially rewarding, and how the anti-cancer mechanisms found in wild animals can help influence and develop more effective cancer treatment in humans is the main focus of this literature review. Due to a lack of research and understanding of the exact molecular mechanisms of the researched species, only a few (Elephants and rodents) that have been extensively researched have made substantive contributions to human oncology. A new research direction is to investigate the positively selective genes that are related to cancer resistance and see if homologous genes are presented in humans. Despite the great obstacle of applying anti-cancer mechanisms to the human body from phylogenetically distant species, this research direction of gaining insights through investigating cancer-resisting evolutionary adaptations in wild animals has great potential in human oncology research.

Keywords Cancer Resistance · Cancer Research · Molecular Biology · Peto's Paradox · Mechanisms

Background Information

Cancer is a disease caused by the uncontrolled division of abnormal cells in a part of the body, induced by genetic mutations caused by inherited diseases, carcinogens, and the largest contributing factor—random mutations arising during DNA replication (Tomasetti and Vogelstein 2015). For cancer to develop, normal cells have to undergo mutations that give rise to the 10 core hallmarks of cancer, specifically sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, tumor-promoting inflammation, avoiding immune destruction, deregulating cellular metabolism, and genome instability and mutation (Hanahan 2022). Despite this, an estimated ten million people die of cancer each year, making it the most fatal disease that the human race faces.

Our bodies, consisting of 30 trillion cells, undergo 2 trillion cell divisions every day, and "about 330 billion cells are replaced daily, equivalent to about 1% of all our cells," which means that a new person is regenerated in 80 to 100 days, biologically speaking (Jen Christiansen, 2021). Therefore, despite all the mutations that cells experience and the odds of a mutation turning a cell cancerous during a single cellular division process being extremely insignificant, the likelihood of being diagnosed with cancer is non-negligible throughout an individual's lifespan.

Indeed, cancer has been the second leading cause of death worldwide since 1990, the first being cardiovascular disease. In 2023, 609,820 cancer deaths were reported in the United States, according to the National Cancer Institute. Before the advent of molecular treatment in the 1950s, most therapies relied on surgery, which is not an effective way to

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treat cancer in its later stages when cancer cells spread to different parts of the body. However, most of the available treatments have severe side effects, cause financial distress, and result in treatment-related time toxicity (the time the patient spends on treatment is greater than the time the treatment extends one's lifespan), as demonstrated by the high mortality rate. Yet, it is interesting to note that cancer cells, although fatal, are cells that originated and mutated from our body cells, not directly caused by pathogen invasion. This accounts for the difficulties in developing specialized drugs or treatments that target only the cancer cells and explains their severe side effects. Therefore, the purpose of this study is to offer cancer researchers a new direction in developing better treatments or preventive measures, and Peto's paradox and positive natural selection offer new insights in the field of human oncology.

Introduction to Peto's Paradox

In 1954, Doll and Armitage proposed a multistage theory that "predicts carcinogenesis as a multistage process of accumulation of genetic and epigenetic mutations in a mitotic cell," leading to the conclusion that cancer prevalence should correlate with the number of cell divisions per time (Nery et al. 2022). Therefore, one might expect to find that the larger and long-lived an individual, the higher the cancer prevalence. While this phenomenon is true within species, individual comparisons across species suggest a different story.

Peto's Paradox is the lack of correlation between body size/longevity and cancer risk across species. In other words, the predicted cancer prevalence across species based on their lifespan and body mass does not align with empirical data. Specifically, hardly any cases were found in the African elephant or the bowhead whale, whereas approximately 23% of aged humans die of cancer, even though elephants and whales have thousands of times more cells than humans (Schraverus et al. 2022). This biological paradox was first discovered by British epidemiologist Richard Peto in 1977 and named after him, and has been confirmed by various empirical research (Vincze et al. 2022; Tomasetti and Vogelstein 2015; Cagan et al. 2022).

Evolution experimentation, or positive natural selection, is an overarching explanation for this paradox. In populations, large body size is often associated with higher fitness, resulting in a greater ability to access resources and avoid predators, thus extending the lifespan of individuals (Tollis et al. 2021). Therefore, it is not surprising that larger body size and longer lifespan is an evolutionary trend, known as Cope's rule. However, larger body mass and longevity increase the risk of cancer, thereby suppressing lifespan. Therefore, large organisms must be cancer-resistant, for it makes no sense to grow large to increase lifespan while simultaneously cultivating a growing threat to it. Indeed, in reality, only a small number of deaths in these large animals are directly caused by cancer, demonstrating a low threat of cancer.

Critical Review Regarding Peto's Paradox

On the other hand, a handful of papers question the theoretical modeling or indirect reasoning in studies of Peto's paradox. Maciak points out that "the crux of Peto's paradox does not lie in body mass," as body mass can be further broken down into cell number, cell size, cell-specific metabolic rate, basal metabolic rate, etc. (2022). Therefore, when comparing solely based on body mass, there are various confounding variables in explaining Peto's paradox. Thus, experiments aimed at proving or explaining Peto's paradox cannot be performed on animals based on their body mass or sizes because of these confounding variables. In other words, the paradox would be solved by finding the relationship between species' risk of cancer and each of these variables independently of the rest.

For instance, cell size plays an important role in determining cancer risk. The smaller the cell size, the faster the dividing rate, and the higher the metabolic rate, which leads to high reactive oxygen species (ROS) production, both of which induce cellular mutation and thus increase the risk of cancer. Another example is the study conducted by Nunney that the increased cancer risk associated with human height is due primarily to an increase in cell number (2018). Therefore, the test of Peto's paradox should focus on comparisons of equal-sized organisms that differ with respect to specific variables, rather than large vs. small organisms, or even among an organ-level approach. This is because division rate, cell size, and stem cell numbers vary among tissues within the organism. Both approaches aim to minimize the effect of other confounding variables (Maciak 2022; Ducasse et al. 2015).

To this day, academia has not reached a consensus on a uniform explanation of Peto's paradox, and some even question the source of the paradox. However, the absence of an answer to the paradox does not imply stagnation in the research of cancer treatment, and in fact, just the opposite. It seems that every species studied so far has its unique pathway of cancer resistance because of different life histories and selective pressures (Callier 2019).

Through reviewing previous articles, we summarized and synthesized achievements made in unveiling cancer-resistant mechanisms in wild animals, specifically elephants, rodents (naked mole rats, blind mole rats, beavers, capybaras), whales, bats, primates (great apes), carnivores, and

non-mammal vertebrates (reptiles (Lonesome George tortoise), birds, and amphibians).

Discussion

Elephants

Elephants are the most extensively researched species on this topic. They demonstrate a low cancer mortality rate despite their large size and lifespan, with an estimated cancer mortality of 4.8%, compared with humans, who have 11–25% cancer mortality. This first made elephants' cancer-resistant mechanisms of interest in research (Abegglen et al. 2015). In addition, while humans have 1 copy (2 alleles) of TP53 (the gene that encodes for tumor suppressor protein p53), African elephants have at least 20 copies (40 alleles), including 19 retrogenes (38 alleles). Various papers have confirmed that those additional copies of TP53 directly increase the sensitivity to apoptosis in response to DNA damage (Abegglen et al. 2015; Sulak et al. 2016; Tollis et al. 2021). Interestingly, the extra copies of TP53 genes result from retrotransposition, a process in which the mRNA is retrotranscribed back to DNA but ends up in a different position with no introns. Therefore, the extra copies are also referred to as TP53 retrogenes (TP53 RTGs), and some of them are successfully transcribed and cause a higher rate of apoptosis following DNA damage (Nery et al. 2022).

Previously, researchers proposed that these additional copies of TP53 genes provide an explanation for Peto's paradox—as elephants grow larger, these extra copies of the TP53 gene are the result of positive selection. However, Nunney shows that it is the other way around: the duplication of tumor suppressor genes (TSGs) may have occurred before the evolution of the elephant's large body size, and expressions of TSGs increase longevity (2022).

Progress has been made in developing new anti-cancer drugs based on p53. Humans have one p53 gene, and "p53 mutations occur in > 50% of all human cancers and almost every type of human cancer" (Zhang et al. 2020). Possible treatment research directions have therefore been proposed: (1) restoration of wtp53 (wild-type p53) genome from missense mutp53 (mutant p53), (2) restoration of p53 nonsense mutations, (3) depletion or degradation of mutp53 proteins, and (4) induction of p53 synthetic lethality or targeting of vulnerabilities imposed by p53 mutations (enhanced YAP/TAZ activities) or deletions (hyperactivated retrotransposons). The synthetic lethal approach seems to be more widely used (Nishikawa & Tomoo Iwakuma, 2023; Hu et al. 2021). Various drugs have been developed, and some of them have undergone successful cell culture and mouse model testing, yet their side effects, clinical safety, and efficacy are yet to be determined and approved by the United States Food and Drug Administration (Nishikawa & Tomoo Iwakuma, 2023). So far, cancer-resistant mechanisms of extra copies of TP53 researched in elephants shine little light on current cancer treatment research.

Another protein that has been extensively researched is leukemia inhibitory factor (LIF). While LIF plays a role in various vital processes in our body, in the context of cancer, LIF can act as a tumor suppressor or as an oncogene, depending on the type of cancer. In elephants, a leukemia inhibitory factor with 11 extra copies of a pseudogene (a gene with no or lost function), and one of those copies of the pseudogene (LIF6), has been re-functionalized. It is transcribed at a very low level under normal conditions but is upregulated by TP53 in response to DNA damage. Later, the LIF-translated protein translocates to the mitochondria, where it induces apoptosis (Trivedi et al. 2023; Vazquez et al. 2018; Nery et al. 2022).

LIF can both boost and slow cancer growth depending on different cancer types. Specifically, breast, bone, and cervical cancer utilize LIF to proliferate, whereas less LIF is produced by thyroid and stomach cancer cells compared to normal cells. The research done in elephants shows LIF triggering apoptosis in response to DNA damage, thereby preventing cancer. LIF may function differently in elephants and humans, and whether LIF triggers apoptosis in response to DNA damage before tumors emerge and after boosting cancerous cell growth requires further research and clarification. Therefore, applying LIF as a tumor suppressor treatment requires extra caution, further research, and a better understanding of the mechanisms of suppressing particular types of cancer ("What Is Leukemia Inhibitory Factor (LIF)?" 2023).

Rodents

Naked mole rats (NMRs) and blind mole rats (BMRs) are two rodent species that have been extensively researched. One unique feature of these two species, in comparison to other wild animals analyzed in this literature review, is that they are small in size yet simultaneously have exceptionally long lifespans compared to their related species and are highly cancer-resistant. (Max lifespan: NMR—32 years; BMR—21 years) (Seluanov et al. 2018). Large animals (weighing more than 5–10 kg), such as beavers and capybaras, had their tumor cells lose their ability to divide and grow after a certain number of divisions due to the shortening of telomeres (Tian et al. 2018). In other words, telomerase is inactivated for replicative senescence as a tumor suppressor mechanism (Vedelek et al. 2020). On the contrary, telomerase in small species is reactivated to ensure the maintenance of telomere length. This is because a relatively small tumor would be fatal due to their small body mass, which is unable to maintain the size of the tumor to undergo

replicative senescence. For example, a 2 g tumor in a mouse weighing 20 g would be fatal, whereas a 2 g tumor in a capybara weighing 50,000 g would be negligible. Therefore, long-lived small-bodied species have to evolve telomere-independent tumor suppressor mechanisms.

Naked Mole Rats

So far, cancer resistance mechanisms for NMRs can be summarized into three categories: efficient DNA repair pathway, cell-autonomous resistance to transformation, and dampened inflammatory response (Yamamura et al. 2022).

DNA Repair Pathway

Sirtuin 6 (SIRT6) is a nuclear NAD+-dependent deacetylase of histone H3 that has been well-studied and is localized to the nucleus and plays a role in DNA repairing and maintaining genomic stability (Klein and Denu 2020). It has been proposed that high SIRT6 activity in NMRs promotes Poly ADP- ribosylation, which promotes the recruitment of DNA repair factors near the sites of DNA damage, see Fig. 1 (Yamamura et al. 2022). Therefore, efficient DNA repair pathways contribute to NMRs' high cancer resistance.

Cell-Autonomous Resistance to Transformation

Firstly, early contact inhibition is a unique mechanism in naked mole rats. Contact inhibition is a process of arresting cell growth when cells come in contact with each other (Seluanov et al. 2009). Naked mole rats' cells trigger contact inhibition at an even lower cell density, with fewer cells present per unit of space. In other words, the Hypersensitivity of contact inhibition is defined as Early Contact Inhibition (ECI) (Seluanov et al. 2009, 2018). ECI is triggered by a protein p16 INK4A, in addition to p27, a protein that triggers normal contact inhibition common to other species such as humans or other rodents (Seluanov et al. 2009, 2018). Therefore, even if the gene (*Cdkn2a*^{INK4A}) that encodes p16 ^{INK4A} is silenced or mutated, then normal contact inhibition through p27 is still activated. This means that ECI or protein p16 ^{INK4A} provides additional protection against loss of contact inhibition, thereby hindering hyperplasia (the initial stage of cancer) (Seluanov et al. 2009, 2018). In other words, the loss of contact inhibition must undergo mutation in the genes that encodes for both p16 ^{INK4A} and p27, whereas other species have only normal contact inhibition through p27 (see Fig. 2). Thus, ECI is one mechanism that contributes to high cancer resistance in NMRs.

Secondly, the exceptionally high density of high-molecular-mass hyaluronan (HMM-HA) in the extracellular matrix has various functions contributing to high cancer resistance.

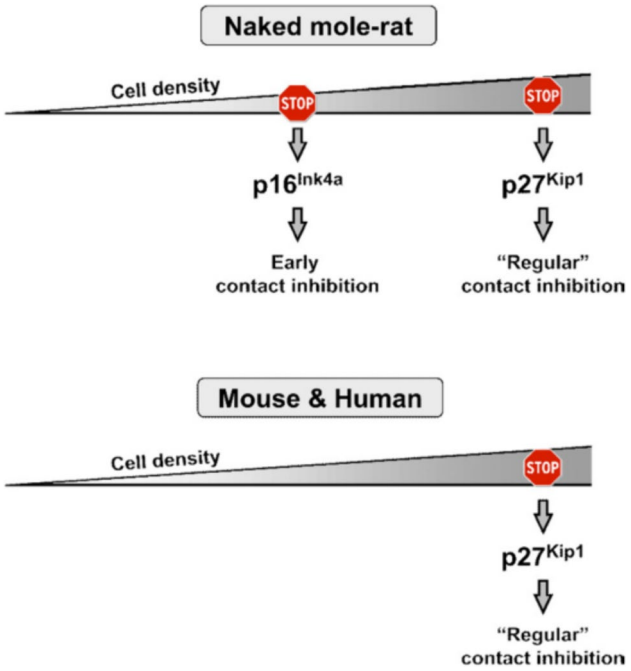

Fig. 2 Additional protective mechanism of Early contact inhibition in NMRs versus only one "regular" contact inhibition and no Early contact inhibition in Mice and Humans. Permission of the figure obtained from Seluanov et al. 2009.

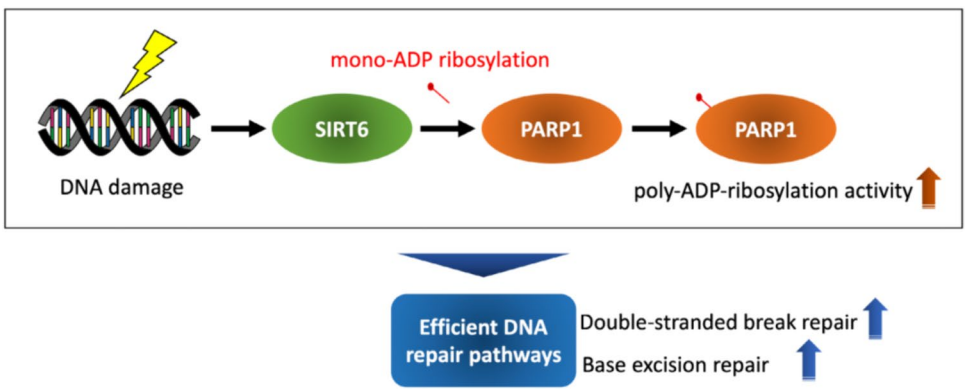

Fig. 1 High SIRT6 activity contributes to the increased activity of PARP1 (poly ADP-ribose polymerase 1). As a result, the activity of poly-ADP-ribosylation increased, which is an important initial response for the initiation of Double-stranded break repair and base excision repair. Permission of the figure obtained from Yamamura et al. 2022.

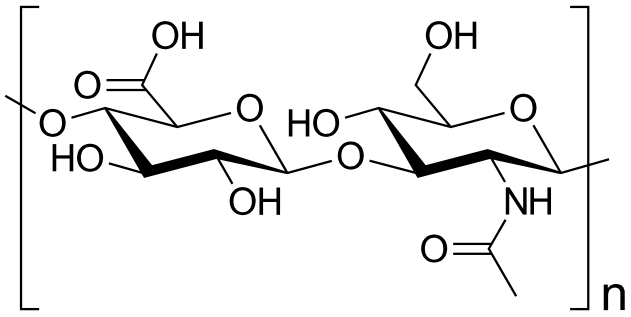

Fig. 3 Skeletal formula of hyaluronic acid (HA). HA has excellent viscoelasticity, high moisture retention capacity, high biocompatibility, and hygroscopic properties (Gupta et al. 2019). These properties made HA suitable to be one of the chief components of the extracellular matrix

HMM-HA exists in the form of polymers, forming HMM-HA matrix or cross-linked networks, see Fig. 3 (Rankin and Frankel 2016). Naked mole-rats fibroblasts produce hyaluronan with an exceptionally large molecular weight, surpassing that of humans or mice by over five times in size and more than six times in weight. (Tian et al. 2013; Rankin and Frankel 2016). HMM-HA binds to CD44 receptors (CD44 is a cell surface adhesion receptor), which in turn activate p16 ^{INK4A} or the naked mole rat-specific product at the INK4 locus, pALT. This eventually leads to the activation of ECI. (Seluanov et al. 2018). HMM-HA also reacts with and lowers the level of reactive oxygen species (ROS), molecules that include oxygen free radicals, thereby reducing ROS-induced damage to nucleic acids and proteins (Seluanov et al. 2018). Additionally, the high density of HMM-HA in the extracellular matrix may also hinder metastasis as cancerous cells have to release enzymes to fragment the HMM-HA to spread to other parts of the body, see Fig. 4 (Rankin and Frankel 2016).

Thirdly, the cells of NMRs undergo apoptosis when sensing the loss of a single tumor suppressor, such as p53, RB1, or p19. And finally, naked mole rats have a more stable epigenome, resisting further epigenetic alternation caused by and favoring malignant transformation (Seluanov et al. 2018; Nery et al. 2022).

Dampened Inflammatory Response

Lastly, NMRs have a dampened inflammatory response to tumorigenesis in the tissue microenvironment. Inflammation is the immune system's response to harmful stimuli by removing the stimuli and initiating the healing process. However, changes in the tissue microenvironment that surround the mutant cells as a result of inflammation strongly promote carcinogenesis. Interestingly, NMRs demonstrate cancer resistance by possessing loss-of-function mutant genes that encode for necroptosis—a type of inflammatory

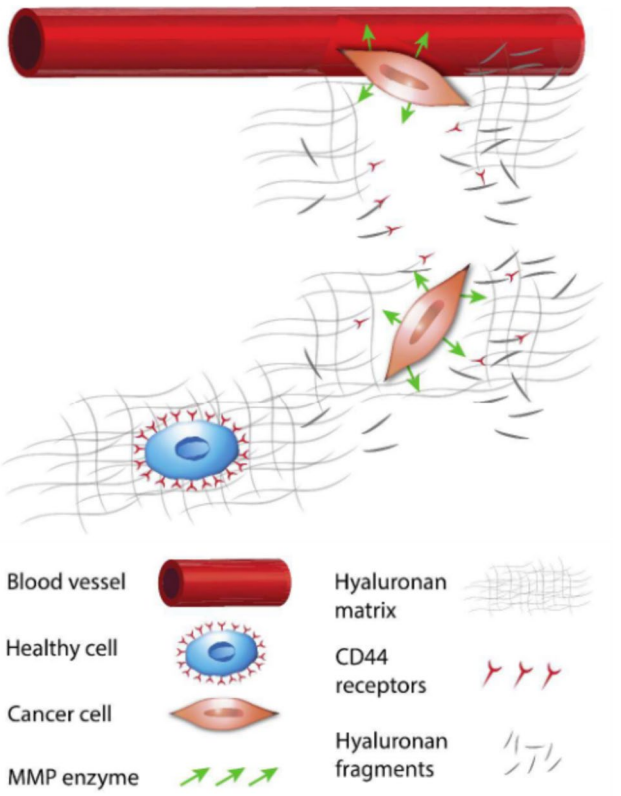

Fig. 4 Illustration of a healthy cell in extracellular matrix versus metastasis of a cancer cell. Healthy cells use CD44 receptors to attach to hyaluronan (HA) in the matrix. However, cancerous cells produce excessive membrane-bound enzymes called MMPs, which cleave CD44 receptors. Additionally, they generate high levels of hyaluronidase, an enzyme that breaks down hyaluronan (HA) into smaller pieces. This process enables cancer cells to penetrate the matrix and enter the circulatory system. Permission of this figure was obtained from Rankin and Frankel 2016.

response that involves programmed necrotic cell death causing a massive release of cellular components into the intercellular space—thereby maintaining tissue microenvironment stability, see Fig. 5 (Yamamura et al. 2022). Additionally, NMRs have fewer natural killer cells (NK) compared to other rodent species due to poor variation of NK cell-controlling genes, resulting in a dampened inflammatory response (Yamamura et al. 2022). However, how NMR tissues perform the function of inflammation while simultaneously limiting the inflammatory response remains unknown.

To our knowledge, research regarding applying those anti-cancer mechanisms in human cancer therapy has not been published. The main difficulty lies in connecting and applying mechanisms from phylogenetically and physiologically distant species to the human body. Recently, Xia & Xu discovered two suppressor genes, programmed cell death molecule 5 (PDCD5) and dickkopf 3 (DKK3), the former

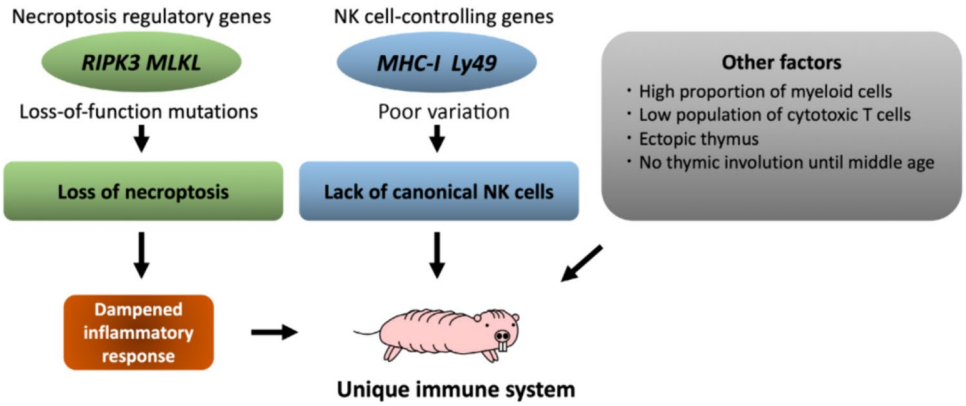

Fig. 5 Naked mole rats (NMRs) exhibit distinctive immunological traits. They lack essential regulators of necroptosis, which could contribute to reducing tissue inflammation in these animals. Additionally, compared to other species, NMRs have lower gene family expansion of MHC-I and Ly49 genes, which are key receptors for NK cells. This suggests a loss of control mechanisms for canonical NK cells, possibly explaining their absence in NMRs. Moreover, NMRs possess unique immune characteristics, including a high ratio of myeloid–to–lymphoid cells, ectopic thymi presence, and thymic involution absence for over 10 years. Permission of the figure obtained from Yamamura et al. (2022)

(PDCD5) derived from the naked mole rat, exhibited potent anti-tumor effects against cells across species, including human and mouse (2023). PDCD5 offers a new research direction in developing human cancer therapies.

Blind Mole Rats

BMRs, similar to NMRs, are exceptionally long-lived and cancer-resistant compared to other rodent species but have evolved different anti-cancer mechanisms.

Firstly, one unique phenomenon displayed by BMR cells is termed Concerted Cell Death (CCD). BMR cells, seeded at 5×10^5 cells per 100-mm dish with 80% confluence, undergo a combination of necrotic and apoptotic processes 3–4 days after 7–20 population doublings (Gorbunova et al. 2012; Seluanov et al. 2018). CCD is triggered by a massive release of interferon β (IFNβ), and its massive expression is a result of rapid cell proliferation (Seluanov et al. 2018). This mechanism is similar to telomerase inactivation for replicative senescence as a 'scorched earth' strategy rather than pinpoint elimination by apoptosis (Seluanov et al. 2018).

Secondly, similar to NMRs, BMRs maintain a high level of HMM-HA in the extracellular matrix. However, the high density of HMM-HA does not function as triggering early contact inhibition, unlike in NMRs. HMM-HA in BMRs functions to protect the cells from ROS-induced DNA damage and, together with another extracellular matrix component, a splice variant of heparanase that acts as a dominant negative, produces a more structured extracellular matrix that hinders tumor growth and metastasis (Seluanov et al. 2018).

While researchers continue working on applying the extensively researched cancer mechanisms in these rodent species, we suggest that more attention should be on mechanisms proven to be applicable and effective in the human body.

Whales

Whales are known for their immense size and remarkable longevity. Species such as the bowhead whale (*Balaena mysticetus*) hold a record lifespan of 211 years. Unlike elephants, whales show no signs of duplications of TP53, indicating different anti-cancer mechanisms despite their similarity as large and long-lived mammals (Nery et al. 2022). In bowhead whales, specific genes related to cancer, aging, the cell cycle, and DNA repair have undergone positive selection (Nery et al. 2022; Keane et al. 2015). Similarly, compelling evidence shows strong positive selection on humpback whales' pathways directly linked to cancer, such as the cell cycle, cell signaling and proliferation, and duplications in genomic portions containing genes related to apoptosis (Nery et al. 2022; Tollis et al. 2019). In cetaceans, CXCR2, ADAMTS8, ANXA1, DAB2, DSC3, EPHA2, and TMPRSS11A are seven tumor suppressor genes reported to be positively selected (Tejada-Martinez et al. 2021; Nery et al. 2022). Additionally, the TSG turnover rate (gene gain and loss) was almost 2.4-fold higher in cetaceans compared to other mammals, facilitating whales' ability to undergo positive selection in developing cancer-resistance traits (Tejada-Martinez et al. 2021).

Research reveals unique molecular-level cell-signaling pathways. Whales demonstrate reduced signaling of the insulin/IGF1 (insulin-like growth factor 1) pathways inside cells that get activated by insulin (or IGF1) binding to the cell. When these signal pathways are impaired, it becomes

harder for the organism to generate new cells, thus hindering tumor growth (Schraverus et al. 2022). Another finding revealed several unique amino acid substitutions and rapidly evolving genes in the bowhead whale compared to other species, including reduced signaling of the insulin/IGF1 pathway, which impairs regenerative capacity and thereby suppresses tumor development (Ma and Gladyshev 2017; Wang et al., 2014). Several genes that encode DNA repair and replication proteins, such as ERCC1 and PNCA, contain these unique amino acid substitutions, resulting in a low mutation rate and thus reducing the emergence of tumors (Keane et al. 2015; Schraverus et al. 2022).

Another hypothesis accounting for cancer resistance in large animals, in general, is that tumors need more time to reach their lethal size in large animals, similar to the point made in rodents. The essence of this hypothesis is that different malignant cell lines, due to their inability to undergo angiogenesis, will compete with existing tumors for nutrients and O_2, resulting in tumors remaining small and sublethal in the individual (Nery et al. 2022). However, this hypothesis has only been tested through mathematical models and computer simulations, and empirical confirmation has yet to be achieved (Nery et al. 2022).

Due to the inaccessibility of empirical data on whales, the exact molecular mechanisms of these confirmed positively selected tumor suppressor genes remain mostly unknown, not to mention shedding light on current human oncology research.

Bats

The insect-eating Brandt's bat (*Myotis brandtii*), native throughout most of Europe and parts of western Asia, is specifically studied due to its exceptionally long lifespan relative to their body size (over 40 years). This study suggests that unique sequence changes in growth hormone and insulin-like growth factor 1 receptor combined with hibernation, cave roosting, and low reproductive rate contribute to *Myoti's* high longevity rate, associated with increased resistance to cancer (Seim et al. 2013; Nery et al. 2022). In addition, *Myoti* shows low mitochondrial damage given their high metabolic rate, a potential mechanism for resisting ROS-induced DNA damage, and maintaining a low oxidative stress (Jebb et al. 2018; Nery et al. 2022). Furthermore, bats exhibit a unique age-related regulation of genes associated with DNA repair, immunity, and tumor suppression that accounts for their longevity. Bats might maintain their telomeres through alternative lengthening of telomeres (ALT) mechanisms. Genes associated with ALT, are *ATM*, *MRE11a*, *RAD50*, and *WRN*, which are significantly expressed in *Myotis* (Foley et al. 2018). The genes ATM and SETX, which are involved in DNA repair and prevention of DNA damage, play a crucial role in telomere maintenance and longevity in *Myotis* bats. Moreover, the MYC gene is an oncogene but induces tumor suppression mechanisms such as apoptosis, cellular senescence, and DNA damage response (Foley et al. 2018). The findings point out the potential of DNA repair genes as therapeutic research targets. Since telomerase expression is present in about 90% of human cancers, understanding how bats maintain telomeres without telomerase could be crucial for developing cancer therapies (Foley et al. 2018).

Additionally, long-lived bats possess specific miRNAs that function as tumor suppressors (Nery et al. 2022). The unique immune system of bats: selection and loss of immunity-related genes (including pro-inflammatory NF-κB regulators) and expansions of anti-viral APOBEC3 genes provide bats with an enhanced ability to manage and tolerate infections without triggering excessive inflammation (Jebb et al. 2018). This balanced immune response may reduce the risk of chronic inflammation, a risk factor for cancer development. Therefore, the evolutionary adaptations in these genes contribute to cancer resistance, but further investigations are needed (specifically six bat species that are experimentally tested: *Rhinolophus ferrumequinum*, *Rousettus aegyptiacus*, *Phyllostomus discolor*, *Myotis myotis*, *Pipistrellus kuhlii and Molossus molossus*) (Jebb et al. 2020; Nery et al. 2022).

Other Animals: Primates, Carnivores, and Other Nonmammalian Vertebrates

Peto's paradox is also demonstrated in animals including primates, carnivores, and other nonmammalian vertebrates. However, since little research has been conducted on these animals, most of the cancer-resistant mechanisms remain to be investigated.

In primates, great apes are the largest-bodied and longest-lived species, and research has discovered five genes (*IRF3*, *SCRN3*, *DIAPH2*, *GASK1B*, and *SELENO*) with positive selection that play a role in cancer resistance. However, the specific molecular mechanisms related to these genes remain to be discovered (Nery et al. 2022). Additionally, a set of oncogenes was significantly more highly expressed in apes than in other primate species, suggesting the complexity of the interaction between expressing those oncogenes and cancer resistance genes, which may be a potential research direction (Nery et al. 2022).

In carnivores, the size of individuals varies significantly from species to species. In carnivores with large lineages, 15 cancer-resistant genes (related to DNA repair, immunity, tumor suppression, and apoptosis) were identified as rapidly evolving, suggesting protection against tumor development (Nery et al. 2022).

Evidence shows that nonmammalian vertebrates report less cancer incidence than mammal species, though research and data are limited. In wild birds, research has

shown that slow developmental rates for their body size and stronger immune responses during development, which are more efficient at detecting tumors, both contribute to low cancer incidence in birds (Møller et al. 2017). In the genome of the Lonesome George tortoise, researchers identified protein-coding genes with functions related to cancer resistance (*SMAD4* and *NF2*) as well as giant-tortoise-specific duplications affecting two putative proto-oncogenes (*MYCN* and *SET*) (Nery et al. 2022). Additionally, a peptide derived from crocodile leukocytes could induce apoptosis in human cancer cells (Nery et al. 2022). Another study reported a natural peptide derived from the South American orange-legged leaf frog exhibiting anticancer properties (Nery et al. 2022).

Suggestions for Future Research

Progress has been made, and there is growing interest in this new area of research analyzing cancer-resisting evolutionary adaptations in wild animals. However, due to a lack of research and understanding of the exact molecular mechanisms in the species studied so far, only a few (such as elephants and rodents) that have been extensively researched have made substantive contributions to human oncology development. Although significant progress has not been achieved in a short time, the research direction of gaining insights through investigating cancer-resisting evolutionary adaptations in wild animals has great potential.

One approach is to explore positively selected genes that contribute to cancer resistance in species like elephants, whales, rodents, and bats, which have already been extensively studied. Researchers can then investigate if the homologous gene is present in the human genome and engineer them in mice. Specifically, this involves overexpressing or activating genes crucial to cancer-resistant mechanisms observed in other cancer-resistant species. If these mouse models demonstrate enhanced resistance to tumors, it could pave the way for developing drugs that replicate the anticancer mechanisms seen in those species resistant to cancer in human patients (Seluanov et al. 2018).

However, critics have questioned the feasibility of transferring and experimenting with anticancer mechanisms from phylogenetically distant species in mice and eventually humans. A major challenge in current research is transferring tumor suppression mechanisms found in one species (for example, elephants with multiple copies of p53 protein) into the genome of another species like rats or humans without affecting other physiological pathways, which has resulted in low success rates in clinical trials (Schraverus et al. 2022). Therefore, further research, rigorous experimentation, and clinical trials are necessary before these mechanisms can be applied to the human body.

Conclusion

Through an extensive review of cancer-resistant mechanisms of elephant, rodents (naked mole rats, blind mole rats, beavers, capybaras), whales, bats, and other wild animals, the exact molecular mechanisms underlying cancer resistance in most wild species remain to be further investigated. A key direction for future research is to investigate the positively selected genes associated with cancer resistance in wild animals and explore their homologous genes in humans. Despite the challenges of applying anti-cancer mechanisms from phylogenetically distant species to humans, this research direction holds great promise for advancing oncology research. By gaining insights into the evolutionary adaptations that confer cancer resistance in wild animals, researchers can potentially identify novel therapeutic targets and treatment strategies for human cancers. Despite the obstacles, the exploration of cancer-resisting mechanisms in wild animals offers a valuable approach to improving cancer treatment outcomes and addressing the limitations of current therapies.

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