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REVIEW ARTICLE

Anticancer Mechanisms in Unconventional Animal Models: An Overview

Stephanie K. Zhang

Kambala School, 794 New South Head Road, Rose Bay, Sydney, NSW 2029, Australia; stephkzh99@gmail.com

ABSTRACT: The development of multicellular life necessitated compensatory mechanisms that could suppress or prevent cancerous mutations from occurring within organisms. If these same mechanisms were shared across all animal lineages, then humans, who are 1000 times larger than mice, should theoretically be 1000 times more susceptible to the disease. That ratio would then mean animal species any larger cannot exist, for they would not be able to mature without dying of cancer. However, that is different. Despite their increased body mass, large animal species do not have a cancer occurrence proportional to their size. This lack of correlation, known as Peto's paradox, suggests that distinct animal lineages have evolved ways to resist the disease. This review discusses several anticancer mechanisms that have been proposed in response to Peto's paradox. It also explains the remarkable cancer resistance exhibited by some animals, such as the naked mole-rat and the elephant, to shed light on possible approaches to reducing human cancer morbidity.

KEYWORDS: Biological Sciences; Disease Prevention; Evolution; Peto's Paradox; Cancer Resistance Mechanisms; Animal Models.

Introduction

Cancer is a disease where infected cells in a multicellular organism divide uncontrollably and spread throughout the organism via metastasis.[1,2] While survival rates have improved significantly in humans since the mid-1900s, the improvement comes primarily from earlier diagnoses and not from advancements in existing treatments such as chemotherapy and radiotherapy.[1,3] The rate of cancer incidence has been increasing dramatically due to early life exposomes (an individual's diet, lifestyle, weight, and environmental exposures) changing substantially over the past decades.[4] The urgency for a more nuanced outlook on creating not just consistent and non-cytotoxic treatment but actual prevention for the onset of the disease requires investigations into carcinogenesis in other species.

The evolutionary perspective has been used to explain cancer origin, tumor development, and metastasis, but there is now a growing recognition that natural selection has impacted cancer defenses.[2] Interestingly, as observed by English epidemiologist Sir Richard Peto in 1977, there is an absence of the expected trend in cancer incidence associated with different body sizes and lifespans across species. This implies the existence of a variety of novel tumour-suppressing mechanisms and, therefore, potential evolutionary prescriptions for cancer.[2,5,6]

Assuming that every cell has the same likelihood of acquiring tumorous mutations from carcinogenic or randomly occurring genetic alterations to their DNA, larger multicellular organisms should have a higher risk of developing cancer.[7] Similarly, organisms with longer lifespans should be more cancer-prone, as their cells have more time to accumulate mutations.[8] Since a human is around 1000 times larger than a mouse and has a significantly longer lifespan, cancer risks should be magnitudes greater in humans than in mice.[2] However, that is not the case, as Peto found that the incidence of carcinogenesis in mice is similar to that in humans. This evolutionary conundrum is Peto's paradox (Figure 1).[9] Abegglen *et al.* (2015) surveyed the necropsy data of 36 mammalian species of varying body sizes/masses and life expectancies. They found that cancer mortality was not correlated with either of the factors above, supporting the validity of the paradox.[10] Furthermore, if massive multicellular organisms such as whales were 1000-3000 times more prone to cancer than humans, those species would go extinct. New cancer-suppressing mechanisms developed due to natural selection must exist for such organisms to survive past the hypothetical onslaughts of carcinogenic growth relative to their sizes.[11]

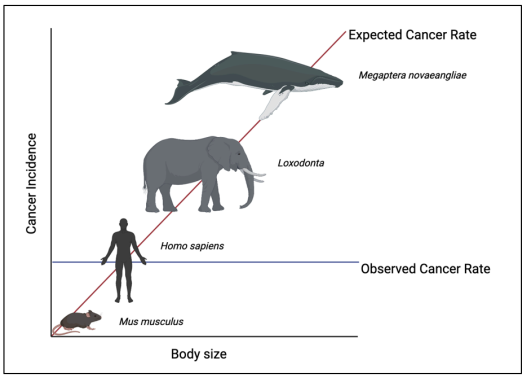

Figure 1: A schematic illustrating Peto's paradox concerning body size. The red line shows the expected relationship between cancer prevalence and body size, and the horizontal blue line represents the observed cancer rate, which appears not to be affected at all by body size (animal sizes not to scale). (Modified from Tollis *et al.*, 2017). (Made using BioRender)

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Interestingly, within a species, size is positively associated with cancer risk.[8] Nunney (2018) showed that the hazard ratio for overall cancer risk per 10 cm increase in human height is about 1:1, indicating that the risk of cancer increases with increasing size because there are more possible targets for somatic mutations. However, this trend only exists when comparing species' body sizes and cell numbers.[12] In this case, it is postulated that there is not enough time for different anticancer defenses to develop in beings that are larger than other individuals in the same species; the members of a species share the same gene pool, resulting in a similar degree of cancer resistance across all individuals.[8,12] This shows that animal lineages that have evolved to be larger or longer-living have found other ways to offset this increased cancer risk.

It will be challenging to thoroughly research these other lineages as we can be using rats and mice, which are shorter-living and easily maintainable organisms. Besides mice being useful models for studying tumorigenesis, these short-lived and highly cancer-prone organisms do not offer much for understanding cancer defense mechanisms.[13-15] Rather, several superior and less standard models exist, including long-lived or particularly cancer-resistant species such as the naked mole rat and the bowhead whale.[16] Studying these unconventional animal models and their evolutionarily-developed compensatory anticancer mechanisms may ultimately be very rewarding for human cancer therapeutics.

In this paper, I will review hypothetical anticancer mechanisms as well as several unconventional or less commonly studied vertebrates that can resist the disease and have the potential to be used as standard model organisms for cancer research.

Potential Cancer Resistance Mechanisms:

While the trends of Peto's paradox have been identified, research into solving the paradox itself is still in its infancy. Though lifestyle and carcinogenic exposures are suggested to have impacted cancer rates across species, they are unlikely explanations for the paradox, as organisms of different sizes can share the same habitat and have a similar diet but still have different predispositions to cancer.[17] Some hypothesized anticancer mechanisms will be reviewed in the following sections. These mechanisms are not solutions to Peto's paradox but are rather ways in which the disease may be resisted within some organisms.

Improved Immunosurveillance:

The concept of immunosurveillance was suggested by Lewis Thomas and Frank Macfarlane Burnet, who pointed out that immunodeficiency in humans was correlated with the increased likelihood of tumorigenesis. Individuals with primary immunodeficiencies have around a 10,000-fold higher incidence of cancer than others of the same age.18 For example, a study performed by Hayward *et al*. (1997) indicated an association between carcinoma incidence in the liver and pancreas and X-linked immunodeficiency with hyper-immunoglobulin M as a result of transmembrane protein CD40 (cluster of differentiation 40) ligand mutations.[19] tumors can progress into their later stages Without a functioning immune system and effective immune responses.

A study that further evidences the importance of the immune system in cancer suppression is Epstein *et al*. (2016), which investigated Tasmanian devil facial tumor disease (DFTD), a transmissible cancer. The study sampled 294 Tasmanian devils from three locations across Tasmania and identified genomic regions with evidence of selection. The regions contained genes associated with immunological function or cancer risk, indicating a developing resistance to DFTD in Tasmanian devils as a result of strong selection pressures.[20]

Cancer cells use many strategies to avoid instigating an immune response. Transforming growth factor and interleukin 10 are two examples of immunosuppressive cytokines that cancer cells secrete to avoid detection. Both proteins are reportedly able to inhibit immune cell functions.[21] Since cancer cells tend to produce abnormally high levels of these cytokines, it can be assumed that a prerequisite for tumor development is the weakening of the immune system.[21] Therefore, it is not unreasonable to assume that better immunity surveillance systems that can detect neoplasia may exist in species with greater resistance against cancer. Therefore, investigating such species may be a promising pathway forward.

Sensitive Apoptotic Processes:

The apoptotic propensity, or how inclined cells are to commit an orchestrated suicide, is hypothesized to differ between cells of different species, determining how cancer-resistant a species might be.[22] In animals less prone to cancer, it is theorized that apoptotic processes are more sensitive to oncogene activation and endogenous and exogenous damage to the DNA. Thus, they are more efficient at eradicating cancer cells.[23]

The p53 protein is a tumor suppressor protein encoded by the tumor suppressor gene (TSG) Tp53 that, upon detecting DNA damage, activates tumor-suppressing responses, including cell-cycle arrest and apoptosis.[24] Defects in Tp53 genes have been associated with 50% of human cancers.[25,26] A study by Avery-Kiejda *et al*. (2011) found that melanoma metastases and melanoma cell lines have low expression levels of p53 target transcripts involved in apoptosis, implicating its direct involvement in preventing cancer progression.[27] Observations have been made that cancer-resistant animal species, such as elephants, have many copies of the Tp53 gene and can use these copies to sensitize responses against carcinogenesis.[28]

Though overexpression of Tp53 is protective against cancer, it is also associated with progeria and early death.[29] However, García-Cao *et al*. (2002) found that transgenic mice with a duplication of the Tp53 locus that contained native regulatory elements exhibited improved cellular stress responses, extended lifespans, and decreased incidences of cancer.[30] Their findings imply that if tumor suppressor duplications have the necessary regulatory architecture to regulate TSG expression in a geographically and temporally appropriate manner, it may enhance cancer resistance.[29]

Telomere Length:

Telomeres, or the non-coding DNA repeats of TTAGGG at the ends of chromosomes, are essential in maintaining genomic stability and chromosomal integrity.[31] Every cell cycle prompts telomeres to shorten. Cell apoptosis eventually occurs once they become too short to protect the ends of the chro

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mosomes.[8] It has been proposed that shortening telomeres can make apoptotic events more common, reducing the likelihood of cancer cells developing. However, shortened telomeres do not equate to low cancer incidence in and of themselves. According to mounting data, many diseases are triggered by short and long telomere length extremes, forming the telomere length paradox.[32] Nonetheless, the risk of developing tissue-specific cancers like melanoma has been shown to increase with increasing telomere length. Therefore, in some cases, shorter telomeres may reduce the opportunities for carcinogenic mutations to accumulate.[31,33,34]

In vertebrate models, there is strong evidence that long telomere length predisposes to cancer. Feldser and Greider (2007) showed that rodents with longer telomeres consistently exhibited more aggressive Burkitt's lymphoma tumors and displayed higher mortality rates when the MYC or KRAS oncogenes were overexpressed.[35] Short telomeres caused the tumors to shrink, even when apoptosis was inhibited, and p53 was necessary for this. Additionally, there was direct evidence that the developed tumors had an active p53-mediated senescence program.[35] These findings suggest that a p53-dependent senescence mechanism that inhibits tumor growth *in vivo* can be mediated by shorter telomeres. This may be a defense against cancer that long-living/cancer-resistant species have evolved.

Replicative Senescence and Slower Cell Proliferation:

Replicative senescence is typically considered a tumor-suppressing process that slows the growth of cancer cells and can be induced by a range of stimuli.[36] While this mechanism is present in many more significant and relatively cancer-resistant species, Seluanov *et al.* (2009) showed that it is absent in small-bodied rodents, even long-living ones.[37] Instead, small cancer-resistant rodents such as the naked mole-rat are shown to have evolved tumor suppressor mechanisms that manifest as extremely slow in vitro cell proliferation compared to human cell proliferation.[15] The study demonstrated that *in vitro* fibroblast proliferation rate negatively correlated with longevity in small rodent species without replicative senescence. Alternative tumor suppressor mechanisms in small-bodied and long-living animals without replicative senescence were proposed as the reason for the slow *in vitro* growth rate.[38]

Hypersensitive Contact Inhibition:

Contact inhibition is a mechanism that arrests cell growth upon cells coming into contact with one another. As a result, the proliferation of normal cells stops once they form a monolayer in a culture dish.[39] Cancer cells lack contact inhibition and continue growing even when a culture dish has been filled, piling on each other and forming multiple layers.[37] Membrane proteins involved in contact inhibition signal growth arrest caused by increased cyclin-dependent kinase inhibitor (CDKN) p27. Cells are stopped in the G1 phase of the cell cycle by the binding of p27 to CDK complexes.[40] The correlation between low levels of p27 expression and unfavorable prognosis in cancer patients highlights the significance of contact inhibition for tumor suppression.[41] It has also been suggested that p16, another CDKN, mediates early contact inhibition (ECI).[41] How this mechanism functions within animals such as naked-mole rats, as observed by Tian *et al.* (2013), will be discussed in a later section of this paper.

Slower Metabolism:

On a more physiological and macroscopic scale of tumor suppression mechanisms, larger animals such as whales are hypothesized to generally have lower cancer incidence because the metabolic (oxygen consumption) rate per unit body mass decreases with increasing body size.[43] The metabolic rate hypothesis states that smaller-bodied vertebrates produce more carcinogenic oxygen radicals than bigger vertebrates due to their greater mass-specific metabolic rates.[44] Mutations are often exacerbated by oxygen radicals, which results in the transformation of normal cells into tumor cells. Because they can better avoid oxidative stress and damage to their DNA, large-bodied animals such as whales have lower cancer rates. As Takemoto *et al.* (2016) point out, p53 is known to limit glycolysis, whereas the MYC oncogene is known to control glycolysis and promote mitochondrial biogenesis.[43,45] Biogenesis and glycolysis are associated with respiration (i.e., metabolic rate). The amount of oncogenes and TSGs is proposed to exhibit negative and positive relationships with body size, assuming that oncogenes typically raise metabolic rate at the cellular level while TSGs lower it. Therefore, slower metabolism appears to offset the cancer risk in larger organisms.

"Hypertumour" Formation:

A more hypothetical explanation as to why large-bodied animals are more "resistant" to cancer exists in that of "hypertumours." "Hypertumours" are parasitic secondary tumors that emerge from aberrant cancer cells that damage or destroy the parent tumor by depriving it of its resources and nutrients.46 Cancer cells that can elicit angiogenesis, the growth of blood vessels into a neoplasm via the secretion of tumor angiogenic factors (TAFs), tend to be favored in a nascent tumor.[47] A simulation run by Nagy *et al.* (2007), which focused on modeling the development of tumor cells that varied in potential and sensitivity, predicted the existence of aggressive cancer cells that were unable to secrete sufficient TAFs, resulting in a population of "cheaters" which capitalized upon the vascular infrastructure that the primary tumor cells had established.46 Since these "cheater" cells cannot sustain themselves without parasitizing the TAF-secreting primary cells, the original tumor either ceases to grow or dies due to the hypertumour's parasitism (Figure 2).

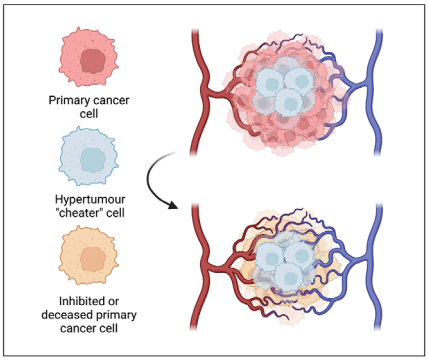

Figure 1: A schematic showing how parasitic "cheater" cells form a hypertumour on the primary neoplasm as cells from the two tumors begin to compete for resources. However, as these "cheater" cells are highly aggressive

and will cut off blood supply to the original tumor, the result is that the parent cancer cells cannot receive sufficient sustenance and either die off or remain at a sublethal size. (Made using BioRender)

Due to the immense number of cells in large-bodied species like whales, it could be possible that they experience cancer at even greater levels. At the same time, these larger organisms would be more predisposed to evolve "hypertumours," which inhibit the growth of parent tumors, implicating a negative relationship between the fatality rate and the body size of the host organisms.46 This is an entirely possible explanation for the longevity of large-bodied species; perhaps they do experience higher rates of carcinogenesis like what the multistage carcinogenesis model suggests, but the constricted primary tumors that develop may be too small in proportion to the size of the animal for them to be significant. For example, a tumor weighing 5 grams is equivalent to 25% of a deer mouse's total body mass. Yet, a tumor of the same size only accounts for 6.25 x 10-8 % of a bowhead whale's body mass, rendering it essentially harmless in the latter animal.

Though "hypertumours" are seen as a potential solution to Peto's paradox, there has been little follow-up work suggesting its validity. Thus, it remains only a hypothetical explanation.

Examples of Cancer Resistance Across Different Mammalian Species:

As stated before, using only mice and rats as standard model organisms for cancer research limits understanding of other non-cytotoxic approaches to combating cancer. That is, mice lack the anticancer defenses that humans already have.[15] The potential for enhancing the development of anticancer therapeutics is significantly greater concerning animals that are innately resistant to cancer. An ecological and evolutionary approach to studying carcinogenesis and tumorigenesis in less standard animal models might result in more creative ways to target and combat the disease in humans.[48] The following sections will explore some examples of cancer-resistant species and their main resistance mechanisms.

Heterocephalus glaber: Early Contact Inhibition:

Naked mole rats (NMRs) (Heterocephalus glaber) are small eusocial animals with the greatest life expectancy out of all rodents (>30 years).[49] In addition, they are notably resistant to age-related diseases and functional decline. More specifically, they seldom get cancer or Alzheimer's disease and do not show increased mortality as they age.[50] Furthermore, NMRs are highly resistant to hypoxia and thrive in hypoxic environments in East African subterranean colonies.[50] In cancer research, NMRs have slowly become more common model organisms like laboratory mice due to the promise of new anticancer mechanisms having evolved within their species.

NMRs are still capable of developing cancer; they are far more resistant to it than most of their rodent relatives (apart from blind mole rats) or mammals of similar lifespans.[51] NMRs fall into the category of small rodents that display negligible senescence and high telomerase activity levels, indicated by slow or non-existent changes in their physiological parameters with age. Therefore, they must have evolved specific compensatory mechanisms that allow them to survive in their unique habitat and live ten times longer than other rodents of the same body mass.[38]

Fundamentally, the most well-studied primary mechanism that prevents NMR cells from undergoing malignant transformations is early contact inhibition (ECI). Unlike regular contact inhibition, where cells form a dense monolayer before their growths are arrested, ECI arrests cell growth even when only a few cells have made contact.

Tian *et al*. (2013) found that the culture media in which they had cultured NMR fibroblasts became more viscous than the media conditioned by the human or mouse cells.[52] They identified the source of the viscosity as the high-molecular-weight form of the glycosaminoglycan hyaluronan (HMW-HA). HMW-HA has anti-metastatic properties and is crucial for lubrication, hydration, tissue osmosis, flow resistance, and molecular exclusion.[53] Lower-weight forms of HA are reported to encourage inflammation and cell proliferation. The HMW-HA in NMRs may have developed to adapt to life underground, giving it the flexible and hairless skin required to fit through small tunnels.[52] It has been established that ECI as a cancer resistance mechanism is mediated by p16. Tian *et al*. (2013) also showed that the digestion of HMW-HA using the enzyme hyaluronidase (HAase) abrogates the ECI phenotype and promotes tumor formation upon the deactivation of Tp53 and other TSGs.15,[52] That is, HMW-HA induces early expression at the CDKN2A locus, which encodes p16.[54] Furthermore, they demonstrated that HA signaling initiates ECI via the CD44 receptor, which is a major HA receptor in human cells.[53,55] The fact that CD44-antibody-grown NMR cells had a greater cell density suggests that the CD44 receptor plays a role in the transmission of the ECI signal from HMW-HA. HA molecules are substantially shorter in other mammals than in NMRs.[56] The high concentration and greater lengths of HMM-HA in NMR can be attributed to how the tissues of NMRs have very low HAase activity. In essence, very high-molecular-weight HA (vHMW-HA) and decreased HAase activity in NMR tissues are crucial in regulating the NMR's resistance to cancer.

As established, the enzymatic digestion of HMW-HA using HAase and blocking CD44 receptors led to in vitro NMR fibroblasts losing the ECI phenotype. This made them vulnerable to cancerous development. Seluanov *et al*. (2009) proposed that ECI may be a solid evolutionarily-developed alternative to replicative senescence.[37] What differentiates the cancer resistance in NMRs from that in humans and mice is that contact inhibition in the latter two species is triggered by the induction of p27. In NMRs, ECI is triggered by the induction of p16. This indicates that ECI is not a mechanism in mice and humans, the two most researched model organisms. Suppose the CDKN2A gene in NMRS is silenced. In that case, regular contact inhibition is activated through the induction of p27.[15] To bypass the NMR's contact inhibition defenses, the loss of both the CDKN2A and CDKN1B (which encodes p27) genes is necessary.[15] Thus, in contrast to the single level of inhibition seen in human and

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mouse cells, NMR cells have two levels of contact inhibition and, therefore, two layers of anticancer protection (Figure 3B).

Spalax: Concerted Cell Death:

Though not as long-living as NMRs (21 years), Middle Eastern blind mole rats (BMRs) (Spalax) still show a remarkable resistance towards both spontaneous and induced tumorigenesis. Like NMRs, BMRs have evolved strong hypoxic tolerance to thrive underground. Again, due to their small size, they are reported to express high levels of telomerase activity in their somatic tissues and do not have replicative senescence as an anticancer mechanism.[15,57,58] However, unlike NMRs, BMRs do not seem to be able to activate ECI. Another form of anticancer defense must have evolved for members of the Spalax genus to be longer-living than most other rodents.

A study on the longevity of two BMR species (S. judaei and S. golani) by Gorbunova *et al.* (2012) identified that BMRs had evolved another mechanism: mediation of necrotic cell death in response to hyperproliferation.[58] "Concerted cell death" (CCD) is a term coined by Gorbunova et al. upon discovering that BMR fibroblasts had a propensity to die after several days via necrotic processes.[15] Rather than a precise pin-point elimination of cancerous rogue cells, BMR cells exhibit an unusual "scorched earth" strategy that works to wipe out entire cell populations.[15] Interestingly, BMR cells prefer to respond to oncogenic assaults by necrosing rather than cell apoptosis. This result can be explained by the particular sequence of their Tp53, which developed as a defense against hypoxic subterranean conditions and is incapable of initiating an apoptotic cascade.[59] Although necrosis was thought to be an ineffective way of removing undesirable cells initially, BMRs have developed a highly effective anticancer mechanism based on necrotic response. Furthermore, necrosis may benefit from removing all surrounding cells. This may have an additional anticancer impact by eliminating reactive tumor stroma.[58]

CCD at the hyperplasia site is triggered by interferon-β (IFN-β) secretion when BMR cells recognize strong pro-growth as potential oncogenic signaling imbalances. This mechanism could compensate for how BMRs have evolved alterations in the Tp53 sequence to prevent hypoxia-induced apoptosis, such as arginine to lysine substitution in the DNA binding domain.[59] This alteration is also found in hypoxia-tolerant human tumors, indicating a decreased pro-apoptotic function of the p53 protein. The trade-off of less effective p53-mediated apoptosis responses for the ability to initiate mass cell necrosis would explain how no spontaneous tumors have been detected in BMRs even after decades of monitoring several hundred individuals (Figure 3A).

The cells of NMRs do not display CCD.[60] NMR cells are more prone to undergoing apoptosis and do not favor necrosis as a stress response, unlike BMR cells. Thus, it can be concluded that the two rodent genera have evolved distinct cancer resistance mechanisms despite both being native to similar hypoxic subterranean conditions. Searching for specific anticancer mechanisms in other relatively long-living rodents, like

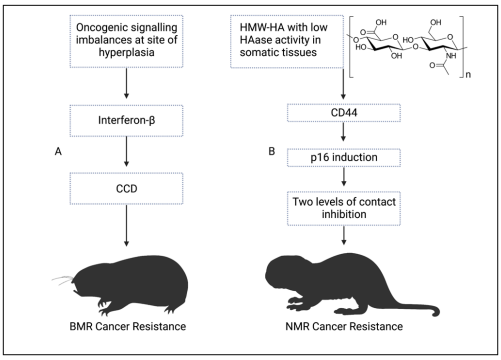

Figure 3: A simplified schematic showing the main cancer resistance mechanisms developed by the BMR (Figure 3A) and the NMR (Figure 3B). Upon BMR cells detecting pro-growth signals, IFN-β is secreted, initiating a necrotic event at the hyperplasia site in the form of CCD. The exact relationship between the Tp53 sequence alterations and IFN-β in BMRs is yet to be determined. NMRs have combined two layers of contact inhibition to prevent cancerous cells from proliferating. By requiring the deactivation of 2 genes rather than 1, NMRs have developed a more robust defense against the disease than in other rodents and humans. (Made using BioRender)

chinchillas and grey squirrels, is beneficial in illuminating new approaches to potential preventative measures.

Proboscidea: Tp53 Retrogenes:

Even though larger animals have evolved replicative senescence to offset the increased cancer risk that comes with increased body size, this mechanism is not enough to compensate for the sheer number of cells in species like elephants and whales.[29] Like the NMR and the BMR, these mammals' shockingly low cancer rates can be attributed to their uniquely evolved anticancer defenses. Gene studies in African and Asian elephants (Proboscidea), the largest terrestrial animals, have revealed that their genomes contain more than 19 copies of Tp53.[6,10,61]

As discussed, p53 plays a significant role in cancer suppression by activating cell-cycle arrest and apoptosis, earning its name as “the guardian of the genome.”[24,62] Due to the sensitivity of elephant cells to genotoxic stress, they have evolved additional copies of Tp53. These copies are called Tp53 retrogenes (Tp53RTGs) and appear transcriptionally inept.[63] The copy numbers could have increased as a result of retrotransposition from the parent Tp53 gene, retrotransposition of expressed Tp53RTG genes, a single retrotransposition event followed by numerous rounds of segmental duplication of Tp53RTG containing loci, or a combination of these models.[64] It was hypothesized that the increase in copies occurred concurrently with the evolution of large bodies in the Proboscidean lineage due to selective pressures from their increase in size. However, Nunney (2022) suggests instead that the duplicates accumulate via genetic drift, allowing them to evolve into larger beings.[61,64]

Elephant cells respond to DNA damage extraordinarily effectively, as even low-dose stimuli can cause their dermal fibroblasts to initiate apoptotic cell death.[63] This is reportedly due to their Tp53RTG copies, which can suppress p53 signaling when no activating stimuli are present and promote increased sensitivity to DNA damage. The discovery that most Tp53RTGs are not transcriptionally active but can shield p53 from degradation via the Mouse double minute 2

homolog proto-oncogene in the absence of stress forms the basis for the suggested mechanism for these functions.[63] Since elephant cells have a lower threshold for DNA damage than human cells, they can more effectively eliminate defective cells before propagating. Apoptotic rates in lymphocytes were shown to increase proportionally in individuals with Li-Fraumeni syndrome (who only have one functioning TP53 allele), human controls (2 TP53 alleles), and elephants (around 40 TP53 alleles).[10,65] Tp53RTGs were translated and up-regulated when transfected into human cells receiving doxorubicin and ionizing radiation.[10] Altogether, this implies that p53 and the TP53RTG duplicates may mediate the increased cell death in elephants (*Figure 4*).[10]

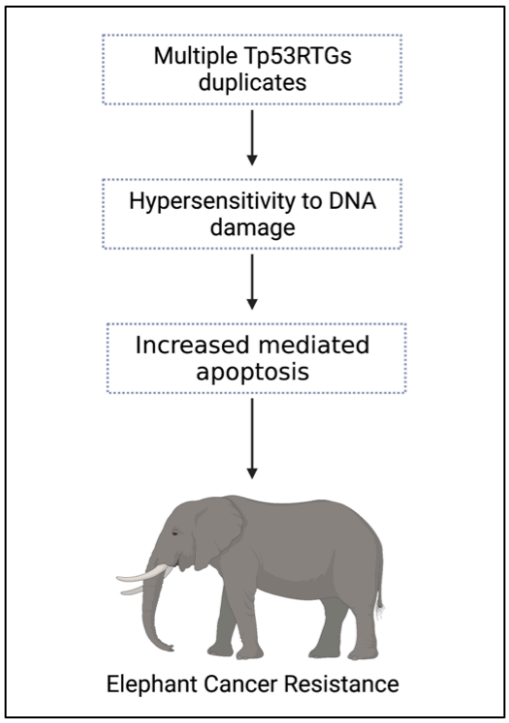

Figure 4: A simplified schematic showing how Proboscidea are able to resist cancer. In all species of elephants, multiple copies of Tp53RTGs have been identified. Interestingly, the number of these duplicates did not seem to affect how big different elephant species became, supporting the theory that the duplicates were a result of genetic drift. (Made using BioRender)

However, frequent apoptotic events would, unfortunately, result in a greater demand for cell replacement. This would decrease the stem and progenitor cell reserves in the tissues. To prevent the premature depletion of stem cells, a heightened apoptotic response must be counterbalanced by additional modifications in elephants.[15] Simply increasing the number of active Tp53 copies in mice resulted in increased cancer resistance but with the side effect of accelerated aging. Fortunately, García-Cao *et al.* (2002) managed to create transgenic "super p53" mice by injecting large genomic DNA segments containing the entire Tp53 gene along with its native regulatory elements into mouse oocytes (Figure 5).[30] The approach did not produce the undesirable side-effect of premature aging, and the mice showed strong cancer resistance with a longer median lifespan.[15,30,66]

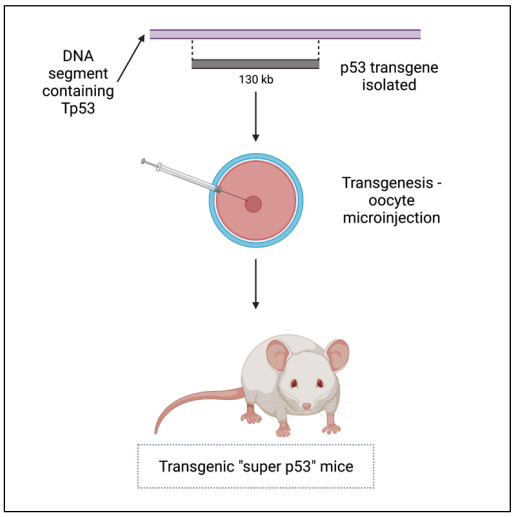

Figure 5: A simplified schematic showing how "super p53" mice were created by García-Cao *et al.* (2002). The oocytes of these mice were injected with either a p53 transgene that was 130 kb long, where the p53 transcriptional unit was in a terminal position, or one that was 175 kb long, where the unit was in a central position. The mice did not suffer any abnormal age-related dysfunctions typically associated with overexpression of Tp53; instead, they showed a more effective p53-mediated response to DNA damage. The mice containing the 175kb segment exhibited an even more enhanced apoptotic response to radiation. (Made using BioRender)

Cetacea:

For large whales to exist and survive in nature for such long periods, they must have evolved their own adaptive mechanisms to offset the increased risk of cancer (Figure 6). Some proposed explanations for the cancer resistance of whales (Cetacea) in general have already been discussed in previous sections. First, since cetacean metabolic rates are much lower than those of smaller mammals due to their large sizes and diving behaviors, less carcinogenic free oxygen radicals would be produced as a product of their metabolic processes.[6,43,67] Whales should thus be able to avoid oxidative stress and, subsequently, cancerous cell transformations. Secondly, due to these animals' sheer size, it could be possible that "hypertumours" are inhibiting the growth of primary neoplasms via parasitism.[46] In that case, the tumors that do arise in a whale usually never reach the juncture where their cells can metastasize and compromise the organism's health. However, this explanation remains hypothetical as "hypertumours" have only been observed via simulations.

While all whale species appear to have exceptional cancer resistance, bowhead whales (BHWs) (Balaena mysticetus) and their incredible longevity (>200 years) stand out in particular. Alongside the aforementioned explanations, multiple copies of tumour-suppressing genes have been reported in many cetaceans. For specificity, only BHW gene duplications will be discussed.[68]

It has been observed that BHWs lack the Tp53 gene duplications that make elephants so cancer-resistant. Genomic and transcriptomic studies have identified a positive selection of genes implicated in insulin signaling and many connected to DNA repair, cell cycle regulation, and cancer and aging resistance.[68,69,70,71] A comparison of duplicate genes across several whale species found a single duplication unique to the BHW

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genome - CDKN2C, which encodes the CDKN p18, another protein that functions as a tumor suppressor.[71,72] The comparison also discovered that the duplication event occurred very recently in the ancestry of BHWs and that the event coincided with the evolution of a longer lifespan. This was thanks to the embedding of the CDKN2CRTG gene in the cetacean-specific LINE L1 that allowed them to identify the locus in other cetacean genomes.[71]

Reportedly, the overexpression of CDKN2C in abnormal places within an organism lengthens the G1 stage of the cell cycle and delays progression through the G1/S checkpoint by inducing cell-cycle arrest and apoptosis.[71,73] Conversely, the inhibition of CDKN2C expression promotes cell proliferation. Studies that have been performed on the inhibitory effect of CDKN2C on tumorigenesis, as well as how its expression is suppressed in human melanomas, indicate that the second copy of CDKN2C in BHWs may be protective against the types of uncontrolled cell proliferation associated with cancers.[74] These findings suggest that the duplication of CDKN2C may be the primary mechanism BHWs utilize to resist cancer. However, this gene duplication has only been reported in BHWs, so this mechanism cannot be generalized to other long-living cetaceans. It would be worthwhile to investigate other whale species' possible cancer resistance mechanisms.

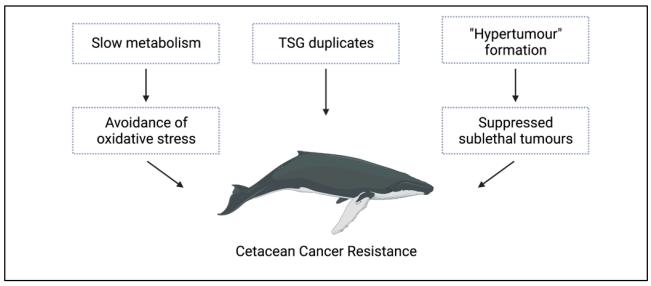

Figure 6: A simplified schematic showing cetaceans' different proposed anticancer mechanisms. Out of all the vertebrates discussed in the previous sections, the least is known about whales and their methods of resisting cancer. (Made using BioRender)

Concluding Remarks:

To initially combat the devastating effects of cancer, species have evolved specific anticancer mechanisms that have allowed them to resist the onset of the disease greatly. The evolution of these mechanisms likely allowed larger-bodied or longer-living animals who faced the increased cancer risk that came with increased size or lifespan to thrive. With the existence of natural defenses like the NMR cells' ECI, the BMR cells' necrosing tendencies, and the TSG duplications of elephants and BHWs, it would be ultimately more rewarding to study these animals as standard cancer model organisms. However, they should not be studied for simulating tumorigenesis but for the unique cancer resistance mechanisms they possess and the insights they offer into the disease as a whole.

The evolutionary relationships between the model organisms mentioned in this review and their anticancer mechanisms can be summarised in Figure 7.

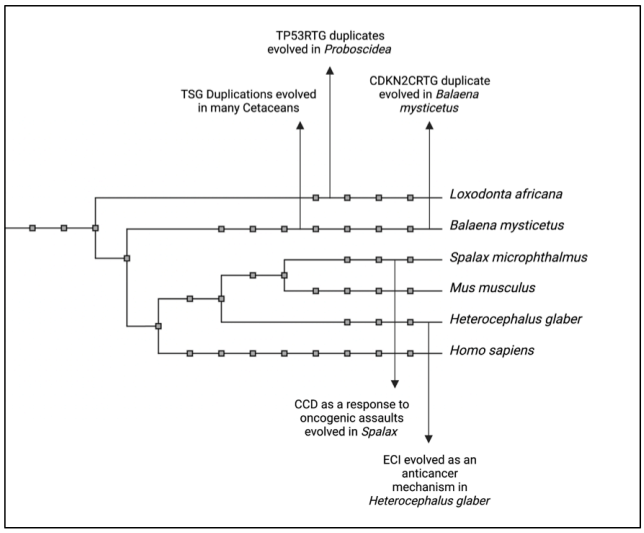

Figure 7: A simplified schematic of a cladogram displaying how model organisms discussed in this review, including mice (Mus musculus) and humans (Homo sapiens), are related. The rectangles represent nodes. The positions of the arrows indicate the point at which an anticancer mechanism has evolved within a particular lineage. (Made using iTOL and BioRender)

This review, while having discussed the aspects it intended to discuss, is limited in that it did not delve particularly deeply into the technicalities of the subtopics. For example, only the main anticancer mechanisms from each cancer-resistant animal have been mentioned/explored. Furthermore, to my knowledge, the potential cancer resistance mechanisms discussed have not yet been tested within a human context.

From a realistic standpoint that may be more suitable for human therapeutics, I am inclined to think that translating the cancer resistance mechanism of the elephant could be a possible first step. I believe, as García-Cao *et al.* (2002) have shown with their transgenic mouse models, that approaching the introduction of other anticancer mechanisms to human cancer therapeutics may first be done by determining the range of effects that arise from inserting additional Tp53 copies (including their regulatory elements) into organisms that do not have such duplicates (Figure 5).[30] This approach appears to be the most clinically researched. Therefore, considering the ethical implications associated with this approach, it appears to be a possible, albeit impractical, avenue for further progression into this field. From it, results that could allow for more efficient and non-cytotoxic treatments to develop in the future may be yielded.

The approaches presented in this paper on larger mammals can also be applied to other taxons on the phylogenetic tree.[75,76] For a more diverse perspective on the disease and the possibility of different intervention methods, research into non-mammalian or non-vertebrate species that resist cancer could also be highly worthwhile.

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Author

Stephanie Zhang is a Year 12 student at Kambala School in Sydney, Australia. She is an enthusiast of many biological fields and wishes to study either medicine or biology in the UK. In her free time, she enjoys painting and reading.

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