Mechanisms of Cancer Resistance Across Mammals

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Abstract

Cancer is a complex disease that threatens the health of a broad range of species. Despite the fact that cancer is the second leading cause of death worldwide, there are a number of species that are remarkably resistant to cancer, including the elephant, naked mole rat, blind mole rat, whale, horse, cow, and microbat. These animals exhibit a natural resistance to cancer through various mechanisms, including enhanced DNA repair, hypersensitivity to genotoxic stress, resistance to metastatic invasion, and duplicate copies of tumor suppressor genes. These mechanisms can provide insight into preventing, as well as treating, cancer in less resistant species. This paper reviews potential mechanisms for cancer resistance across a variety of mammals and provides insight as to why some mammals are more resistant to cancer than others.

Introduction

Cancer is characterized by the uncontrolled proliferation of abnormal cells. As the second leading cause of death worldwide (World Health Organization: WHO), this complex disease threatens the health of people globally. While treatments for cancer exist, treatment options are often ineffective, and access to treatment is a barrier in many countries. Research on cancer prevention is becoming an important focus, as prevention is not only more cost-effective but also circumvents the need to go through onerous treatment regimens.

Previously, cancer prevention research has mainly focused on conscious choices humans can make to decrease their risk of cancer. Lifestyle changes, such as being physically active, having a healthy diet, and limiting alcohol consumption have all been identified as ways to prevent cancer (American Institute for Cancer Research). Although these strategies don't entirely prevent cancer, they can empower people to decrease their risk of cancer by making conscious lifestyle choices. Discovering strategies to more effectively prevent cancer in humans may be possible by examining the characteristics of naturally cancer-resistant mammals.

Body mass is thought to be a factor contributing to cancer resistance. Statistically, animals with a higher body mass should have a higher rate of developing cancer, as they have more cells than smaller animals, meaning they have a higher chance of mutagenesis which can result in cancer. However, some large animals actually have a much lower rate of cancer compared to humans and mice. Peto's Paradox states that there is no real correlation between body mass and cancer incidence, suggesting that larger animals have developed natural tumor-suppressing mechanisms to counteract their increased cancer risk. In support of this theory, research has found that mammals larger than 5-10 kg possess an important anticancer mechanism known as replicative senescence. During replicative senescence, cells enter a state of permanent growth cycle arrest when telomeres, the regions of repetitive DNA sequences found at the end of the chromosomes, reach a critically short length (Chadwick; Seluanov et al. "Telomerase Activity"). This is due to the repression of telomerase activity, which maintains the length of telomeres, in somatic tissues, causing telomeres to continue shortening as cells divide

(Seluanov et al. “Telomerase Activity”). Replicative senescence is thought to be an anticancer mechanism that limits cell proliferation, thus working to prevent cancer. Telomerase must be active to form human tumors and is used to extend the lifespan of cancer cells. Since larger mammals have inactive telomerase, they have an extra defense mechanism against tumorigenesis.

The lifespan of an animal also plays a large role in the animal’s resistance to cancer. Long-lived mammals tend to display cancer resistance due to evolutionary adaptations that keep them cancer-free until post-reproductive age (Seluanov et al. “Mechanisms”). Therefore, long-lived mammals capable of reproducing later in life may have evolved cancer resistance to support their prolonged reproductive period. On the other hand, it is possible that because these animals developed mechanisms that decrease their risk of cancer, they now have longer lifespans. In either case, lifespan and cancer resistance are both linked.

Diets can also impact cancer resistance. In humans, a healthy diet that limits red or processed meat can decrease cancer risk (Gonzales and Riboli; Key et al.). Similarly, herbivorous mammals have a lower cancer mortality rate compared to carnivorous mammals (Vincze et al.). While the diet of a mammal is not the sole determining factor on the lifespan or cancer resistance, analyzing characteristics that cancer-resistant mammals possess, such as herbivorous diets, could allow for a better understanding of cancer resistance across mammals.

Mice and rats are commonly used as research models for various fields, including cancer. Information from these mammals has allowed for extraordinary breakthroughs in the development of treatment for human cancers (Anisimov et al.). However, these short-lived, cancer-prone mammals may not be the ideal research models to uncover novel mechanisms of cancer prevention that could be translated to human cancer prevention. Using inherently cancer-resistant mammals, such as elephants, whales, naked mole rats, blind mole rats, horses, cattle, and bats, as models for cancer research may allow for breakthroughs in the field of cancer research, resulting in treatment strategies and methods for cancer prevention. This paper explores the mechanisms that contribute to cancer resistance in mammals and proposes potential focuses of future research to advance our understanding of cancer prevention and resistance.

Elephants

Elephants, of the family Elephantidae and the order Proboscidea, are large land mammals of three species: the African forest elephant, the Asian elephant, and the African bush elephant, which is the largest living land mammal. Found in parts of Africa, South Asia, and Southeast Asia, elephants are herbivorous mammals that live in deserts, marshes, and forests.

The size of an elephant mainly depends on the sex and species of the individual but can vary from 2000 kg to 7000 kg (Shoshani). Similarly, the lifespan of elephants varies depending on the captivity status of the elephant. Captive elephants tend to have an average lifespan of around 17-20 years (Clubb et al.), while those that live in the wild may live anywhere from 40-80 years old (Shoshani; Clubb et al.).

The majority of research surrounding elephants of the Loxodanta genus and cancer resistance focuses on African bush elephants. When results are specific to African forest elephants, a distinction will be noted. Otherwise, African bush elephants may simply be referred to as "African elephants."

Cancer in Elephants

Elephants are large, long-lived mammals. Thus, they have developed anticancer mechanisms to decrease their cancer risk until they are past their reproductive age. Elephants are thought to be extremely resistant to cancer and have a significantly lower cancer incidence rate compared to other mammals, such as humans, cats, and dogs.

Cancer rates in elephants differ between species. Asian elephants are much more prone to cancer than African bush elephants. One study found that 41% of Asian elephants (17/41) displayed evidence of neoplasia, compared to 6% of African elephants (2/35) ("Elephant" Tollis et al.). Out of the 41 Asian elephants, 6 were diagnosed with malignant cancer, making the malignant cancer incidence rate in Asian elephants 14%. There were no cases of malignant cancer found in the African elephants ("Elephant" Tollis et al.). Another study reported a cancer incidence rate of over 40% in elephants, with a malignancy rate of 24% (Boddy et al.). However, this study combined Asian and African bush elephants and had a small sample size of 17, which can impact the results.

Asian elephants display a higher cancer incidence rate compared to African bush elephants because neoplasia in mature female Asian elephants is extremely common. Neoplasia of the reproductive tract seems to be common in adult, female Asian elephants and was observed in 80% of 80 adult female Asian elephants (Landolfi et al.). Myometrial leiomyomas were the most common tumor observed and have a reported prevalence of anywhere from 71-100% in mature, female Asian elephants (Landolfi et al.; Montali et al.). Malignant tumors accounted for 12 of the 63 reported uterine neoplasms (19%), and 67% of those malignant tumors were found to have metastasized (Landolfi et al.). It's important to note that this high rate of neoplasia only seems to be prevalent in the reproductive tract of mature, female Asian elephants, and does not appear to be a prevalent issue in other elephant subcategories.

Prior to studies reporting a high rate of neoplasia in female Asian elephants, incidences of neoplasia across elephants were thought to be extremely uncommon. While elephants do have a low cancer mortality rate of less than 5% (Abegglen et al.), researchers now know that cancer incidence in elephants varies depending on the sex, age, and species of the elephant, and neoplasia is common in some groups of elephants. While this may seem to challenge the notion of elephants' cancer resistance, it's important to note that only a specific subset of elephants is susceptible to only a single type of cancer. Overall, elephants are remarkably resistant to cancer due to their remarkable anticancer mechanisms.

Cancer Resistance in Elephants: The TP53 Gene

Although female Asian elephants have a higher rate of neoplasia than previously thought, these mammals still possess remarkable strategies that protect themselves against the devastating disease that is cancer.

Elephants have multiple pseudogene copies of a tumor suppressor gene known as TP53 (Abegglen et al.). TP53 triggers apoptosis, or programmed cell death, in response to a variety of signals sent by sensors that track stressors such as DNA damage or radiation (Abegglen et al.). If the degree of damage to the cell is excessive, TP53 can halt the cell cycle until conditions become normalized within the cell. If the cell is irreparably damaged, TP53 can trigger apoptosis, causing the cell to die (Hanahan and Weinburg). This makes it an essential tumor-suppressor gene across mammals.

African bush elephants tend to have anywhere from 19-23 extra copies of the gene, while the Asian elephant genome indicates that Asian elephants harbor anywhere from 10-37 copies of the gene("Elephant" Tollis et al.; Abegglen et al.; Sulak et al.). For comparison, humans have only one copy of TP53 (Abegglen et al.). The extra copies that elephants harbor appear to be all pseudogenes and house a variety of changes in the sequence of the gene but are still associated with a heightened apoptotic response in elephants.

Elephants are extremely sensitive to cellular stress because of their extra copies of TP53. This causes them to demonstrate apoptosis at much lower rates of DNA damage compared to humans and other species (Abegglen et al.). While this early-apoptosis strategy is efficient, it's also possibly very draining. Elephants likely have to deal with constant cell death, which increases their need for cell replacement. Elephants have most likely evolved adaptations that counteract the damage caused by frequent apoptosis ("Mechanisms" Seluanov et al.). Studies done on mice support this theory, as mice with active p53 display symptoms such as accelerated aging, reduced fertility, shorter lifespan, reduced size, atrophy across organ systems, loss of stem cells, and tissue cellularity (Tyler et al.; Maier et al.). However, mice that were engineered to carry extra copies of wild-type Trp53 transgenic alleles did not display similar symptoms and instead were protected from cancer (Garcia-Cao et al.).

Additionally, older Asian elephants were found to display a lower rate of apoptosis, suggesting an age-related decrease in hypersensitivity and apoptosis across Asian elephants (Abegglen et al.). This may provide reasoning as to why neoplasia is common in adult, female Asian elephants. However, further research would have to be done to confirm this, as well as determine why it is so prevalent in female Asian elephants only.

Naked Mole Rats

The naked mole rat (*Heterocephalus glaber*) is a small, subterranean rodent commonly found in the drier areas of East Africa. Mature naked mole rats typically weigh around 35 grams but can reach a mass of over 110 grams (Buffeinstein et al.). They are the longest-lived rodents, with an average lifespan of 28 years in captivity (Buffeinstein).

Cancer and Cancer Resistance

Although mammals have some of the highest cancer rates, cases of neoplasia in naked mole rats are rare. Multi-year-long observations of naked mole rat colonies have recorded no incidences of cancer (Buffeinstein; "Spontaneous" Delaney et al.). In fact, only a few cases of spontaneous neoplasia in naked mole rats have been reported ("Initial Case" Delaney et al.).

Not only are they inherently resistant to natural cancer development, but they are also highly resistant to induced tumorigenesis (“Hypersensitivity” Seluanov et al.; Liang et al.; Manov et al.).

Naked mole rats use an early-acting anticancer mechanism known as early contact inhibition (“Hypersensitivity” Seluanov et al.). Regular contact inhibition, a characteristic of normal cells, is a natural process that arrests cell division once cells reach a high density or come into close contact with each other, preventing hyperproliferation. Contact inhibition is often lost in cancer cells. Unlike most other species, naked mole rats exhibit early contact inhibition, which causes cells to proliferate very slowly in culture and arrest cell division earlier than human and mouse cells(“Hypersensitivity” Seluanov et al.; “Distinct” Seluanov et al.). Early contact inhibition requires less cell contact to inhibit growth compared to regular contact inhibition and acts as a barrier defense against tumorigenesis and malignant growth by restricting cell proliferation.

Early contact inhibition is a result of the production of a large amount of the extracellular signal high molecular mass hyaluronan (HMM-HA), a substance that is secreted by naked mole rat cells at a five times larger rate than human or mouse cells (Tian et al.). The oversecretion of HMM-HA is likely an adaptation that initially served as a way to improve the skin elasticity of naked mole rats for their subterranean lifestyle (Tian et al.). However, the larger amount of HMM-HA secreted serves as a critical anticancer mechanism in naked mole rat cells. When the signaling pathway that leads from HMM-HA to p16, the gene that triggers the activation of early contact inhibition, is removed, naked mole rat cells are more susceptible to hyperplasia and cancer development (Tian et al.). The signaling pathway also requires the presence of the CD44 receptor, which is a cell surface adhesion receptor that is expressed in many cancers and plays a role in regulating metastasis (Tian et al.).

Early contact inhibition is strongest when both tumor suppressor pathways p53, which triggers apoptosis, and pRb, which controls cell division, are expressed (Hanahan and Weinburg). Naked mole rat cells only lose early contact inhibition when both p53 and pRb are inactive, thus causing their cells to proliferate beyond the standard rate and undergo regular contact inhibition (“Hypersensitivity” Seluanov et al.). When naked mole rat cells undergo regular contact inhibition upon deletion of p53 and pRb, it is triggered by the activation of the gene p27 instead of p16, similar to human and mouse cells (“Hypersensitivity” Seluanov et al.). When only one of the two tumor suppressor genes, p53 and pRb, in the naked mole rat is active, cells may proliferate beyond the naked mole rat’s standard rate but undergo apoptosis when the cells become too close in proximity (“Hypersensitivity” Seluanov et al.). As a result, cell density remains low. Similarly, when alternative reading frame (ARF), a gene specific to naked mole rats that plays a role in tumor suppression, is inactivated, naked mole rat cells induce senescence to protect the cells against oncogenic transformation (Miyawaki et al.). This indicates that naked mole rats can sense the loss of one of their tumor suppressor pathways and use backup methods to protect themselves against cancer and hyperproliferation.

Aging and cancer are both the result of an accumulation of cell damage (Lopez-Otin et al.). The two processes share many similarities and are linked in a variety of ways. When a species exhibits resistance to aging, it may also possess notable adaptations that affect cancer development. Naked mole rats are an example of a species that does not display evident signs

of aging (Buffeinstein). They have excellent anti-aging defenses, display adequate reproductive potential well into their third decade of living, and have minimal age-related physiological changes (Buffeinstein; O'Connor et al.). It is possible that the mechanisms that contribute to the naked mole rat's lack of aging may play a role in its cancer resistance. For example, the accuracy of protein translation is thought to play an important part in aging. Naked mole rats have more precise protein translation, which decreases the risk of anomalous proteins that can cause cancer (Azpurua et al.). It is possible that the naked mole rat's accurate protein translation may contribute to both its cancer resistance and lack of aging.

Naked mole rats are also capable of fructose-driven glycolysis (Park et al.). Similarly to their overproduction of HMM-HA, this adaptation evolved as a way for naked mole rats to be better suited to life underground. The ability to use fructose instead of glucose to fuel glycolysis is an example of an adaptation that allows naked mole rats to be more resistant to hypoxic environments. Interestingly, fructose-mediated actions are thought to be a possible risk factor for cancer, and fructose has been found to induce the proliferation of tumors (Liu et al.). However, it is possible that the potential increase in cancer risk due to fructose utilization has been counteracted by the various anticancer strategies employed by the naked mole rat.

Blind Mole Rats

Blind mole rats (*Nannospalax ehrenbergi* superspecies) are subterranean mammals commonly found in mountain valleys and forests in the Middle East. They are long-lived rodents that weigh 100-200 grams and have a documented maximum lifespan of 21 years (Edrey et al.). Although blind mole rats are closer to mice than to naked mole rats, the two both possess long lifespans relative to their body mass and remarkable abilities, such as inherent cancer resistance.

Cancer and Cancer Resistance

Blind mole rats are incredibly resistant to cancer. A 40-year-long observation of thousands of blind mole rats reported zero spontaneous tumors in the animals (Gorbunova et al.). There have been zero confirmed cases of cancer in blind mole rats, suggesting these animals are one of the most cancer-resistant mammals. They are also incredibly resistant to induced tumorigenesis and were shown to kill cancer cells of other species, proving they possess incredibly efficient anticancer mechanisms (Manov et al.).

Blind mole rats employ an anticancer mechanism known as concerted cell death. Concerted cell death is triggered by the release of IFN-β (Gorbunova et al.). Interferons (IFNs) are proteins that play a role in the immune response by signaling that pathogens, such as viruses, are present. They also play crucial roles in tumor suppression. Unlike naked mole rat cells, blind mole rat cells proliferate rapidly for around 7-20 population doublings. Due to their sensitivity to hyperplasia, likely evolving as a way to recognize specific preludes to cancer, blind mole rat cells release IFN-β once they've reached a high density and then undergo concerted cell death. *In vitro* cells arrest proliferation for around 3 days, after which all cells on the plate detach and die within 4 days by a mix of both necrotic and apoptotic responses (Gorbunova et al.). Concerted cell death primarily uses necrosis, a process that is usually associated with the uncontrolled death of a large group of cells which is often harmful to the organism. On the other

hand, apoptosis is a programmed process of cells that usually has beneficial, healing effects because it does not lead to widespread cell death (D'Arcy). Due to the major differences between the two cell death pathways, necrosis is seen as an inefficient way of eliminating unwanted cells compared to apoptosis. However, the response of necrosis in blind mole rats virtually eliminates all of the possibly oncogenic cells by not only killing off the possibly pre-malignant cells but also the cells surrounding them, making it a strong anticancer mechanism. The reasoning as to why blind mole rats primarily employ necrotic responses instead of apoptotic responses in concerted cell death may lie in their unusual p53 sequence, which was found to be unable to induce apoptosis, yet was more sensitive to inducing growth arrest (Ashur-Fabian et al.). This unique p53 gene substituted lysine for arginine, a substitution that has been found in human tumors that display a resistance to hypoxia. This suggests that this adaptation evolved to better suit blind mole rats in their subterranean habitat (Ashur-Fabian et al.). Additionally, both tumor suppressor pathways, p53 and pRb, must be inactivated to abrogate concerted cell death (Gorbunova et al.).

Concerted cell death is not the only cancer resistance mechanism used by the blind mole rat. These animals possess a higher rate of DNA/RNA editing, reduced chromosome arrangements, and an over-representation of short interspersed elements (SINEs), non-coding sequences that play a role in cell survival against stressors such as DNA damage, compared to mice and rats, which is most likely linked to the rodent's resistance to cancer and tolerance of hypoxia (Fang et al.).

Blind mole rats also produce a large amount of HMM-HA (Tian et al.). The large amount of HMM-HA in blind mole rats is likely an adaptation that protects the rodents from oxidative damage. This adaptation may contribute to cancer resistance. However, blind mole rats do not exhibit early contact inhibition, and HMM-HA has not been identified as a property of concerted cell death (Manov et al.). Therefore, there is no substantial evidence that points to HMM-HA playing a role in the cancer resistance of the blind mole rat. Further research is required to determine whether HMM-HA has anticancer mechanisms in the blind mole rat.

Another factor that may contribute to cancer resistance in the blind mole rat is its uniquely modified variant of heparanase, an enzyme that degrades heparan sulfate on the cell surface and extracellular matrix (Nasser et al.). Heparanase is mainly overexpressed in tumors, and its overexpression is associated with increased metastasis. The uniquely spliced variant found in the blind mole rat inhibits heparan sulfate degradation and suppresses glioma tumor growth, which may play a role in cancer resistance (Nasser et al.).

Bowhead Whales: Large Mammals with No Cancer

The bowhead whale (*Balaena mysticetus*) is a large aquatic mammal that resides in Arctic and subarctic waters. Weighing in at 75-100 tons, bowhead whales are estimated to have a natural lifespan of over 200 years and are one of the longest-living mammals (NOAA Fisheries).

The bowhead whale possesses many genes that result in enhanced DNA repair, immune response, and cell-cycle regulation (Table 1) (Keane et al.). Genes under positive selection in

the bowhead whale include the excision repair cross-complementing group 1 (ERCC1) and histone deacetylase (HDAC1 & HDAC2). ERCC1 is involved in DNA repair, while HDAC1 and HDAC2 both play roles in the regulation of chromatin structure and have been associated with longevity in fruit flies (Keane et al.). These genes are also involved in death receptor signaling, which detects death outside the cell and triggers apoptosis (Keane et al.; "Death Receptor Pathway").

The bowhead whale also possesses multiple copies of various genes, such as PCNA, LAMTOR1, and UVRAG which contribute to cancer resistance (Keane et al.; "Return" Tollis et al.). Proliferating cell nuclear antigen, or PCNA, is involved in DNA repair. In the bowhead whale, LAMTOR1 is not only copied multiple times, but it also has unique changes in its amino acids. LAMTOR1 is involved in activating the mTORC1 gene, which is associated with cancer and aging (Keane et al.; "Return" Tollis et al.). It also plays a role in controlling cellular growth. UVRAG genes are tumor suppressor genes. Other duplicated genes found in the bowhead whale that have roles in the cell cycle, DNA repair, and cellular stress response include PSMD4, UCHL3, ARPP19, and STOML2 (Keane et al.). Additionally, the bowhead whale has unique substitutions in the POLE gene, which is a cancer-related gene that is involved in DNA repair and replication ("Return" Tollis et al.).

Genes associated with tumor suppression are overexpressed in the kidney of the bowhead whale ("Transcriptome" Seim et al.). An example of one of these genes is E4F transcription factor 1 (E4f1), which directly interacts with p53 and plays a role in growth arrest and apoptotic responses. Interestingly, the bowhead whale's liver exhibited a reduced expression of tumor suppressors, yet a higher expression of proto-oncogenes such as WSB1 and PDGFRB ("Transcriptome" Seim et al.). Additionally, the bowhead whale genome is virtually devoid of short interspersed nuclear elements (SINEs), which are short, repetitive non-coding sequences that are involved in cell survival when facing stressors such as DNA damage and infection (Keane et al.). On the other hand, other cancer-resistant mammals, such as the blind mole rat, have a numerous amount of SINEs. This indicates that the bowhead whale relies on mechanisms other than SINEs for their cancer resistance.

Gene(s)	Mutation(s)	Role(s)
Excision repair cross-complementing group 1 (ERCC 1)	Under positive selection	- DNA Repair - Death receptor signaling
Histone deacetylase (HDAC 1 & 2)	Under positive selection	- Regulation of chromatin structure - Longevity - Death Receptor Signaling
Proliferating cell nuclear antigen (PCNA)	Duplicate copies	- DNA Repair

LAMTOR1	Multiple copies; Unique amino acid changes	- Activates the mTORC1 gene (associated with cancer and aging) - Controls cellular growth
UVRAG	Multiple copies	- Tumor suppressor
PSMD4, UCHL3, ARPP19, and STOML2	Multiple copies	- DNA repair - Cellular stress response - Plays a role in mitosis
POLE	Unique substitutions	- Cancer-related - DNA repair - DNA replication
E4F transcription factor 1 (E4f1)	Overexpressed	- Directly interacts with p53 - Growth arrest - Apoptotic responses
WSB1 and PDGFRB	Overexpressed	- Proto-oncogenes (promotes cancer).

Table 1: Genetic mutations in the bowhead whale genome that contribute to cancer resistance. Data from. Keane et al.; "Return" Tollis et al.; "Transcriptome" Seim et al.

Currently, there have been no reports of cancer in bowhead whales. However, it is extremely likely that cancer in bowhead whales goes undetected due to the fact that we do not know much about their natural causes of death. Moreover, it is very rare to find a stranded bowhead whale. When samples are collected from dead bowhead whales, there is usually a delay between when the whale died and when the samples are collected and analyzed, increasing the chance of compromised data. Further research on cancer resistance in the bowhead whale should focus on sample collection of dead bowhead whales to gather comprehensive data surrounding bowhead whales and cancer incidence. Nonetheless, bowhead whales are thought to be resistant to cancer due to their unique genetic changes and slow mutation rate ("Return" Tollis et al.).

Cattle and Horses

Cattle (*Bos taurus*) are large, herbivorous, hoofed mammals. Although the weight of cattle can vary from 300 kg to 1500 kg, the size of these animals primarily depends on the breed and sex of the individual. Bulls tend to weigh more than cows of the same breed. Since cattle are mainly used in food production, these animals are typically slaughtered before they reach the natural end of their life. However, the average natural lifespan of cattle is around 20-25 years.

Horses (*Equus ferus caballus*) are domesticated, herbivorous, hoofed mammals that vary in size, shape, and color, depending on various factors. The size of a horse is largely determined by its breed, ranging from under 400 kg to over 1000 kg. The lifespan of a horse also varies depending on factors such as breed, care, and environment. Most horses can live anywhere from 25-30 years, with some horses living well into their 30s and 40s, and rarely into their 50s and 60s.

Loss of Placental Invasion = Loss of Metastatic Cancers?

Cows and horses are thought to have a lower rate of malignant cancers due to their method of placentation (D'Souza and Wagner). The placenta is a necessary part of pregnancy in mammals, as it allows maternal and fetal blood to come into close proximity with each other to exchange molecules. Many species, including humans, dogs, and cats, accomplish this task by placental invasion, whether endotheliochorial or hemochorial (Moffett and Loke). During placental invasion, the trophoblast cells of the placenta invade the uterus and maternal blood vessels (Moffett and Loke; Graham and Lala). Hemochorial placentation, employed by humans and rodents, is the most invasive placentation in mammals. Hoofed mammals, such as horses and cows, as well as their relatives, like whales, use epitheliochorial placentation (D'Souza and Wagner). Epitheliochorial placentation has no trophoblast invasion at all and instead exchanges molecules between maternal and fetal blood via noninvasive mechanisms. Species with no placental invasion may have evolved mechanisms to suppress trophoblast invasion, in turn also increasing the body's ability to suppress metastatic invasion in certain locations (D'Souza and Wagner). One study reviewed the rate of malignant cancer in animals with differing levels of placental invasion (D'Souza and Wagner). The study found that horses and cows, animals with a loss of invasive placentation, had a much lower rate of malignant cancers in certain locations compared to dogs and cats, animals with invasive placentation (D'Souza and Wagner) (Table 2). Bovine stroma has been proven to be much more resistant to cell invasion when tested *in vitro* (Kshitiz et al.). On the other hand, human stroma is more permissive to invasion (Kshitiz et al.). While research on the permissiveness of stroma of all mammals that employ epitheliochorial placentation has not been done, it is theorized that mammals that use non-invasive placentation, including horses, are better equipped to resist metastatic invasion (Kshitiz et al.).

One study reported that out of 4407 cows examined, only 98 showed evidence of neoplasia (2.22%) (Ramos et al.). The most common tumors in cattle were lymphomas and epithelial tumors, namely squamous cell carcinoma. Lymphomas in bovine have been associated with the bovine leukemia virus, as well as the size of the herd, which may indicate a genetic predisposition to the cancer (Ramos et al.).

Another study found that out of 1.3 million cattle examined, only 302 tumors were found (0.02%) (Anderson and Sandison). However, the cattle examined were confirmed to be a part of the dairy/meat industries and were slaughtered before reaching the natural end of their life, possibly skewing results. Cancer risk increases along with age, making it possible for it to appear as if cattle (that have been slaughtered at a relatively young age) have a lower rate of cancer than normal. Additionally, the study was done in 1969, making it possible that the technology and/or methods used may have made it so that some incidences of neoplasia were not identified.

A study of 774 horses examined, found that only 65 possessed neoplasms (8.39%) (Ramos et al.). Skin cancers are typically the most common type of cancer found in horses, which varies in frequency depending on the breed and pigmentation of the horse. Pale-pigmented horses develop skin cancers such as melanoma more frequently than other horses with darker pigmentation. In addition to melanomas, other common cancers found in horses include equine sarcoids, squamous cell carcinomas, and granulosa cell tumors (Cotchin). Equine sarcoids are usually benign and non-metastatic but can become locally aggressive under certain circumstances and have a high chance of recurrence due to their resistance to therapy (Ogluszka et al.). While these tumors aren't typically life-threatening, they can negatively affect the horse's quality of life (Ogluszka et al.).

Location	Species	Malignant Tumors	Total Tumors	Malignancy Rate
Skin	Cow	11	105	10%
	Horse	26	437	6%
	Dog	338	1691	20%
	Cat	35	51	41%
Glandular Epithelium	Cow	10	45	22%
	Horse	15	175	8%
	Dog	553	1184	47%
	Cat	45	57	79%
Non-glandular epithelium	Cow	187	200	94%
	Horse	119	136	88%
	Dog	263	316	83%
	Cat	46	50	93%
Connective Tissue	Cow	0	22	0%
	Horse	13	127	10%
	Dog	323	626	52%
	Cat	18	31	59%

Table 2: Frequency of malignant tumors in the cow, dog, horse, and cat at four anatomical locations. Table from D'Souza and Wagner.

It's important to remember that although there is a correlation between lower malignancy rates and loss of placental invasion, this may not be causal. Other factors that may contribute to these results include body mass, age, environment, and diet. It is also possible that cows and horses possess other anticancer mechanisms that contribute to their cancer resistance. However, the data is consistent with the theory that only certain anatomical locations of animals with a loss of placental invasion are resistant to malignant tumors, as cancer malignancy rates

are significantly higher in the non-glandular epithelium and lower in other areas, such as the skin and connective tissues.

Bats

Bats, mammals of the order Chiroptera, live relatively long lives compared to what is expected for mammals of their size. Bats are largely diverse mammals, with over 1300 species across 20 families, and comprise 20% of all classified mammalian species, second only to rodents. Most bats have an average lifespan of 10-20 years, depending on the species. Certain microbat species, such as the little brown bat (*Myotis lucifugus*), have been reported to live for over 30 years. The longest-living individual bat was a Siberian bat and was determined to be around 41 years old. Bats can be found virtually anywhere in the world and have a diet that ranges from fruits to blood depending on the species.

Bats are reservoirs for a variety of viruses that are damaging to multiple species, including humans. However, these viruses appear to cause no clinical disease in bats. Experimentally infecting laboratory bats with a virus only led to, at most, a subclinical infection with few symptoms (Middleton et al.). This indicates that bats possess a variety of effective antiviral mechanisms, some of which may contribute to cancer resistance in the bat.

Cancer and Cancer Resistance

Only a few cases of cancer have been reported in bats, despite their prevalence in scientific research (“Mechanisms” Seluanov et al.; Olds et al.). Mutations that may contribute to cancer resistance in bats are only present in some species and, due to the diversity of bats, there is no confirmation that adaptations found in some species of bats are similar across all bat species. It is likely that different species and lineages of bats have evolved their own cancer-resistance mechanisms, a theory that should be tested with further research into the subject.

It is possible that factors that affect the exceptional longevity of bats may have anticancer effects. For example, bats possess an altered growth hormone/insulin-like growth factor 1 axis (“Genome” Seim et al.). Some species of bat, such as the Brandt’s bat (*Myotis brandtii*) and the big brown bat (*Eptesicus fuscus*), harbor a deletion in the growth hormone receptor transmembrane (“Genome” Seim et al.). GHR mutations and dysfunction have been associated with a decreased risk of diabetes and cancer in humans and mice (“Genome” Seim et al.). Multiple insulin signaling-associated genes were also expressed at a higher level in Brandt’s bats (“Genome” Seim et al.). This was similarly expressed in GHR dysfunctional long-lived mice, supporting the idea that the GHR in *M. brandtii* is dysfunctional and may cause these bats to exhibit a longer lifespan. Various other aging-related changes in bats may also contribute to cancer resistance.

One study showed that long-lived bats share similarities with the naked mole rat (Ricci et al.). These shared similarities may contribute to these mammals’ unique cancer resistance and long lifespans. Both long-lived bats and naked mole rats showed reduced non-LTR retrotransposon, a type of transposable element (TE), accumulation when compared to short-lived species of bats and rodents (Ricci et al.). TEs play a major role in eukaryotic life and

are key properties of gene duplication, gene expression regulation, and eukaryotic evolution (Ricci et al.). Furthermore, they also play a role in many devastating human diseases and can ultimately lead to cancer in certain conditions (Ricci et al.; Callinan and Batzer). Therefore, the reduced non-LTR retrotransposon accumulation may enhance cancer resistance (Ricci et al.). Bats may also possess mechanisms to dampen potential health issues related to transposable elements, thus contributing to the antiviral properties of bats (Ricci et al.). Bats and naked mole rats also share an adaptive sequence convergence of ADAMTS9, a novel tumor suppressor that inhibits tumor growth by blocking the IGF1/mTOR pathway, which is associated with cancer, aging, and various diseases (Lambert and Portfors). Additionally, the gene has been indicated in many other age-related conditions (Lambert and Portfors). This shared adaptation may be a reason why both naked mole rats and certain bat species have an apparent resistance to cancer and aging.

Long-lived bat species may also have developed superior mechanisms against cellular injury and damage. For example, long-lived bat species produce more 53BP1 foci compared to short-lived species, even when the same amount of DNA damage occurs (Croco et al.). This DNA damage response pathway results in the activation of genes associated with cell cycle arrest, apoptosis, or senescence. Certain species of bats, such as the *Myotis davidii*, have DNA repair and tumor suppressor genes such as TP53 and BRCA2 under positive selection (Zhang et al.). Myotis bats also possess upregulated telomere maintenance genes, many of which play a role in DNA repair (Foley et al.). However, they are hypersensitive to ultraviolet light (Harper et al.). Another reason why bats may not develop cancer as frequently as other mammals is because of the fact that they possess a lower amount of direct repeats in their mitochondrial DNA (mtDNA), lowering the chance for mutagenesis (Khaidakov et al.). Direct repeats in the mitochondrial DNA are known to contribute to harmful mitochondrial mutations that are suspected to have a significant impact on the aging process (Khaidakov et al.). Mutations in the mitochondrial DNA have also been associated with cancer (Cavalcante et al.). Species with lower levels of direct mtDNA repeats have greater mtDNA stability, allowing for a longer lifespan and a decreased risk of cancer (Khaidakov et al.). This is consistent with the theory that certain species of bats, particularly long-lived ones, have advanced DNA repair strategies that may contribute to cancer resistance.

Greater mouse-eared bats (*Myotis myotis*) have numerous amounts of unique, bat-specific miRNA that are associated with the immune system, aging, and tumor formation pathways. miRNA such as the miR-101-3p and miR-155-5p were upregulated in bats and are associated with apoptosis and immunity (Huang et al.). *M. myotis* bats also downregulate the oncogenic miR-221-5p, which promotes tumor formation in human breast and pancreatic cancers. Over 100 upregulated genes in *M. myotis* bats were enhanced in the mitotic cell cycle, while over 300 down-regulated genes were primarily involved in mitochondrial activity (Huang et al.).

Certain bat species also possess multiple antiviral and anticancer mutations (Scheben et al.). DNA repair genes, including PALB2, IFIT2, POLA1, and POLK, were under positive selection in bats. PALB2 is a part of the BRCA complex and plays a role in tumor suppression. Bats also possess multiple copies of IFIT2, which plays a role in apoptosis and cancer progression (Scheben et al.). CDH1 and CAT were also found to be under positive selection.

However, these genes have been linked to cancer, and their evolutionary value to bats is not yet clear.

Other potential reasons for cancer resistance in bats include resistance to oxidative damage (Shen et al.), better maintenance of proteostasis (Pride et al; Salmon et al.), and diet, as frugivorous bats tend to live shorter lifespans than insectivorous bats, likely due to high glucose consumption (Wilkinson and South).

Cancer-resistant Mammals as Models for Cancer Research

Cancer is a disease that has existed long before humans. While the term “cancer” first appeared in around 400 BCE by the Greek physician Hippocrates, the oldest description of the disease dates back to an Egyptian textbook on trauma surgery in around 3000 BCE (American Cancer Society). In this textbook, cancer was described as having no treatment other than removal by cauterization (American Cancer Society). However, due to our enhanced understanding of the disease, there are now a variety of treatment options for cancer, including surgery, hormone therapy, chemotherapy, and radiation therapy.

Since cancer existed before humans, it’s not surprising that cancer is not limited to humans. In fact, cancer can behave quite similarly in humans and other animals. As a result, certain animals are commonly used as cancer research models as they allow for the study of the biology of cancer in a more physiological context *in vivo* instead of in individual cells or tissues *in vitro* (Cancer Research UK). The use of animal models in cancer research allows researchers to better understand cancer as a whole. Using animal models for cancer research has several benefits, including studying how cancer cells grow and metastasize, how effective treatment options are, how certain factors impact risk, and how cancer interacts with other cell types (Pharma Models). Due to this, animal models of cancer have contributed largely to cancer research and the increasing survival rates of cancer patients.

Cancer research primarily uses short-lived, cancer-prone mammals such as mice and rats as research models, both of which have biological and anatomical similarities to humans. These animals play valuable roles in our understanding of cancer, and their use in laboratories has led to various discoveries for cancer treatment, such as the breast cancer drug tamoxifen and the leukemia medication imatinib (Pharma Models). However, compared to mammals that have remarkable characteristics related to cancer, mice and rats may offer limited information regarding cancer resistance, due to their proneness to the disease and lack of genetic variation (de Magalhães).

The field of biomimicry, or biologically inspired engineering, focuses on mimicking elements of nature to invent solutions to human problems (Detanico). The Wright Brothers, for example, observed the flight of birds to invent human flight, leading to the creation of the first airplanes. Similarly, mammals that are resistant to cancer can provide valuable insight into preventing cancer in humans. Cancer-resistant mammals, such as the blind mole rat, have evolved unique and efficient mechanisms to decrease their risk of cancer. These mammals tend to possess a form of efficient and sensitive surveillance of hyperplasia, which allows them to detect and eliminate possible cancer cells in an effective manner. Research that focuses on

studying the immune system of these mammals could allow us to emulate their resistance in humans through vaccines or other therapies that enhance the human's immune response to cancer. Other research may focus on using the elephant as a model to engineer extra p53 copies in humans or using the bat as a model to engineer bat-specific gene mutations (BRCA2, IFIT2, and PALB2) that increase cancer resistance.

While cancer-resistant mammals could prove to be invaluable research models, various challenges arise in working with non-traditional animal models. Housing some cancer-resistant mammals, such as elephants, in a laboratory setting is impractical. However, elephants and other cancer-resistant mammals do not have to be housed in a laboratory to be used as models for cancer research. Genes from these mammals can be studied and researchers can partner with zoos to study cancer-resistant mammals such as the elephant and naked mole rat. Additionally, non-traditional animals that are not commonly used as research models have much fewer species-specific resources. Compared to traditional research models, using non-traditional animals as research models can be more difficult, time-consuming, and expensive due to the lack of knowledge surrounding these animals in a research context. To facilitate the research process, methods, protocols, and databases should be further developed for these species. Expanding pre-existing research programs to study how cancer development and resistance work in these remarkably cancer-resistant mammals could lead to extraordinary discoveries that could be applied to cancer prevention and treatment in humans, as well as advance our understanding of cancer across species.

Conclusion

Cancer-resistant mammals tend to exhibit enhanced DNA repair and unique responses to cell proliferation and tumorigenesis. The reasons behind these remarkable adaptations that contribute to cancer resistance vary. Certain species evolved novel adaptations due to their unique lifestyles, and these adaptations have subsequently led to an increased lifespan and decreased cancer risk. The naked mole secretes a high amount of HMM-HA, an adaptation that initially allowed these mammals to live comfortably underground. Now, HMM-HA plays an essential role in early contact inhibition in the naked mole rat, a mechanism that has led to cancer resistance. Similarly, blind mole rats possess a unique p53 sequence which initially evolved to increase their hypoxia resistance. This p53 sequence now contributes to concerted cell death in the blind mole rat, a remarkable anticancer mechanism. Elephants evolved to have multiple copies of TP53, likely as a way to counteract the increased cancer risk associated with their large size. Bowhead whales, animals that are much larger than elephants, do not possess multiple copies of TP53 but instead possess many genetic changes that result in advanced DNA repair and immune response. Cows and horses are likely resistant to specific metastatic cancers due to their lack of placental invasion, which leads to a less permissive stroma. Bats are diverse mammals that have unique resistance to viral infections, and these mechanisms, along with genetic changes, are thought to have anticancer effects. Analyzing these mechanisms of cancer resistance found in cancer-resistant mammals, uncovering novel strategies, and discovering how these mechanisms can be utilized for cancer treatment and prevention in humans may lead to key breakthroughs in the fight against cancer.

Acknowledgments

Huge thanks to my mentor, Victoria Tobin, for her invaluable guidance throughout the creation of this paper. This paper truly would not have been possible without her feedback and guidance. Thank you.

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