



The Mystery of Cancer Resistance: A Revelation Within Nature

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Abstract

Cancer, a disease due to uncontrolled cell proliferation is as ancient as multicellular organisms. A 255-million-years-old fossilized forerunner mammal gorgonopsian is probably the oldest evidence of cancer, to date. Cancer seems to have evolved by adapting to the microenvironment occupied by immune sentinel, modulating the cellular behavior from cytotoxic to regulatory, acquiring resistance to chemotherapy and surviving hypoxia. The interaction of genes with environmental carcinogens is central to cancer onset, seen as a spectrum of cancer susceptibility among human population. Cancer occurs in life forms other than human also, although their exposure to environmental carcinogens can be different. Role of genetic etiology in cancer in multiple species can be interesting with regard to not only cancer susceptibility, but also genetic conservation and adaptation in speciation. The widely used model organisms for cancer research are mouse and rat which are short-lived and reproduce rapidly. Research in these cancer prone animal models has been valuable as these have led to cancer therapy. However, another rewarding area of cancer research can be the cancer-resistant animal species. The Peto's paradox and G-value paradox are evident when natural cancer resistance is observed in large mammals, like elephant and whale, small rodents viz. Naked Mole Rat and Blind Mole Rat, and Bat. The cancer resistance remains to be explored in other small or large and long-living animals like giraffe, camel, rhinoceros, water buffalo, Indian bison, Shire horse, polar bear, manatee, elephant seal, walrus, hippopotamus, turtle and tortoise, sloth, and squirrel. Indeed, understanding the molecular mechanisms of avoiding neoplastic transformation across various life forms can be potentially having translational value for human cancer management.

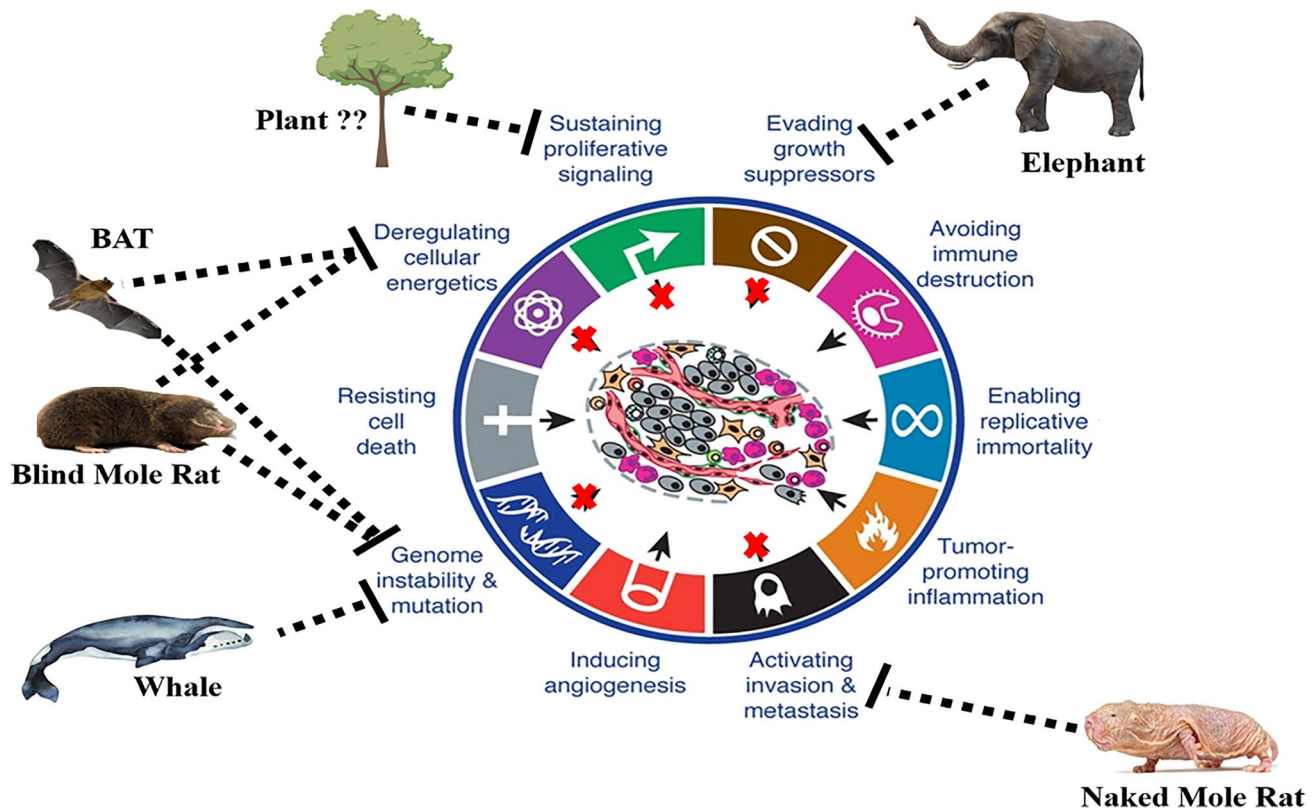
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Graphical Abstract

Adapted and Modified from (Hanahan and Weinberg 2011)



Keywords Cancer resistance · Hypoxia · Evolution · Peto's paradox · Antagonistic pleiotropy · Mammal · Plant · Genome

Abbreviations

ARs	Accelerated regions
BB	Brandt's bat
BW	Bowhead whale
cGAS-Sting	Cyclic GMP-AMP synthase stimulator of interferon genes
CTC	Circulating tumor cell
ECI	Early contact inhibition
ECM	Extracellular matrix
GH	Growth hormone
HIF	Hypoxia-inducible factor
HS	Heparan sulfate
IGF1	Insulin-like growth factor-1
LIF	Leukemia inhibitory factor
ROS	Reactive oxygen species
RTEs	Retrotransposable elements

Introduction

Cancer is a disease of genetic alteration at the somatic level that manifests as uncontrolled cell proliferation and differentiation. The estimated worldwide cancer mortality is 10 million with 19.3 million new cases reported in 2020 (Sung et al. 2021). While some of the targeted anticancer drugs are considerably successful and immunotherapy has shown promising results, there is still a dire need for effective cancer therapy to reduce cancer mortality. Recognizing environmental carcinogens like chemicals, viruses, and radiation did raise hope of preventing cancer by avoiding exposure to them. However, it was soon evident that cancer onset is a result of interplay between individual genetic make-up and external agents, like certain chemicals, light pollution, accidental or intentional wildlife feeding, or reduction of genetic diversity in human-impacted habitats (Giraudeau et al. 2018a; Hochberg and Noble 2017), which can be observed as a spectrum of cancer susceptibility (Dujon et al. 2021d).

Exposure to poisons have a uniform outcome in humans at given concentrations, i.e., toxicity and death. However, the outcome of carcinogenic exposure remains uncertain and unpredictable due to the genetic variability. The optimistic scenario of avoiding cancer by avoiding exposure to environmental agents like UV radiation and chemical carcinogen in genus of *Planaria* (Kalafatić et al. 2006; Van Roten et al. 2018) and *Trichoplax* (Fortunato et al. 2021), kindled our interest in prevalence and molecular mechanisms of cancer in life forms other than humans.

The cancer etiology in humans is categorized as follows: (a) genetic, (b) environment, (c) genetic and environment, and (d) none of these, i.e., spontaneous, in the absence of any carcinogen exposure or genetic predisposition. The last category is attributed to baseline mutation rates due to errors in DNA replication and repair in proliferating cells. In the absence of comparable environmental exposure, it can be significant to understand the genetic and molecular mechanisms responsible for cancer risk in these animal species.

Cancer can result from breakdown in five foundations of multicellularity that are central to development, maintenance, and reproduction of multicellular organisms (Aktipis et al. 2015). Every living creature is the result of evolution, humans, and other life forms alike. Nowell P. C. described “clonal development of tumor cell populations” which led to evaluating cancer also in light of evolution (Nowell 1976). The evolutionary basis of cancer is summarized in four principles viz., (1) neoplasms develop in intricate ecosystems, (2) somatic selection drives the evolution of cancer, (3) natural selection can build potent cancer defenses, and (4) those defenses have limitations (Aktipis and Nesse 2013). Most multicellular organisms naturally accumulate oncogenic processes during life. Notably, pregnancy in mammals is known to exacerbate the progression of existing tumors in females (Thomas et al. 2019). The oncogenic processes viz a viz host defenses could play a major role in the selection of post-reproductive life in animals. The post-reproductive life stages, early ceasing of reproduction, &/or menopause may impart females better fitness, i.e., in terms of anti-cancer mechanism also (Thomas et al. 2019). As cancer evolves, its survival in dynamic microenvironment (Brutovsky 2022) and cancer suppression mechanisms may also evolve. The adaptation is affected by age at first reproduction (delayed reproduction), increasing fecundity with age, age at last reproduction, and survival from other causes of mortality (Brown et al. 2015). The cancer suppression as an adaptation increasing with age can be understood using relevant model with varying levels of parental factors in

order to predict variation in cancer susceptibility across species (Brown and Aktipis 2015).

In comparison to their wild predecessors, domesticated species exhibit specific health effects depending on the biology of the species and the nature and degree of the domestication process (referred to as domesticated syndrome) (Wilkins et al. 2014). The evolutionary consequences of domestication on cancer development and progression are also discussed (Thomas et al. 2020). The domestic animals with high cancer incidence may show specific traits under positive selection pressure that can favor “anticancer adaptations” in humans and wildlife. Therefore, it would be useful to compare cancer incidence across the tree of life in various multicellular organisms or among similar organisms living under different conditions. Albuquerque Thales A. F. and others have reported cancer across species from human to hydra and show that differential evolutionary pressures acting on cancer onset early in life versus later in life that escapes natural selection. The human cancers are considered to result from environmental exposures as well as from evolutionary accidents (Albuquerque et al. 2018).

Cancer is as ancient as the multicellular organisms. The oldest are fossilized evidence of an odontoma tumor in a 255-million-year-old forerunner mammal gorgonopsian (Whitney et al. 2017) and a case of bone cancer in a 240-million-year-old shell-less turtle Pappochelysrosinae (Haridy et al. 2019). Cancer is also reported in hadrosaurs or duck-billed dinosaurs around 70 million years ago (Rothschild et al. 2003). The incidence in various animals differs significantly (Albuquerque et al. 2018; Madsen et al. 2017; Vincze et al. 2022). Very low incidence of cancer is reported in elephant (Abegglen et al. 2015), no or low evidence of spontaneous tumor in spalacids like blind mole rat (Assi 2017) and naked mole rat (Hadi et al. 2021), and low incidence in hibernating bat (Koh et al. 2019) and marine mammals like orca, dolphin, whale, as well as other wild life animals (Hamede et al. 2020; McAloose and Newton 2009; Pesavento et al. 2018). Whereas, the dog and cat (Vail and Macewen 2000), ferret (Dillberger and Altman 1989), sea turtle (Dujon et al. 2021c), and Tasmanian devil (Hamede et al. 2015) have either comparable or higher cancer incidence than humans. In the context of evolution, larger and more evolved animals can be expected to have higher amount of genetic material, but this is not the case (G-value paradox). British epidemiologist Peto R. reasoned that the cells in large-bodied, long-lived animals undergo more cell divisions than small, short-lived animals. Each cell division carries a small but non-negligible risk of introducing mutations in the daughter cells due to baseline replication and related

errors. Thus, there can be higher chances of acquiring necessary and sufficient combination of cancer-causing mutations with increased cell division events. Long-lived and larger animals can be assumed to have a higher cancer risk than small, short-lived animals (Callier 2019; Gaughran et al. 2016). Models suggest that if elephants and whales had the same risk for cancer mutations per cell division as humans, they should die of cancer at a young age and hence should have been extinct (Caulin and Maley 2011). The elephants and whales do not exhibit this phenomenon; however, described as Peto's paradox (Peto et al. 1975; Vincze et al. 2022). Peto's paradox and G-value paradox both defy the obvious assumption!

Understanding interspecies differences in terms of cancer vulnerability can be significant for employing better clinical interventions. Cross-species variation in cancer risk have been reported (Boddy et al. 2020; Møller et al. 2017); however, the small sample size, (Abegglen et al. 2015; Cairns 1981, Leroi et al. 2003), lack of information about the age distribution of cancer (Abegglen et al. 2015; Boddy et al. 2020; Møller et al. 2017), data heterogeneity, or lack of control for phylogenetic relatedness among species (Abegglen et al. 2015; Tollis et al. 2021) according to (Vincze et al. 2022). These studies suggest that the risk of developing cancer is independent of body size and adult life expectancy. Universal oncogenesis processes and significant variations in cancer mortality across the mammals can be related to diet in case of carnivorous mammals (Vincze et al. 2022). Apart from elephant and whale, small rodents like naked mole rat and blind mole rat and bat also show resistance to cancer. The novel cancer resistance mechanisms could be attributed to novel evolutionary paths in these species. Plant tumors are mainly pathogen induced and rarely spontaneous.

New cell mass acquired by neoplastic transformation helps evolve novel genes that are expressed in tumor (Makashov et al. 2019). The human cancer genes, i.e., oncogenes and tumor suppressor genes, are considered to be significantly under purifying selection as compared to the other genes; however, these are not found to impart cancer resistance (Thomas et al. 2003).

Antagonistic Pleiotropy and Cancer

Natural selection shapes organisms to maximize reproductive fitness, which also involves trade-offs around which major traits evolve (Harshman and Zera 2007; Roff 1993, 2002; Stearns 1989; Williams 1966). The genes under positive selection that confer fitness during early life (e.g., increased reproductive output) increase the risk of various pathologies later in life, a phenomena known as antagonistic pleiotropy (Mitteldorf 2019). This observation was first

proposed by Medawar P. B. (Medawar 1946) and further articulated by Williams G. C. (Williams 2001), Hamilton W. D. (Hamilton 1966), and Wallace D. C. (Wallace 1967), leading to population genetic theory of aging (Byars and Voskarides 2020). Pleiotropy is a mechanism of gene action (Barreiro et al. 2008; Knight et al. 2006), that explains why patterns of positive selection in humans are linked to risks of diseases, like cancer (Nielsen et al. 2005; Vasseur and Quintana-Murci 2013). Since cancer is reported in all forms of multicellular life, including hydra and whales (Aktipis et al. 2015; Leroi et al. 2003), Frédéric Thomas suggested that cancer could be a key player in mediating life-history trade-offs as a cost of reproduction, where energy is diverted away from maintenance (cell repair and immune function) and toward reproduction and also a contributor to life-history evolution (Dujon et al. 2022a).

The antagonistic pleiotropy is observed in animals, like fish (Fernandez 2010; Summers and Crespi 2010; Voskarides et al. 2022); however, its role in humans is debatable (Austad and Hoffman 2018; Byars and Voskarides 2019; Voskarides 2018). Based on the evidence for a variety of diseases, including neurodegenerative, cancer, and host–pathogen interactions, antagonistic pleiotropy may be a common mechanism significant for understanding various human diseases (Byars and Voskarides 2020). The invasive placentation (placenta development) and metastasis (cancer) could be correlated in terms of antagonistic pleiotropy (Costanzo et al. 2018; D'Souza and Wagner 2014). The selection for mutations that improve male reproductive success, selfish genes, and various genetic conflicts might be explained in terms of antagonistic pleiotropy that shows strong evolutionary forces known as sexual selection. The patterns of gene expression in spermatogenic cells are suggested to be shaped by selection-driven processes (Kleene 2005). Thus the ecological and evolutionary consequences in terms of antagonistic pleiotropy can be exemplified for anticancer defense; p53 and cellular senescence that could paradoxically favor the development of cancer in later life (Boutry et al. 2020).

Research in cancer resistance mechanisms in 'unconventional' model organisms related with animal body mass, life span, and cancer provide novel insights (Seluanov et al. 2018). We aim to update and correlate various cancer resisting mechanisms in these animals and also in invertebrates and plants. Unraveling novel cancer resistance mechanisms in animals can be promising candidates for evolving cancer therapy and prevention. We give an overview of current progress on novel cancer resistance mechanisms in vertebrates (elephant, blind mole rat, naked mole rat, whale, and bat) and invertebrates. We also discuss low incidence and carcinogenesis mechanisms in plants.

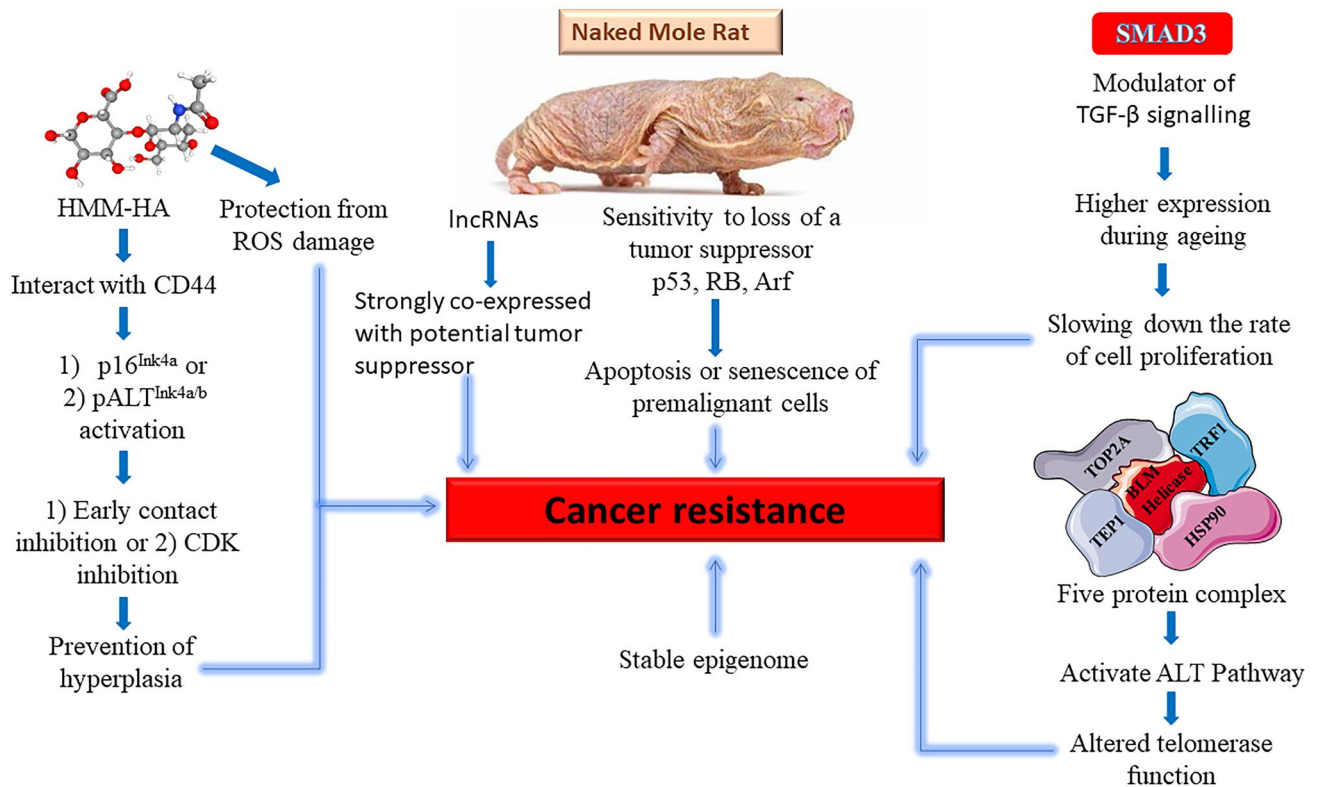


Figure. 1 Anticancer mechanisms in the naked mole rat. Naked mole rat cells and tissues produce five times larger high-molecular mass hyaluronan (HMM-HA) that interacts with various cell surface receptors like CD44 and trigger early contact inhibition regulated by p16^{Ink4a} or the naked mole rat-specific INK4a/b locus product pALT^{Ink4a/b}. Both of the molecules act as a CDK inhibitor that resulted in arresting the cell cycle at low density thus preventing hyperplasia. HMM-HA also act as an antioxidant to protect DNA and protein from reactive oxygen species-induced damage and also protecting from metastasis by maintaining a stronger extracellular matrix. Naked mole rat have a more stable epigenome compared to mouse cells, which can resist reprogramming by Yamanaka factors

(*Oct4*, *Sox2*, *Klf4*, and *Myc*) and may similarly resist reprogramming associate with malignant transformation. They also possess unique ability to sense the loss of a single tumor suppressor such as p53, RB, or p19^{ARF} and undergo apoptosis or senescence. Higher expression of SMAD3 product (TGF- β regulator) during aging play a key role in cancer development by slowing down the rate of cell proliferation and may optimize the rate of cell death. Furthermore, activation of alternate lengthening pathway by five protein complex (BML helicase, TOP2A, TRF1, TEP1, and HSP90) altered telomerase function and co-expression of long non-coding RNA (lncRNAs) with potential tumor suppressor might help naked mole rat to resist cancer

Animals with the Ability to Resist Cancer

Vertebrates

Longest Living Rodent

Naked Mole Rat The naked mole rat (*Heterocephalus glaber*) is the longest living rodent species with around 30 yrs of life expectancy and a small body mass (Tian et al. 2013) that inhabits the subterranean tunnel in East Africa. It is reported that the individual animals that live in captivity (e.g., Zoo) and live longer compared to the animals living in natural habitat. Delaney M. A. first reported cancer in a 20-yr and a 22-yr-old naked mole rats for the first time in animals living in the Zoo (Delaney et al. 2016) that might be the result of exposure to light and greater temperature ranges than in its natural environment as underground tem-

perature is constant. Loss of contact inhibition is a characteristic of in vitro-transformed cells (Pavel et al. 2018). The naked mole rat fibroblasts are reported to secrete five times larger high-molecular mass hyaluronan (HMM-HA) compared to the human or mouse, a possible mechanism of cancer resistance (Fig. 1). Similar role of HA was observed by knocking down *HAS2* or, overexpressing the HA-degrading enzyme *HYAL2* affecting increased susceptibility to malignant transformation (Tian et al. 2013). The reprogramming process of induced pluripotent stem cells (Blum and Benvenisty 2008; Folmes et al. 2011; Suvà et al. 2013) resembles malignant transformation that can be explained by stable epigenome of the naked mole rat that can resist reprogramming by Yamanaka factors (*Oct4*, *Sox2*, *Klf4*, and *Myc*) with low reprogramming efficiency, like mouse cells (Toole 2004).

Multiple factors for cancer resistance are understood in naked mole rat that are phenotypically unchanged since 30–50 million years ago, suggesting a high level of genomic stability (Bredberg and Schmitz 2019). Genome sequencing revealed the mechanism for longevity and physiology as a set of genes under selection viz., *APEX1*, *RFC1*, and proteins *TOP2A*, *TEP1*, and *TRF1* (Kim et al. 2011) directly bind to *BLM* helicase along with *HSP90* to form a five protein complex playing role in lengthening telomere pathway (Bhattacharyya et al. 2009). They also found elevated expression of *SMAD3* in the naked mole rat during aging that may optimize the rate of the cell death and protect against cancer. Together these molecular mechanisms may extend life span and impart cancer resistance of the naked mole rat (Kim et al. 2011). Somatic cells of naked mole rat contain additional p53/pRb-dependent mechanism for early contact inhibition (ECI) in fibroblasts; however, the replicative senescence is missing, which can control cell proliferation and ARF-dependant aging (Petruseva et al. 2017). The SV40 virus is known for its transformation activity. An independent study with RAS activation and SV40 Large-T failed to induce robust

anchorage-independent growth in the naked mole rat cells, while it readily transformed mouse fibroblasts (Seluanov et al. 2009).

In human or mouse, the contact inhibition mechanism is mainly regulated by *p27^{Kip1}*, while naked mole rat shows two-tier contact inhibition, an ECI mechanism which is regulated by *p16^{Ink4a}* which inhibits cells accumulation. Normally contact inhibition is controlled by *p27^{Kip1}*; whereas, in case of mutation or silencing of *p16^{Ink4a}* it may impart cancer resistance (Seluanov et al. 2009). The *INK4a/b* (*Cdkn2a-Cdkn2b*) locus is among the most frequently mutated in human cancers (Gu et al. 2015). This locus is a rapidly evolving one which contains three key tumor suppressor genes, encoding cyclin-dependent kinase inhibitors in human and mice *p15^{Ink4b}*, regulator of RB pathway *p16^{Ink4a}*, and *ARF* (alternate reading frame), a regulator for p53 pathway (Gu et al. 2015) (Sharpless and DePinho 2005). A novel transcript *pALT^{Ink4a/b}* is generated as a result of fusion between *p15^{Ink4b}* exon 1 and *p16^{Ink4a}* exon 2 and 3 in the process of alternative splicing in naked mole rat and acts as a potent CDK inhibitor, an additional

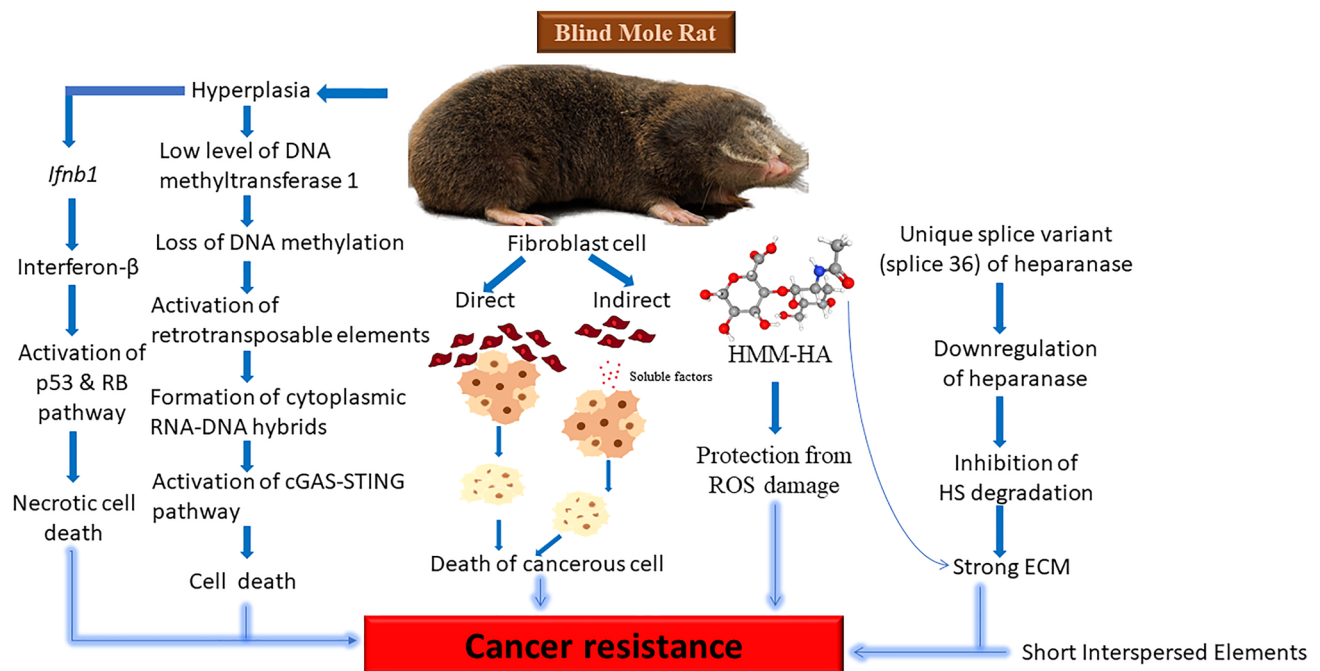


Figure. 2 Anticancer mechanisms in the blind mole rat. Blind mole rat also secretes HMM-HA but did not show early contact inhibition. However, it may contribute to protecting the cells from reactive oxygen species (ROS)-mediated damage. In vivo and in vitro experiments of blind mole rat fibroblast show that fibroblast can kill cancerous cells in two ways either through direct interaction or via secreting soluble factors. Expression of unique dominant splice variant of heparanase, together with HMM-HA, may contribute to stronger ECM and prevent tumor growth and metastasis. In response to hyperplasia cause by carcinogens in vivo or by hyperproliferative cells in vitro,

BMR cells secrete IFN- β that activates P53 and Rb pathway; as a result cancer cells die through necrotic and apoptotic mechanisms. Blind mole rat showed overexpression of Short Interspersed Elements (SINEs) which is linked to hypoxia tolerance and resistance to cancer as well as loss of DNA methylation triggers the upregulations of retrotransposable elements due to which cytoplasmic RNA–DNA hybrids occur that leads to activation of cGAS–STING pathway and resulted in cell death. All these together may lead to cancer resistance in BMR

mode of cell cycle control in the naked mole rat cells (Gu et al. 2015).

Blind Mole Rat The subterranean rodent, blind mole rat lives longer than mouse and rat, with a lifespan of around 21 yrs. (Edrey et al. 2012). It shows various mechanisms for cancer resistance which may hold cellular clues for effective treatments in humans. The underground habitat of blind mole rat is extremely hypoxic (up to 3% O₂) compared to on the ground. Adaptation to this environment could be by regression of some tissues, organs, and progression of others (Nevo 2007). The tumor suppressor genes control cellular response to variety of stress conditions like hypoxia and DNA damage leading to cell growth arrest and/or apoptosis. Inactivation of p53 is found in approximately 40–50% of human cancers which leads to tumor progression under hypoxic environment (Ashur-Fabian et al. 2004). Blind moles have evolved to survive under hypoxic conditions. The hypoxia-tolerant human tumors were found to have a *TP53* gene mutation Arg174Lys, which is also reported in blind mole rat suggesting more than 40 million yrs. of evolutionary adaptation to underground hypoxic life (Ashur-Fabian et al. 2004).

Heparanase is an endoglycosidase enzyme that degrades heparan sulfate (HS) at the cell surface and in the extracellular matrix (ECM), which is mainly expressed by aggressive cancer cells associated with metastasis and angiogenesis (Vlodavsky and Friedmann 2001). The cloning of a unique splice variant (splice 36 results from skipping part of exon 3, exons 4 and 5, and part of exon 6 and it functions as dominant negative) of heparanase downregulates the tumorigenic potential and inhibits its ability to degrade HS in the ECM (Nasser et al. 2009). The heparanase inhibiting strategies could be employed in the treatment of cancer (Fig. 2). The in vivo and in vitro study reveal resistance to chemical carcinogen that blind mole rat (*Spalax*). Fibroblasts isolated from normal *Spalax* have a unique ability to inhibit growth and to kill cancer cells, either through direct fibroblast–cancer cell interaction or via soluble factors, without affecting the normal cells. This was accompanied by decreased cancer cell viability, reduced colony formation in soft agar, disturbed cell cycle progression, chromatin condensation, and mitochondrial fragmentation (Manov et al. 2013).

An in vitro study of two different blind mole rat (*Spalax judaei* and *Spalax golani*) fibroblast cells showed cancer resistance by massive necrotic response to over proliferation mediated by P53 and Rb pathways triggered by the release of IFN- β (Gorbunova et al. 2012). Blind mole rat (*Spalax galili*) may have evolved a unique mechanism involving genes playing role in regulation of necrosis and inflammation like *Ifnb1*, *Mx1*, *Nfkb*, *Tnfrsf1*, *Birc3*, *Fem1b*, and *Aifm1* which underwent duplication

events compared to mouse, rat, and naked mole rat. Genes such as *Tnfrsf1a* and *Nfkb1* are also positively selected for necrosis and immunoinflammatory responses to partly replace apoptosis due to its remarkable hypoxia tolerance, cancer resistance, and aging (Fang et al. 2014). Role of these genes, mainly *Ifnb1*, is likely to be an effective compensatory mechanism to complement insufficient p53-mediated tumor suppression in blind mole rat. High rates of RNA/DNA editing, reduced chromosome rearrangements, an over-representation of short interspersed elements (SINEs) probably linked to hypoxia & hypercapnia tolerance, degeneration of vision, and progression of photoperiodic perception and resistance to cancer have been reported (Fang et al. 2014).

The mode of cancer resistance in in vitro study of *Spalax carmeli* fibroblasts was found to be due to various stress responses: 1) oxidative stress treatment (serum free medium containing H₂O₂); 2) topoisomerase inhibition (medium containing etoposide dissolved in DMSO), and 3) DNA damage using UV-C radiation given at doses from 2000 to 8000 jm⁻² using UV-C-500 cross-linker instrument (Domankevich et al. 2018). Their results showed that the DNA repair capacity was five times more active in *S. carmeli* than in rat, for the H₂O₂-induced lesions. There was also significant difference in viability following etoposide treatment and repair capacity of UV-C induced lesions, suggesting role of nucleotide excision repair and base excision repair pathways. Other DNA repair pathways, like the DSBs and cross-links, for example, the homologous recombination and Fanconi anemia (FA) pathways may also be involved.

Cytosolic DNA sensing, the cyclic GMP-AMP synthase stimulator of interferon genes (cGAS-STING) pathway has a novel role in the immune system to respond to infection, inflammation, and cancer (Burdette and Vance 2013; Dhanwani et al. 2018). It is a candidate pathway for cancer immunotherapy as many STING agonists were developed with satisfactory results in preclinical study (Jiang et al. 2020). Recent study reported retro-transposable elements (RTEs)-mediated cancer resistance in blind mole rat which showed very low level of DNA methyltransferase-1 and reduced DNA methylation in hyperplasia which activate RTEs. Further, upregulation of RTEs resulted in cytoplasmic RNA–DNA hybrids, which activate the cGAS-STING pathway inducing cell death. Thus, tumor suppressor function of RTEs is an important cancer resistance mechanism in blind mole rat (Zhao et al. 2021).

Largest and Longest Living Mammal on Land: Elephant

The elephant is one of the largest living land mammals and shows cancer resistance. Peto R. speculated a biological mechanism in case of large, long-lived mammals for

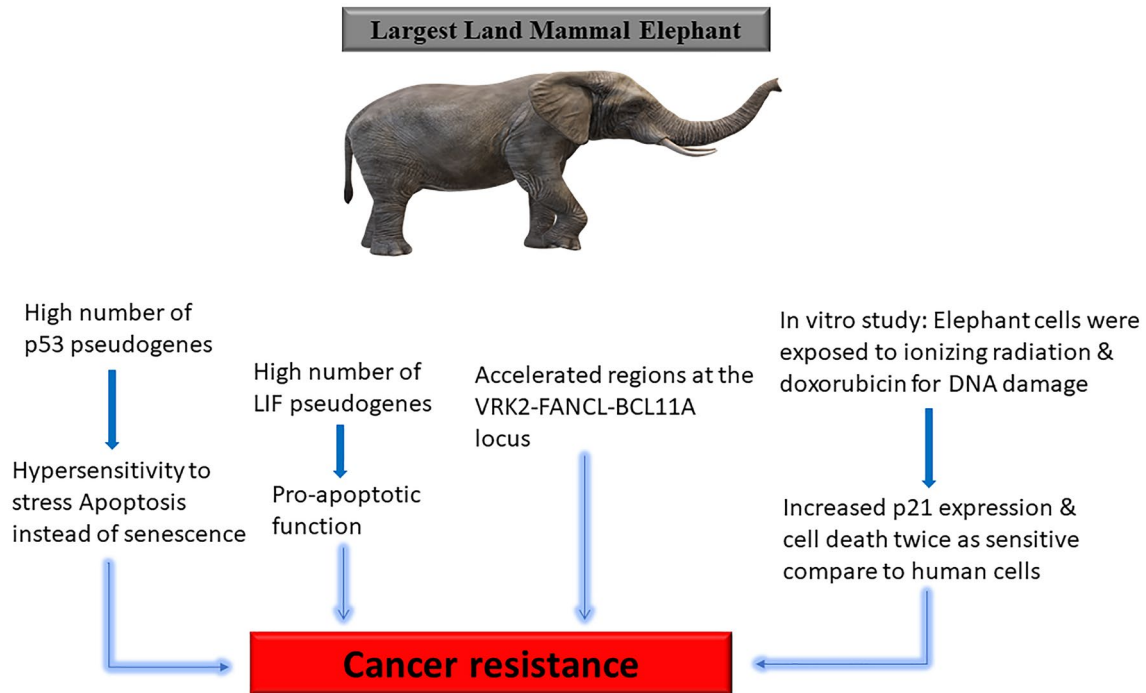


Figure. 3 Anticancer mechanisms in the Elephant. Elephants are the largest living land mammal. They have 19 copies of *TP53* gene, likely to prevent cancer formation as in vitro study using elephant cells exposed to various doses of Ionizing radiation and doxorubicin drug shows increased expression of p21 twice as higher sensitivity to DNA damage-induced apoptosis compare to human cells. It was also

shown that elephant genome comprises Accelerated regions uniquely enriched at the VRK2-FANCL-BCL11A locus for shaping mammalian mutation and cancer resistance phenotype. Elephant also have 11 copies of *LIF* among *LIF6* which is upregulated by *TP53* in response to DNA damage. Together *TP53* and *LIF* might be protecting elephant from acquiring cancer despite the larger size

avoiding cancer-causing somatic mutations protecting them from cancer (Caulin and Maley 2011; Peto et al. 1975; Tollis et al. 2017). Two independent studies report extra copies of the gene *TP53* in elephants that might help to avoid cell transformation (Abegglen et al. 2015; Sulak et al. 2016). The gene *TP53* rightly called master guardian of the genome is known to play a central role in cancer suppression as it gets activated when DNA damage takes place. P53 protein plays a role in DNA repair, cell cycle arrest, and apoptosis (Abegglen et al. 2015; Callaway 2015). Inactivation or mutation in p53 facilitates three major hallmarks of cancer cells viz., suppression of apoptosis, increased proliferation, and genomic instability (Hanahan 2022; Hanahan and Weinberg 2000, 2011; Lane 1992). Compared with one pair in humans and other mammals, the 19 copies of *TP53* retrogenes in elephants originated by segmental duplication and drift serve as a stronger barrier against neoplastic cell proliferation (Fig. 3). The presence of numerous copies of the *TP53* retrogene in elephants needs to be further substantiated before being cited as a classic example of tumor suppression in large-bodied animals, according to (Nunney 2022), who notes that study does not indicate a direct (via conserved *TP53* activity) or indirect (via supporting canonical *TP53* function) role of retrogene sequences.

A study lead by Schiffman J. D. shows that elephant cells exposed to DNA damage had increased p21 expression (a downstream target of p53 activation) and increased cell death which was twice as sensitive to DNA damage-induced apoptosis as compared to human cells. The increased cell death in the elephant may be a p53 driven process, further enhanced by the additional *TP53* retrogenes (Abegglen et al. 2015). However, it remains unclear which *TP53* retrogene loci code for functional genes and which code for pseudogenes. Another study showed the expression of *TP53RTG12*, *TP53RTG 18/19*, and *TP53RTG13* in the dermal fibroblasts of the elephant using RNA-Sequencing and RT-PCR/ Sanger sequencing (Sulak et al. 2016). A team lead by (Abegglen et al. 2015) show two distinct transcripts by RT-PCR and Sanger sequencing from elephant PBMC; however, the transcript loci was not assigned. However, Schiffman J. D. et al. when analyzed the chromatograms shown in Abegglen et al. 2015 Fig. 4 found that 185-bp and 201-bp products likely to be from the transcripts *TP53RTG14* and *TP53RTG5*, respectively. However, they did not observe these retrogenes in adipose, placenta, or fibroblasts suggesting tissue-specific expression of some *TP53RTG* genes. Thus, their combined data suggest that at least five *TP53RTG* genes are transcribed.

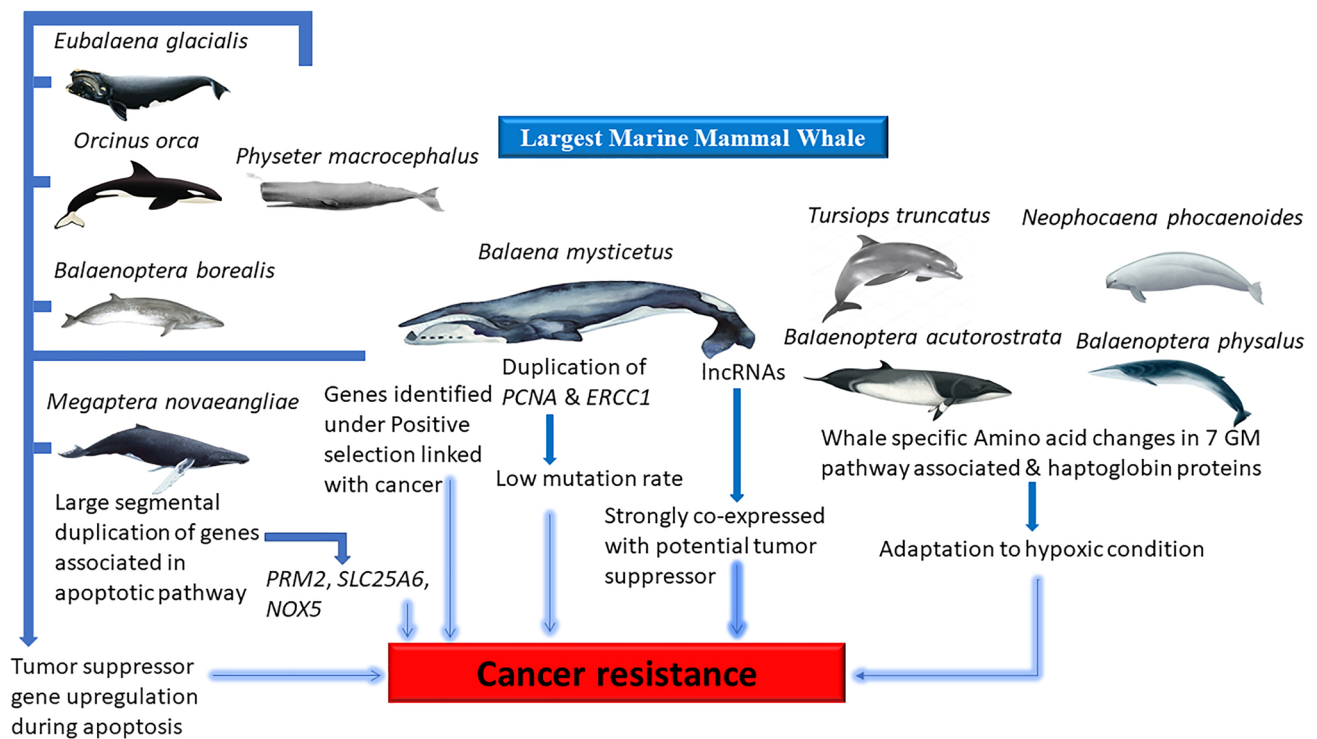


Figure. 4 Anticancer mechanisms in the whale. Whales are the largest living marine mammal with longer lifespan. Despite having largest body, very few cases of cancer found in whales and most of them due to environmental factors. Genomic study in bowhead whale identifies several genes under positive selection that are linked with cancer as well as copy number gains and losses in genes associated with cancer and aging that are involved in DNA damage repair. Further, lncRNAs strongly co-expressed with tumor suppressor likely to help Bowhead whale to avoid cancer. Minke whale genomic study reveals

cetacean-specific amino acid changes in 7 glutathione metabolism pathway-associated genes and heptoglobin proteins which indicating adaptation to hypoxic condition. Another comparative analysis study of Humpback whale genome with other ten cetaceans identified large segmental duplication of genes associated with apoptosis pathway as well as upregulation of tumor suppressor gene during apoptosis. All these together suggest that whales evolved with various unique characteristics that might help them to resist cancer

A comparative genomic analysis of Accelerated regions (ARs) in species with distinctive traits could facilitate identification of conserved functional elements that play important roles, e.g., adaptations to different environments, acquiring physiological, anatomical, and other biomedically important traits, such as mutations and cancer resistance in elephants (Ferris et al. 2018). The elephant ARs were found to be enriched at the VRK2-FANCL-BCL11A locus and at genes that respond to DNA damage in elephant blood cells. These are important candidate genetic elements affecting mammalian mutation and cancer resistance phenotype. *TP53* is not the only factor protecting elephants against cancer as another study in elephant and their extinct relatives resolved Peto's paradox. They report re-functionalizing of a leukemia inhibitory factor (*LIF*; 11 extra copies) pseudogene with pro-apoptotic functions (Callier 2019). One of the copies of *LIF6* is transcribed at a very low level under basal conditions but is upregulated by *TP53* in response to DNA damage (Vazquez et al. 2018). Their experiments suggested that the *LIF* functions in a manner analogous to the pro-apoptotic *BCL-2* family members by inducing the opening of the

outer mitochondrial membrane pore through interaction with membrane-bound BAK/BAX protein. These together suggest that extra copies of *TP53* and *LIF* in the elephants may have synergistic role to protect against cancer in an evolutionary process; however, more studies are required.

Largest and Longest Living Marine Mammal: Whale

The largest and longest living aquatic mammal whales differ in length, weight, and lifespan among different species. The Blue whale can grow up to 33 m in length and weigh more than 181 tonnes (McClain et al. 2015). Bowhead whale is the only whale known to live for more than 150 to 200 yrs. Lifespan of 211 yrs. has been reported in a Bowhead whale using Aspartic acid racemization technique (George et al. 1999). A study in 2019 reported age of a living Bowhead whale to be 268 yrs. They hypothesised that aging is associated with epigenetic changes involving DNA methylation mainly at CpG sites in promoters that are targets of DNA methylation associated with lifespan. This study reported

accurate lifespan clock in vertebrates based on CpG islands density in selected 42 promoters (Mayne et al. 2019).

The whales can be expected to have increased mutation rates due to thousand times higher number of cells and longer lifespan than any other owing to increased cell division events. However, cancer rates reported in whale have been controversial. A case study in Beluga whale at St. Lawrence Estuary reported 18% death due to cancer in 263 examined Beluga whales. Other cetaceans including Pilot whale, Fin whale, Killer whale, Blue whale, Pigmy sperm whale, and different species of dolphins and porpoise were found to have various forms of cancer which might be due to agricultural and industrial pollution of the estuary; whereas, cancer was rare among beluga whale in the Beaufort Sea (Martineau et al. 1994, 2002). These suggest that cancer incidence does not correlate with the body size, and external factors might be playing role.

The primary cancer can metastasize to a distant site, the specificity of which is explained in seed and soil theory. In larger organisms, longer time can be required for the tumor to reach lethal stage, and in the process hyper-tumor can evolve. The cancer metastasis is also considered an evolutionary adaptation against competition of resources within a growing tumor (Nagy 2005). It was also hypothesized that the natural selection is acting on the competing phenotypes of neoplastic cell population which tend to favor aggressive “cheaters” that grow on their parent tumor, creating a hyper-tumor that outgrows the original neoplasm (Nagy et al. 2007). The *in silico* hyper-tumor model illustrated this hypothesis which showed that malignant neoplasms in larger organisms should be disproportionately necrotic, aggressive, and vascularized than the similar deadly tumors in small mammals. Deeper studies of metastasis patterns in varied sizes of mammals can be of great interest.

Marine mammals are deep divers spending more time at deeper level of ocean except during the feed time close to the surface where density of prey is higher in photic zone compared to the deeper areas. Their locomotor muscles have a major contributors to total muscle O₂ stores due to their high myoglobin concentration and large muscle mass (Arregui et al. 2021). However, deep diving increases the risk of cellular stress such as hypoxia, oxidative, and osmotic stress induced by the level of O-Linked N-acetylglucosaminylation (O-GlcNAcylation) in numerous nucleo-cytoplasmic proteins (Jones et al. 2008; Ngoh et al. 2011; Zachara et al. 2004). Under hypoxic conditions the reactive oxygen species are generated by several cellular mechanisms that can induce cellular damage (Blokina et al. 2003; Gonchar and Mankovska 2010). Hypoxia and reactive oxygen species can act as dual-edge sword able to serve as a foe as well as a friend. Cancer cells adapt to survive in hypoxic condition as well as against accumulated reactive oxygen species.

The ability to sense and respond to changes in oxygen levels is crucial for the survival of prokaryotic and eukaryotic organisms. It helps to maintain cell and tissue homeostasis, as well as to adapt to the chronic hypoxic conditions, systemically or localized, as in the case of cancer. The proteomic and genomic changes induced by hypoxic conditions within tumor cells can lead to cell cycle arrest, necrosis, and apoptosis (Lee and Lin 2013). The hypoxia-induced proteomic changes may also stimulate tumor growth, invasion, and metastasis by facilitating the acclimatization and survival in unsupportive, nutrient-deprived environment (Vaupel and Harrison 2004). Overall, hypoxia-activating transcriptional programs involving HIF, NFκB, PI3k, and MAPK pathways control each steps of cancer-adaptive processes and contributes to EMT-like cancer cell migration and cancer stem cell-like properties, including resistance to treatment (Muz et al. 2015). The treatment targeting hypoxia might be relevant to overcome hypoxia-associated therapy resistance in cancer (Jing et al. 2019). Thus, hypoxia and the miscoupling between the increased uptake of nutrients triggered by reduced energy efficiency, and cell proliferation signaling induced by increased accumulation of nutrients serve as driving force for the cancer growth (Cui et al. 2012).

Adaptation of tumor cells at a molecular level to hypoxic stress is largely regulated by hypoxia-inducible factor (HIF), a transcription factor which accumulates in response to decreased cellular oxygen levels (Schito and Rey 2017; Wolff et al. 2017). The HIF stimulates neovascularisation to improve oxygen delivery via accumulation of vascular endothelial growth factor (VEGF), hence HIF and VEGF are promising targets for using inhibitors to fight cancer (Akanji et al. 2019; Choueiri and Kaelin 2020). However, it is recently reported that VEGF targeting reduces primary tumor size but leads to intra-tumor hypoxia, resulting in a cell–cell junction upregulation that form circulating tumor cell (CTC) clusters that show intravasation and metastasis. It was concluded that the pro-angiogenic therapy with EpB2 reduces hypoxia and suppresses metastasis formation through prevention of CTC clusters generation (Donato et al. 2020).

The role of ROS generated as a by-product of hypoxic cellular metabolism has long been associated with cancer. A neutral balance in redox processes is a must to maintain physiological homeostasis of normal metabolically active cells. A moderate level of ROS plays a substantial role in signaling cascade to induce tumorigenesis, tumor promulgation, metastasis and survival (Kumari et al. 2018). Whereas, with tumor progression the higher ROS levels induce apoptosis and cellular damage (Assi 2017; Raza et al. 2017). The failure in effective neutralization of cellular ROS can lead to transition of normal cells into cancerous cells through various signaling pathways viz., PI3/Akt/mTOR/

PTEN/MAPK/VEGF/VEGFR and MMPs (Aggarwal et al. 2019). The double-edge sword effect by ROS provides an opportunity for cancer therapeutics. Rising evidences for dual role of ROS suggest that antitumor therapy may use dietary antioxidants to reduce ROS formation thus preventing carcinogenesis or use chemical agents like phytochemicals that promote a sudden increase in ROS which can cause oxidative stress in tumor mass (de Sá Junior et al. 2017).

Glutathione is a widely studied antioxidant involved in protection of cells from ROS; both directly and as a cofactor of glutathione peroxidases (Pompella and Corti 2015; Pompella et al. 2003). A study conducted on glutathione metabolism pathway (GMP) showed cetacean-specific amino acid changes in seven GMP (*GPX2*, *ODCI*, *GSR*, *GGT6*, *GGT7*, *GGLC*, and *ANPEP*) genes and these changes were present in four minke whale, a fin whale and two bottlenose dolphin and porpoise (Yim et al. 2014). It is known that increased expression of GSR increase antioxidant capacity of cells (Foyer et al. 1995). The first deep-sequenced genome of marine mammal as reference, the minke whale revealed expansion of antioxidant-related genes. The whale-specific variations in glutathione-associated and haptoglobin proteins indicate adaptation to hypoxic condition during the deep diving (Yim et al. 2014) and support their hypothesis regarding adaptation for metabolism under low-oxygen and high-salt conditions and development of unique morphological traits (Fig. 4). This might be a reason for low cancer incidence in large marine mammals. More studies are required to support this hypothesis.

The first genome-wide transcriptome of the Bowhead whale based on de novo assembly identified genes under positive selection linked to cancer; mitochondrial tumor suppressor 1 (*Mtus1*); glycogen synthase kinase 3 alpha (*Gsk3a*); and prune exopolyphosphatase (*Prune*), which act in concert to regulate cell migration; cytoplasmic FMR1-interacting protein 1 (*Cyfi1*); and genes involved in insulin signaling (Seim et al. 2014). Another genomic and transcriptomic study in bowhead whale reports copy number gains and losses in genes associated with cancer and aging and remarkably a duplication in the proliferating cell nuclear antigen (*PCNA*) and excision repair cross-complementation group 1 (*ERCC1*) which encodes a DNA repair protein (Keane et al. 2015). Unlike elephant, in spite of having a higher number of cells, the whale does not have extra copies of *TP53* gene. The *ERCC1* and *PCNA1* proteins that are involved in DNA damage repair might be protecting the whale from cancer by lowering mutation rate or by decreasing cell proliferation as in aged rat liver (Tanno et al. 1996).

A comparative analysis of humpback whales de novo genome assembly with the genomes of ten cetacean species identified large segmental duplications (LSDs) in whale

genome that contained genes (*PRMT2*, *SLC25A6*, and *NOX5*, specifically in humpback whale) controlling the apoptotic pathway. The study showed that the genes under accelerated evolution and positive selection in cetaceans were enriched for biological processes, like cell cycle checkpoint, cell signaling, and proliferation, in case of tumor suppressor genes. Tumor suppressor genes include *SALL4* in the Sei whale, *TGM3* and *SEMA3B* in the orca, *UVRAG* in the sperm whale, North Atlantic right whale, and bowhead whale; and *PDCD5* in humpback whale which is upregulated during apoptosis (Tollis et al. 2019). A single copy of *PDCD5* in humpback whale and 3 and 2 annotated copies of *SALL4* and *UVRAG* were observed, respectively, in its skin.

These genomic studies suggest that larger animals have evolved compensatory adaptations to cope up with the negative effects of the huge number of cell divisions and the subsequent cancer risk. Another illustration can be seen in ruminants, the only extant mammalian group possessing bony headgear having extremely rapid growth rate (Davis et al. 2011) and with rapid growth, risk of cancer come handy. According to research from (Wang et al. 2019), fast-growing cervid antlers show expression profiles that are more comparable to those of osteosarcoma than those of healthy bone tissues. On the other hand, cervids have a much lower incidence of cancer than other mammals (Griner 1983; Lombard and Witte 1959), which may be due to effective cancer-defensive mechanisms with positive selection of genes (*PML*, *NMT2*, *CD2AP*, *ELOVL6*, *S100A8*, *ISG15*, and *CCDC69*) functioning in the p53 pathway reveals the genetic mechanisms underlying the evolutionary, developmental, and histological origins of pecoran headgear and provides insight into the molecular mechanisms of regeneration of deer antler and its relevance to cancer resistance (Wang et al. 2019).

In addition to reports regarding association of protein coding genes with cancer resistance in long-live mammals, the role of epigenetic factors like long non-coding RNAs (lncRNAs) remains largely unknown. A study in longest living mammal like Bowhead whale (BW) and Brandt's bat (BB) identified lncRNAs to correlate with cancer resistance. Thousands of BB and BW lncRNAs are strongly co-expressed, with potential tumor suppressor function, probably involved in the anticancer regulation in long-lived mammals (Jiang and Kong 2020).

Only Mammal with Flying Ability: Bat

Bats are the sole flying mammals with small size and longer lifespan of 7 to 42 yrs. There are around 1100 species of bats accounting almost one-fourth of all mammal species (Jiang and Kong 2020). However, only a few cases of tumors have ever been described in bats (Bradford et al. 2010; McLelland

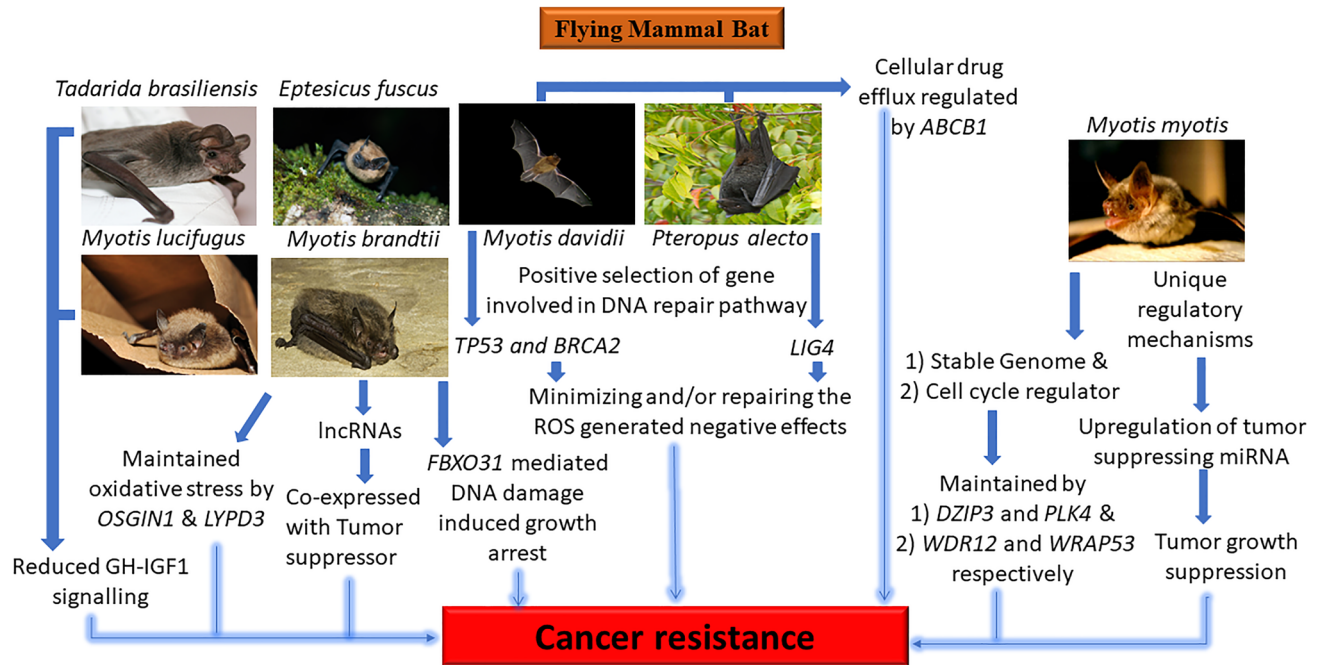


Figure. 5 Anticancer mechanisms in the Bat. Bats comprise the one-fourth part of all the mammal species. Bat like *M. davidii* and *P. alecto* minimizing and/or repairing the ROS generated negative effects mediated through *TP53*, *BRCA2*, and *LIG4*, respectively, which may lead to cancer resistance. In vitro study of cells derived from *M. davidii* and *P. alecto* to find the drug efflux role of *ABCB1* shows that these cells effectively transport the drug out of the cellular system and that may suggest the role of *ABCB1* acquiring cancer resistance toward chemicals that are carcinogenic in nature. Long-eared bat (*M. myotis*) have unique regulatory mechanism which

involved upregulation of miRNA likely to function as tumor suppressor. *M. myotis* also have stable genome and anticancer activity, respectively, maintained by (*DZIP3* and *PLK4*) and (*WDR12* and *WRAP53*). *FBXO31* protein in *M. brandtii* involved in DNA damage-induced growth arrest and maintenance of oxidative stress by genes like *OSGIN1* and *LYPD3* as well as IncRNAs strongly associated with potential tumor suppressor may lead to cancer resistance. Reduced signaling of GH-IGF1 in four different bats *M. brandtii*, *M. lucifugus*, *E. fuscus*, and *T. brasiliensis* may be responsible for cancer resistance

et al. 2009; Siegal-Willott et al. 2007). Bats require more energy to fly which increase the metabolic rate and fluctuation in body temperature. High metabolic rates tend to generate high ROS levels and this oxidative stress can damage the mitochondria and DNA. However, bat mitochondrial function seems to have evolved the ability to reduce the ROS levels through forming autophagosomes to get rid of the damaged mitochondria for cell survival. This can increase the lifespan as inducing apoptosis signal when high ROS level present for apoptotic necrobiosis. A review comprising last few decades studies on mitochondrial role, it suggests that these organelles might be responsible for tumor resistance as well as pathogen control in the bats (Brook and Dobson 2015). A pioneering study reported that Blood miRNomes and transcriptomes in *Myotis myotis* (mouse-eared bat) may possess unique regulatory mechanisms for resisting tumorigenesis and repairing cellular damage and to mitigate oxidative stresses (Huang et al. 2016). A genome-wide comparative analyses were conducted between the bat *M. myotis* and non-bat mammals (human, pig, and cow), in both blood miRNomes and transcriptomes deep sequence, including 246.5 million small RNA reads. In the case of

bats, 3 out of 4 upregulated miRNAs (miR-101-3p, miR-16-5p, miR-143-3p) were likely to function as tumor suppressor against various kinds of cancer, while a downregulated miRNA (miR-221-5p) was a tumorigenesis promoter in human breast and pancreatic cancers (Fig. 5).

Comparative analysis of two bat genomes viz., *Myotis davidii* and *Pteropus alecto* suggested that genes in the DNA damage checkpoint DNA repair pathway like *ATM*, *DNA-PKc*, *RAD50*, *KU80*, and *MDM2* were under positive selection. The *TP53* and *BRCA2* were under positive selection in *M. Davidii*, and *LIG4* was positively selected in *P. Alecto*. These genes were directly related to minimizing and/or repairing the ROS generated negative effects as a consequence of flight (Zhang et al. 2013). Another comparative study of transcriptomes between *M. myotis* and 3 other species like *Homo sapiens* (human), *Mus musculus* (mouse), and *Canis lupus* (wolf) revealed a transcriptomic signature of bat aging after network analysis, showing that genes related to DNA repair pathway, similar to the mammalian DNA repair pathway ones. When they conducted longitudinal age-related signatures across mammals, they found that age-correlated genes were mainly

related to the maintenance of genome stability (*DZIP3* and *PLK4*) and anticancer activity (*WDR12* and *WRAP53*) in *M. myotis* and the majority of these have not been associated directly with aging in humans or model species (Huang et al. 2019). From these data it can be suggested that similar kind of studies in another bat species can decipher more about the bat longevity and cancer resistance.

Genome analysis of *Myotis brandtii* syntenic regions reveals that *M. brandtii* has five copies of *FBXO31* that encode for a protein, which mediates DNA damage-induced growth arrest by targeting CDK1 for ubiquitin-mediated degradation and suggests additional possible 52 copies of *FBXO31* in the *M. brandtii* genome (Seim et al. 2013). They also observed that the genes *OSGIN1* and *LYPD3* were involved in the maintenance of oxidative stress. The role of *OSGIN1* as a tumor suppressor is observable in human kidney (Ong et al. 2004), liver (Liu et al. 2014), airway epithelium (Wang et al. 2017), and astrocytes (Brennan et al. 2017). Insensitivity of growth hormone (GH) was envired by an extent of genomic abnormalities of GH-insulin like growth factor-1 (IGF1). It has been shown that mutations in the single transmembrane receptor GHR, including the transmembrane domain-coding exon 8, resulted in human Laron-type dwarfism (short-stature), a subtype of GH insensitivity (David et al. 2011). It was evident that GHR mutations or GH signaling deficiencies including those associated with Laron-type dwarfism have been associated with increased resistance to cancer and diabetes in humans (Guevara-Aguirre et al. 2011) and mice (Coschigano et al. 2000; Ikeno et al. 2009). Seim I. and team members found that Leu284 in the transmembrane domain of GHR, which is highly conserved in tetrapods, is deleted in *M. brandtii*, *M. lucifugus*, as well as in two other echolocating bat species, the big brown bat (*Eptesicus fuscus*) and the Mexican free-tailed bat (*Tadarida brasiliensis*) (Seim et al. 2013). Therefore, these data suggest that reduced GH-IGF1 signaling may be responsible for cancer resistance in long-lived bats.

As all living species grow old in terms of cellular division, cells at certain point acquire aging and that can be led by telomere shortening, which resulted in replicative senescence, differentiation, or apoptosis and these can be act as tumor suppressor. However, cancer cells avoid this fate through upregulating of the enzyme of telomerase, which extends telomeres, or by activating a mechanism termed alternative lengthening of telomeres (ALT), which is based on a common method of DNA repair, homologous recombination (Roake and Artandi 2016). It appears as the relationship between telomere length and cancer risk is likely nonlinear with evidence showing that both too long and too short telomeres can be associated with increased cancer risk (Ujvari et al. 2022). Transcriptome study of telomere in various bat blood reveal that telomeres shorten

with age in *Rhinolophus ferrumequinum* (horseshoe bat) and *Miniopterus schreibersii* (common bent-wing bat), but not in the bat genus with the greatest longevity, *Myotis* (Foley et al. 2018). They found that 21 telomere maintenance genes that are differentially expressed in *Myotis*, of which 14 are related to DNA repair and 5 with alternative telomere-lengthening mechanisms. Their data suggest that affected DNA repair, controlled regulation, and maintenance of telomere mediated by the DNA repair genes *ATM* and *SETX* contributed to the evolution of exceptional longevity in *M. myotis* and this may be responsible for bat resistance toward cancer and also for longer life span compare to their size.

ATP-Binding Cassette (ABC) protein like ABCB1 (ABC subfamily B member 1) is well known for regulation of cellular drug efflux (Robey et al. 2018) specially expressed in region of detoxification, excretion, and protective barriers, such as the intestinal epithelium, lumens of the liver, proximal tubule of the kidney, as well as blood-tissue barriers of the brain (Kathawala et al. 2015). It was originally discovered in cancer cells where its high and functional expression promotes resistance to variety of chemotherapeutic drugs, such as paclitaxel, vinblastine, etoposide, and doxorubicin, responsible for one of the major causes of cancer relapse (Kathawala et al. 2015; Robey et al. 2018; Ueda et al. 1987). In a study using a bat-derived cell line (*M. myotis* and *P. alecto*) for finding the drug efflux role of ABCB1 protein, in the presence of various genotoxic drugs, reveal that ABCB1 effectively transports the drug out of the cellular system and toxic drugs cause less damage in bat cells compare to human cells (Koh et al. 2019). Also, when they inhibited ABCB1 in bat cells, it triggered an accumulation of doxorubicin, DNA damage, as well as cell death, suggesting a protective role of ABCB1 toward genotoxic drugs that induce DNA damage.

Invertebrates

Previously, it was thought that animals of lower evolutionary scale than fishes, they could not acquire tumors (Teutschlaender 1920), and the reason why invertebrates are incapable of developing cancer was thoroughly explained by (Engel 1930). Indeed, a meticulous review published in the middle of the nineteenth century by (Scharrer and Lochhead 1950) offers insights on the evidence of neoplastic growth studies in a number of invertebrate phyla, and tumors of either epithelia or connective tissue origin have been reported in annelids, sipunculids, arthropods, molluscs, and ascidians. These tumors can be classified as spontaneous growths, hereditary, or of other factors like parasites, endocrine imbalance, and disturbance of innervation, as well as chemical carcinogen and radiation in case of experimental studies on insects and molluscs (Tascedda and Ottaviani 2014). Aktipis C. A. and group members searched

for cancer in all lineages containing multicellular organisms and found cancer or cancer-like diseases in all but 5 lineages: Choanoflagellata, Ctenophora and Placozoa, Porifera, and Hemicordata (Aktipis et al. 2015).

According to the study of two distinct species of Hydra revealed that the cellular and molecular characteristics of their tumor cells seem to share some similarities with the previously described hallmarks of cancer cells in vertebrates, and the proposed mechanism for tumorigenesis is the accumulation of stem cells that are not properly removed by programmed cell death (Domazet-Lošo et al. 2014). This indicates that even pre-bilaterian cnidarians can develop naturally occurring tumors. Numerous anthropogenic stressors, including local ones like poor water quality (Baker et al. 2007; Bruno et al. 2003; Kim and Harvell 2002; Kuta and Richardson 2002; Voss and Richardson 2006; Williams et al. 2010), as well as global ones like abnormal sea surface temperatures (Bruno et al. 2007), increased the prevalence of various diseases in coral among cnidarians, which led to coral bleaching (Brandt and McManus 2009; Harvell et al. 2001; McClanahan et al. 2009; Muller et al. 2008). Growth anomalies or tumor-like diseases, which were also detected in two coral genera, *Acropora* and *Porites*, were widespread throughout the Indo-Pacific, appearing in eleven of the thirteen study regions that is strongly associated with host density and human population size (Aeby et al. 2011).

On the contrary arm, planarians and placozoans have been discovered to be cancer resistant. There have been no reports of placozoan cancer or any that have yet to be found, as radiation (X-ray) study on *Trichoplax adhaerens* showed tolerating high levels of radiation damage (218.6 Gy), with the aid of overexpression of genes involved in DNA repair and apoptosis (e.g., MDM2) and also able to extrude clusters of inviable cells after X-ray exposures (Fortunato et al. 2021). Planarians are a perfect model to investigate proliferation, mutagenicity, and cancer because of their long-known capacity for regeneration, which hinges on pluripotency. *Smed-MmpB* is a planarian tumor suppressor gene that prevents stem cells from proliferating and differentiating to create tumors outside the appropriate milieu, according to an investigation employing *CDC12* on *Schmidtea mediterranea* to explore the function of tumor suppressor genes (Van Roten et al. 2018).

The *Drosophila* genus of flies, one of the most well-studied groups of invertebrates, serves as a model organism for genetic analysis of many aspects of developmental biology, including cell migration (Jang et al. 2007) as well as in understanding the role of tumor suppressor genes in how cell and tissue growth are coordinated during organismal development and perturbed in disease states, like cancer (Hariharan and Bilder 2006). The most common tumors in this species are those of the lymph glands (which have hematopoietic function in *Drosophila*) and of

hematocytes (Scharrer and Lochhead 1950). Molluscs and their hematopoietic tumors are another excellent example from the invertebrates (Leavitt et al. 1990; Odintsova et al. 2011). In mussel *Mytilus trossulus*, cells that make up these malignant hematocytes overexpress the gene of heat shock protein 70, which codes for a protein that deactivates the tumor suppressor *TP53* (Muttray et al. 2010), making the molluscs an emerging animal model for human cancer displaying a mortalin-based phenotype (De Vico and Carella 2015; Walker et al. 2009). The signal transduction pathways that control differentiation and cell proliferation are being revealed by genetic studies in other invertebrates, such as nematodes (*Caenorhabditis elegans*), *Drosophila*, and yeast. Important molecules involved in these pathways are homologous to proto-oncogenes, and others are likely to be analogous to the products of tumor suppressor genes (Hoffmann et al. 1992). In fact, the mammalian homologs of genes identified through invertebrate genetics may also offer fresh perspectives and scientific tools to comprehend the molecular underpinnings of cancer.

In terms of vertebrates, transmissible or contagious cancer is uncommon, with the majority of cases being two in Tasmanian Devils (Loh et al. 2006; Pearse et al. 2012; Pye et al. 2016) and one in dogs (Ganguly et al. 2016), whereas there is a wealth of evidence revealing that it may be common in invertebrates (six out of six species of bivalve) (Burioli et al. 2021; Garcia-Souto et al. 2022; Hammel et al. 2022; Metzger and Goff 2016; Metzger et al. 2015, 2016; Skazina et al. 2021; Ujvari et al. 2017; Yonemitsu et al. 2019). A fascinating and understudied host–pathogen system with important ecological and evolutionary implications is the transmission of cancer cells across individuals. According to (Dujon et al. 2020) only nine transmissible cancer lineages in eight host species, from both terrestrial and marine environments (mammals and bivalves; Dujon et al. 2021b; Ujvari et al. 2017)), have been investigated. They discuss the prerequisites and necessary conditions for cancer transmission and give a thorough analysis of the evolutionary dynamics between transmissible cancers and their hosts.

Human activities significantly increased oncogenic pressures on ecosystems (Acevedo-Whitehouse and Duffus 2009; Giraudeau et al. 2018b; Pesavento et al. 2018). Tumor-bearing individuals frequently have amended interactions with other individuals or species present in the ecosystem (e.g., predator–prey interactions, host–parasite interactions, and/or intra- and interspecific competition Boutry et al. 2022a, 2022b; Comte et al. 2020; Cunningham et al. 2018; Hollings et al. 2014). Understanding the effects of cancer on species and ecosystems remains a key question to answer in order to mitigate their consequences on biodiversity and ecosystems functioning (Dujon et al. 2021a; Hamede et al. 2020; Hochberg and Noble 2017; Vittecoq et al. 2013).

At last, invertebrate species have the potential to provide novel and unprecedented information on the significance of oncogenic processes in animal evolutionary ecology. Tumors can be induced in invertebrates for studying the effects of cancer on individuals that possess the disease on their movement, reproduction, feeding behaviors, social interactions, holobiont, and predation risk (Dujon et al. 2022b).

Multicellular Eukaryote that Rarely Get Cancer: Plant

Among multicellular eukaryotes, the plants are also not free from tumor although rare as compared to human. Plant tumors have more than a century of research history. There are mainly two types of plants tumors: pathogen-induced tumors (bacteria, viruses, fungi, insects, etc.) and spontaneous form of tumors that are mainly due to altered genotypes (e.g., interspecific hybrids, inbred lines, and mutants) (Dodueva et al. 2020). The first ever documented evidence of a pathogen-induced plant tumor is a crown gall caused by *Agrobacterium* reported by (Smith and Townsend 1907). The first spontaneous plant tumor was reported in a tobacco interspecific hybrid by (Kostoff 1930). The plant tumor studies have led to many important discoveries including the agrobacterial transformation (Chilton et al. 1977), the ability of certain pathogens to synthesize plant growth regulators (Garfinkel et al. 1981; Wang et al. 2001), and horizontal gene transfer from bacteria to plants (Furner et al. 1986).

The plants are more “resistant” to tumor formation than animals. Excepting pathogen-induced tumors, the spontaneous tumor induction is very rare. The disruption of stem cell maintenance or deregulation in mitogenic signals (Doonan and Sablowski 2010; Ullrich et al. 2019) change in balance of the key component of cell cycle like Indole Acetic Acid and Cytokinin in plants and the upregulation of meristem-specific regulators play a role in plant tumors (Dodueva et al. 2020). There is significant difference in plants and animals’ tumor formation; however, both exhibit similarity in hyperplasia (increased cell numbers), hypertrophy (increased tissue size), reduced cell differentiation, pronounced cellular atypia, and a high level of vascularization (Ullrich and Aloni 2000).

Plant tumors can develop on leaves, stems, roots, and floral organs and may exhibit different degrees of cell differentiation (Ahuja 1998). There are individual guidelines for animal and human tumor grading and staging, while plant tumor can be distinguished in two categories: (i) tumors with indeterminate, i.e., “Calli”-like growth and (ii) tumors with determinate, i.e., “gall”-like growth (Dodueva et al. 2020) and references therein). Both animal and human

tumors show metastasis which is not reported in plant tumors. The surgical transplantation of tumor part into a healthy plant show new focus of cell proliferation involving only the transferred material (De Ropp 1948) or only healthy cells of its own (White 1944), but plant tumors are not able to self-metastasize.

The basic principles of animal tumorigenesis are the classical concepts of proto-oncogenes and oncogenes (Todd and Wong 1999), which are poorly applicable to plants. Many animal tumor suppressors and oncogenes are present in higher plants as functional orthologs; however, the mutations in these genes tend to be non-oncogenic for plants (Dodueva et al. 2020). The downregulation of *Arabidopsis* retinoblastoma-related (*RBR*) gene lead to altered stem cell division in the meristems but did not cause tumor formation (Borghini et al. 2010). The low incidence of spontaneous tumors in plants may hold an evolutionary significance, which we believe to be due to the insufficient or incompatible multicellular organization that cannot support irregularities of cell proliferation. On the other hand, the role of phytohormones in pathogen-induced plant tumor may give important clues regarding potential medicinal value of phytohormone or similar conserved bio-molecule.

This overview of cellular and molecular mechanisms across species explains the loss of regulation of cell proliferation which may be of translational value for the human cancers.

Discussion

Globally, cancer is one of the leading cause of death, and regardless of its type, the morbidity and mortality rates are escalating annually (Sung et al. 2021). Cancer is an ancient disease that predates multicellular organisms by millions of years, not just a few decades (Whitney et al. 2017). It may have been favored by natural selection at some point during the course of development, becoming a component of nature and dispersing across the chain of life (multicellular organism) (Albuquerque et al. 2018). One of the central mechanisms of evolutionary change is natural selection, which drives the evolution of adaptive traits (Gregory 2009), such as certain physical characteristics, or phenotypes, that are passed on to offspring to make them more adapted to their environment (Fillon 2012). Natural selection has also been applied in parallel for the evolution of cancer (Goymer 2008) as differences between individual cells within the tumor favor the fittest (cell with the mutations that alter their microenvironment for their own benefit, favor uncontrolled growth, by promoting angiogenesis, changing the function of stromal cells, inducing neural damage, neutralizing immune cells as well as promoting an immunosuppressive

environment to escape immune surveillance) to survive (Dujon et al. 2021a).

In addition to favoring cancer throughout the tree of life, natural selection also incorporates anticancer defenses evolved during the evolutionary process in various multicellular species at the expense of fitness and other elements of life, leading to ecological and evolutionary repercussions (Boutry et al. 2020). Boutry et al. 2020 discuss these effects in detail and highlight several areas of the evolutionary ecology of multicellular organisms that have been significantly constrained at the cell, individual, population, species, and ecosystem levels by the evolution of anticancer adaptations and offer some avenues for further study (Boutry et al. 2020). When it comes to natural defenses against cancer, they can be divided into two groups: non-immune defenses against cancer (anti-carcinogenic substances present in foods, molecules that cleanse cells of cancer-causing substances, repair of DNA damage, tumor suppressor genes, cellular senescence, natural inhibitors of angiogenesis, and natural defenses at the invasion and metastasis stages) and immune defenses against cancer (comprising various sentinels of innate and adaptive immune surveillances) (Jakóbiśiak et al. 2003).

However, cancer defense mechanisms vary across species (comprising physical, molecular and microenvironmental, and immune mediated), especially in the long lived or large bodied which have evolved different cancer defense mechanisms, such as high-molecular mass hyaluronan in the naked mole rat and p53 amplification in elephants (Harris et al. 2017). Indeed, known as Peto's paradox and the evolution is solution for it (Nunney 2013), as understanding of evolutionary perspectives, an increasing frequency of pre-reproductive cancer death results in selection for enhanced cancer suppression. It has been supported by the work of (Nunney 2013) for the evolutionary model of cancer suppression. It is believed that the existence of cancer indicates that it must be in some sense of beneficial; otherwise, natural selection would surely have eliminated it (Garcia-Garcia 2009; Lichtenstein 2005), which is supported with the action of natural selection acting against a detrimental pathology: prereproductive cancer is rare, while the incidence of post-reproductive cancer is much higher (Nunney 2013). Numerous questions remain unanswered regarding the effects of cancer development on biotic interactions and the dynamics of entire ecosystems, as well as the impact of altered biotic interactions on the evolution of cancer resistance in the context of community ecology (Perret et al. 2020). According to the novel viewpoints through theoretical investigation in predator–prey model system, their evolutionary analysis clarified how biotic interactions can result in various levels of resistance in predator populations and showed that cancer

in wildlife is an important ecological and evolutionary force to take into account (Perret et al. 2020).

Cancer develops resistance and survival tactics inside the host systems in spite of the defense or protection mechanisms against it. This is a main hallmark of cancer (Hanahan 2022). The development of defense mechanisms by some multicellular organisms, while the vulnerability of others to cancer is an intriguing question to investigate from an evolutionary perspective. In our opinion, examining the prevalence of cancer and potential protective mechanisms in other wild and domesticated animals, whether they are free-ranging or kept in captivity, it can help to clarify the Peto's paradox, the idea that certain species are vulnerable to cancer while others are not. In this article, we highlighted possible cancer defense mechanisms in well-studied vertebrates (mammals and rodents), invertebrates, and plants that may be beneficial in future for developing cancer therapies for humans.

Conclusion

- (1) The chances of cancer are not directly correlated with body mass, number of cells, and number of cell divisions, as this is explained by Peto's paradox.
- (2) The antagonistic pleiotropy, mutation accumulation, and other factors of natural selection toward oncogenes and tumor suppressor genes seem to play a role in protecting or predisposing the animals against cancer, although all the genetic players are still to be identified for their developmental stage-specific roles.
- (3) Organisms have various mechanisms to avoid cancer by altered cell characteristics (Figs. 1–5)
- (4) It remains to see if cancer therapy in humans can be evolved based on the cancer resistance mechanisms observed in various animal species.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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