

Mechanisms of Cancer-Resistant Mammals

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Abstract. Cancer is a medical disorder when a few of the body's cells multiply uncontrollably and extend in a considerable amount of time. Researchers are trying everything to find a solution for cancer. This review is mainly focused on elephants, bowhead whales, naked mole rats and their inner mechanisms, which make them resistant to cancer. Statistically, larger animals such as elephants have much more cells than human, which means that they ought to have more cases of cancer, but there is an inner mechanism, which works in these animals and makes them cancer resistant. Elephants possess unique p53 genes with 20 copies, while people only have one. If cells are severely damaged, the p53 genes instructs the cells to be destroyed due to potential cancer risk. This process appeared to cause them to activate the LIF6 gene, and that leads to apoptosis of shattered cells. Bowhead whales are able to repair double-strand breaks more accurately and more efficiently. Bowhead whales are less likely than humans to create removals when repairing mismatched DNA termini. Naked mole rat cells are immune to cancer as they are more susceptible to early and firsthand suppression, which is a mechanism that prevents tumors from forming. Unfortunately, humans are still clueless about how to transfer the cancer preventing methods which exist in these three magical organisms into human. Hopefully, with the rapid development of technology and advances in the biomedical field, one day scientists will be able to put these theories into practice.

Keywords: Cancer, animals, resistance, mechanisms.

1. Introduction

For decades, cancer is widely considered the most catastrophic disease with incredibly high death rate in the world. A wide range of people of different ages suffer from cancer. Unfortunately, about ten million people die from cancer every year [1]. The leading cause of fatalities is lung and bronchus cancer, with 127,070 losses of life anticipated in this condition [2]. It exists to be the cause of every sixth death, and it is one of the largest health problems in the world. People are curious and are desperate enough to find effective methods to treat it. In the past, the most common methods used to cure cancer is radiation therapy and chemotherapy. These approaches can sometimes positively alter the condition of hopeless patients, but they do have side effects which are not beneficial to them of radiotherapy being the main reason. Loss of appetite, digestive difficulties including constipation or diarrhoea, mouth sores, and skin and nail concerns are all potential negative consequences of chemotherapy [3]. People could struggle to focus or recall things. There may also be changes in the hearing, a heightened risk of infections, and effects on the nerves and muscles. Therefore, it is utterly important to search for alternatives that could replace the traditional way. It has been observed that many animals are able to prevent cancer or to some extent reduce the effect of cancer with special genes inside their bodies. This review's core assertion is on cancer resistant animals, especially elephants, bowhead whales and naked mole rats, and their inner mechanisms on how they are able to be resistant to cancer. Additionally, after answering the question of cancer resistance in animals, hopefully, a possible and therapeutic strategy can be provided to researchers in the field of biomedical sciences to treat cancer in humans in the future.

2. Cancer Theory

Cancer is characterized as any one of a wide range of illnesses marked by the emergence of abnormal cells with the capacity to invade and kill healthy human tissue while also proliferating uncontrolled [4]. Mutations to the DNA within cells are the major causes of cancer. Errors in the genes which control the activity of the cells can lead to infinite cell growth and interaction with other mutated genes. Reasons that are involved in causing gene mutation consist of inherited genes, external exposure to carcinogen and radiation. A mammal's body is made up of hundreds of millions of cells, and cancer can appear almost everywhere. Animal cells often multiply and develop when the body requires new cells. New cells replace those that are lost as a result of damage or ageing. Occasionally, this meticulous process fails, allowing damaged or aberrant cells to reproduce when they shouldn't. The process of disregarding signals to stop reproducing or to start self-destruction is known as apoptosis, also referred to as programmed cell death. Tumours, which are tissue lumps, can develop from these cells as they continue to grow. It is extremely dangerous for cancerous tumours to have the ability to move to other parts of the body, infiltrate surrounding tissues, and grow new tumours. Some benign tumours, including those in the brain, can have deadly outcomes or even cause significant symptoms.

3. Cancer resistance mechanisms in animals

3.1. Elephants

Elephants are one of the typical examples that are quite resistant to cancer even though they are supposed to get a multitude of diseases according to their size. They're enormous creatures, gauging as much as eight tons. The cells emerged from a solitary treated egg, and each time a cell partitions, quite possibly it will acquire a change — one that might prompt disease. Interestingly, elephants are less likely to develop cancer compared to relatively tiny creatures. A few studies suggest that the possibility of them suffering to cancer is negligible. Therefore, statistically speaking, larger animals with more cells ought to have more cases of cancer. Regarding that thought, elephants with a greater number of cells than more modest, well evolved creatures ought to experience the ill effects of the infection at higher rates [5].

However, the notion is surprisingly invalid. According to research in the diary Cell Reports, new hints about late restored "zombie" quality are provided. Scientists have revealed a potential partial explanation to the enigma: elephants safeguard themselves using a distinct gene that actively eliminates cells with damaged DNA [6]. At some point during their evolutionary history, this gene became inactive, but somehow it was revived like zombie DNA, proving to be incredibly beneficial. When faced with DNA damage, a cell can either repair its broken genes or undergo self-destruction to prevent passing on further mutations to its offspring. Comparatively, elephants possess unique p53 genes with 20 copies, while humans only have one. These p53 genes in elephants respond aggressively to DNA damage, prioritizing the demise of damaged cells instead of trying to repair them. LIF6 protein is activated, and experiments have shown that these substances are carried to the mitochondria of organisms, responsible for energy production. They create openings in the mitochondria, allowing harmful molecules to escape, ultimately leading to the cell's demise.

Recently, Schiffman, together with his collaborators released a paper explaining a crucial finding that led to the conundrum that is now what people refer to Peto's Paradox: the discrepancy between organism size and cancer rates. Animals that swing their trunks around have more copies of the P53 tumor-suppressing gene. These duplicates were created more than 80 million years ago by careless mutations in the ancestors of manatees and elephants. The P53 gene instructs cells to be destroyed when they are badly damaged because they provide a cancer risk and cannot be repaired. Elephant cells favour the latter strategy over repair, which is chosen by the majority of animals. LIF6 may have another purpose, which is to eliminate harmed cells. LIF6 is in charge of following out P53's directives to get rid of damaged cells if P53 is the physician in charge of genetic triage. In African

elephant cells, the LIF6 gene can cause DNA damage. The LIF6 gene is activated as a result of this process, and injured cells die as a result. Elephant-specific sensitivity to cell injury will vanish if they stop LIF6 from working.

3.2. Bowhead whales

Up to now, not a lot of research have been done on this animal, so it is quite a challenge to conclude on it. The only remaining member of the genus *Balaena* is the bowhead whale (*Balaena mysticetus*), a species of baleen whale in the family Balaenidae [7]. Being the second-largest animal on Earth, they also follow “Peto’s Paradox”. It could be explained by the fact that they are able to repair double-strand breaks more accurately and more efficiently [8]. Due to external agents like radiation and certain chemicals being exposed during DNA replication, there is normally a huge risk of double-strand breaking and might lead to cancer in lots of animals. Nucleotide excision repair (NER) and base excision repair (BER), however, are present in bowhead whales [9]. They are mainly responsible for five mechanisms: failure detection; subunit assembly; multiple preforations leading to the removal of the damage-containing oligomer; Resynthesis to fill in the void; and Ligation to regenerate a complete molecule [10]. That repairs DNA defects caused on by deamination, alkylation, and oxidation.

Additionally, while maintaining incompatible DNA termini, the bowhead whale is less likely to create deletions and unites ends much more frequently without removing any bases outside of the little overhang region. Furthermore, an RNA- and PAR- binding protein called CIRBP plays an important role in DNA repair. Target mRNA must be post-transcriptionally regulated in order to govern DNA repair, circadian rhythms, cell proliferation, telomere integrity, and heart physiology. CIRBP can alter this process. Despite being largely thought of as an oncogene, CIRBP may potentially play a part in tumour suppression. CIRBP’s DSB repair and inhibition of micronucleus production are both aided by PARP-1-dependent localization of CIRBP to DNA damage sites. As a conclusion, the ‘conservative’ strategy that bowhead whales use, does not necessarily eliminate cells but repair them.

3.3. Naked Mole Rats

Small, hairless creatures known as naked mole rats can be found throughout eastern Africa. They inhabit grassy, semi-arid areas in underground tunnels and burrows. The most amazing thing about them is that, in contrast to regular rats, they have a lifespan of up to 30 years. They surprisingly never get cancer. A total of 11 individual naked mole rats’ five main tissues—the skin, lung, kidney, pancreas, and intestine—were developed into 79 separate cell lines for analysis. They introduced cancer-causing genes into cells by infecting them with engineered viruses. In the lab, the infected naked mole-rat cell colonies multiplied and formed. They were malignant now. The team gave these cells to mice, and after a few weeks, the mice started to develop tumors.

Researchers also observed that cells wouldn’t cluster too closely together when they were grown in a lab dish from naked mole rat cells. Over time, the dish’s contents became quite sticky. The cells would group together when the technicians removed the goo, indicating that they might now become tumors. They discovered that the stickiness was caused by hyaluronan, a complex chemical that cells produce and release into the extracellular matrix [11]. All mammals contain this sugar, which aids in lubricating joints and is a crucial part of skin and cartilage. The chemical also functions as a signal to limit the development of specific cell types. Because they are particularly vulnerable to early contact inhibition, a technique that limits tumor formation, naked mole rat cells are shielded against cancer from fibroblasts in naked mole rats (HAS2) [12].

Ageing, cancer formation are significantly influenced by hyaluronic acid. Different molecular weights of this complex sugar have an impact on how it behaves and performs physiologically. Hyaluronic acid with a high molecular weight has multiple properties. It promotes wound healing. Nearly all human tissues have high molecular weight hyaluronic acid, which is hyaluronan in homeostasis. But pathological circumstances like inflammation or cancerogenesis show signs of

increased hyaluronan fragmentation, which leads to a higher percentage of hyaluronic acid polymers. Therefore, the changing mass of the polymer is commonly linked to the actions of hyaluronic acid in the pathogenic environment. Surprisingly, the range of hyaluronan's molecular weights in various species.

The naked mole rat cells have a greater attraction to hyaluronic acid than other organisms, making them more susceptible to hyaluronic acid signaling [13]. Cells from naked mole-rats do not undergo the malignant transformation that can be caused by perturbing the signaling pathways in mouse fibroblasts. However, after high molecular weight hyaluronic acid is eliminated by either overexpressing the hyaluronic acid-degrading enzyme, Hyal2, or knocking down HAS2, they are more prone to malignant development of tumors. It is now understood that these rats have revolutionized to possess skin with more hyaluronic acid in tunnels. It's possible that this characteristic was later utilized to give this species cancer resistance and longevity.

The bigger hyaluronan physically confines prospective cancer cells, preventing them from escaping and developing into tumors, but it also permits cells to inhibit one another's growth if they get too crowded. As was already mentioned, the naked mole-rat has an early anticancer mechanism. When cells interact with the extracellular matrix or one another, the proliferation of those cells is halted. Because they lack the early contact inhibition, their cells have considerably lower density than cells of mice, which increases their susceptibility to malignant transformation. But it was unclear whether signals in naked mole-rats caused early contact inhibition.

Furthermore, this acid's interaction with hyaladherin binding partners, such CD44, is crucial for maintaining tissue integrity and is also connected to malignancy. The rodent species known as the naked mole rat has a unique type of hyaluronic acid with an extremely high molecular weight that is thought to be responsible for the animal's exceptional longevity and resistance to cancer. There is a difference between the high quantities of hyaluronic acid observed in human neoplastic cells, and the high levels of same acid discovered in naked mole rats, help them with their resistance to the disease. Understanding how HA works may inspire us to take a fresh approach to researching cancer control pathways. HA is a component of many cancer-related pathways and is found in the surroundings of cancer cells.

4. Discussion

In around 50% of human malignancies, the p53 tumour suppressor gene is often altered, which causes more aggressive malignancy and higher resistance to conventional cancer therapies. The development of gene therapy presents a viable strategy for p53 function restoration. An envision making polymeric nanoparticles was produced from poly, which facilitate sustained transfer of plasmid deoxyribonucleic acid into cells, leading to a prolonged gene expression without causing harmful effects. P53 gene-loaded nanoparticles demonstrated long-lasting antiproliferative effects on cancer cells of laboratory settings. The aim of this trail is to assess the effectiveness of these p53-loaded nanoparticles in living organisms. In mice, the prostate cancer cells of humans that were implanted as tumor xenografts were treated with p53-loaded nanoparticles either through direct injections at the tumor site or by administering the nanoparticles systemically throughout the body [14].

Control groups are treated with saline, p53 DNA alone, and nanoparticles without the p53 gene. Mice receiving local injections of p53-loaded nanoparticles exhibited significant limitation of tumor spreading and improved survival rate when comparing with control groups. The tumor inhibition correlated with sustained and higher levels of the p53 gene and protein expression in tumors treated with the p53-loaded nanoparticles, in contrast to using p53 DNA alone. Additionally, an individual intravenous dosage of p53-loaded nanoparticles effectively reduced tumor growth. Proficient studies pointed out that the nanoparticles accumulated in the affected area after administration, suggesting potential for further improvement in the nanoparticles' ability to specifically target tumors. In

conclusion, the gene therapy utilizing these polymeric nanoparticles effectively inhibited tumor growth.

People are only now starting to understand how defenses used by bowhead whales could function as well in humans to fight cancer. The prevalence of cancer can be reduced if increasing DNA repair to whale-like levels. A system of epigenetic markers that help cells "remember" what they are meant to be doing organises the DNA in our cells. These markers control gene expression, activating or inactivating certain genes to make sure that cells carry out their duties as intended. CIRBP may act as a tumor suppressor, which means it can inhibit the growth and spread of cancer cells. Understanding how CIRBP exerts this effect may offer new strategies for cancer treatment in humans. By modulating stress responses, CIRBP could potentially influence cancer cell survival and death. CIRBP binds to RNA molecules and is involved in gene expression which might provide insights into new therapeutic targets. By giving people more copies of the p53 gene or regularly overexpressing the bowhead whale form of CIRBP in human cells, people may soon be able to use CRISPR and gene therapies to boost human DNA repair processes.

Sodium salt (sodium hyaluronate), a naturally occurring type of hyaluronic acid, can be found in the extracellular matrix of the human body. Numerous studies have established the role of HA in wound healing and tissue hydration. Additionally, hyaluronic acid's specific and non-specific interactions support organ structural stability, tissue regeneration, differentiation, adherence of cells to one another, and embryonic development. The protective effects of high molecular weight hyaluronic acid in the human body are seen in cancer as well as in inflammation, embryogenesis, and wound healing. In numerous tumor models, high molecular weight hyaluronic acid has been demonstrated to prevent the spread and regeneration of cancer cells [15].

HA with a massive molecular mass is thought to be an appealing ingredient to improve chemotherapy. Unusual properties can be seen in distribution of HA in naked mole rats. In comparison to other species, they have larger concentrations of hyaluronic acid in many of their organs and tissues. The distinct very high produced by fibroblasts causes a tight layer to form around the cells. This layer is supposed to prevent the spread of tumor cells as well as carcinogenicity. High molecular weight hyaluronic acid has been found to inhibit the proliferation of vascular smooth muscle cells by keeping the cells in the G1 phase. In order to stop an invasion, it strengthens cell-cell interactions and reduces extracellular matrix permeability.

High molecular weight hyaluronic acid may aid in the prevention of metastasis by producing a thicker extracellular matrix. Cancer lymphatic endothelial cells' monolayer integrity was strengthened by treatment with high molecular weight hyaluronic acid, which reduced the proliferation of cancer cells. Hyaluronic acid with a high molecular weight is thought to be an attractive additive to adjuvant and neoadjuvant chemotherapy [16]. Human cells are better protected from stress by high molecular weight hyaluronic acid than by shorter high molecular weight hyaluronic acid. Hyaluronic acid with a high molecular weight also serves as an antioxidant, reducing the harm done by reactive oxygen species. Human skin fibroblasts can be protected by hyaluronic acid from the cancer-causing effects of oxidative stress. Furthermore, it was discovered that high molecular weight hyaluronic acid offers protection against mtDNA damage, which accumulates as a result of exposure to pro-inflammatory cytokines. Different hyaluronic acid molecular weights result in various cell messages. Cluster differentiation (CD44), a member of the family of transmembrane glycoproteins, and the hyaluronic acid mediated mobility receptor are the two main hyaluronic acid receptors, also known as hyaladherins. The expression of CD44 is elevated in human malignancies. When cancer is developing, CD44 is expressed. Hyaluronic acid and CD44 work together to promote tumor growth and cancer spread.

5. Conclusion

To conclude, a lot has been learned and people are able to utilize functions of these cancer resistant animals to promote the development of medicine. What people learned from elephants and bowhead

whales is that they are able to use CIRBP to repair DNA, which has the same function as P53 gene and is carried by nano particles which can enter the human body. Furthermore, it is hyaluronan that prevents the risk of cancer in mole rats. In humans, however, hyaluronan influences development, invasion and treatment resistance of cancer, but other evidence shows that it can also prevent it. The reason people are still not able to cure this disease is because each symptom of cancer is brought on by a unique set of individual mutations and every time the tumour enlarges, additional mutations multiply. Therefore, a drug that is helpful to one patient could be totally ineffective for others. In order to prevent, identify, treat, and eventually cure the many diseases, safe and efficient prevention, diagnosis, and treatment procedures must be developed. Research about cancer-related topics can transform and save lives and it also benefits the next generation. Unfortunately, humans are still clueless about how to transfer the cancer preventing methods which exist in these three magical organisms into human. Hopefully, with the rapid development of technology and advances in the biomedical field, one day people will be able to put these theories into practice.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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