UNLOCKING PETO'S PARADOX

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What separates you, a human, from other animals, like a hamster or a blue whale? On the molecular level, we are all multicellular creatures composed of varying numbers of cells. Generally speaking, human beings have an average mass of around 70 kg, while blue whales living in the Northern Hemisphere have an average mass of 100,000 kg.[1,2] Since blue whales are several orders of magnitude more massive than humans, researchers generally assume that blue whales possess a much greater number of cells. Despite this difference in size, humans and whales do have some similarities—as multicellular animals, both species are susceptible to death from cancer.

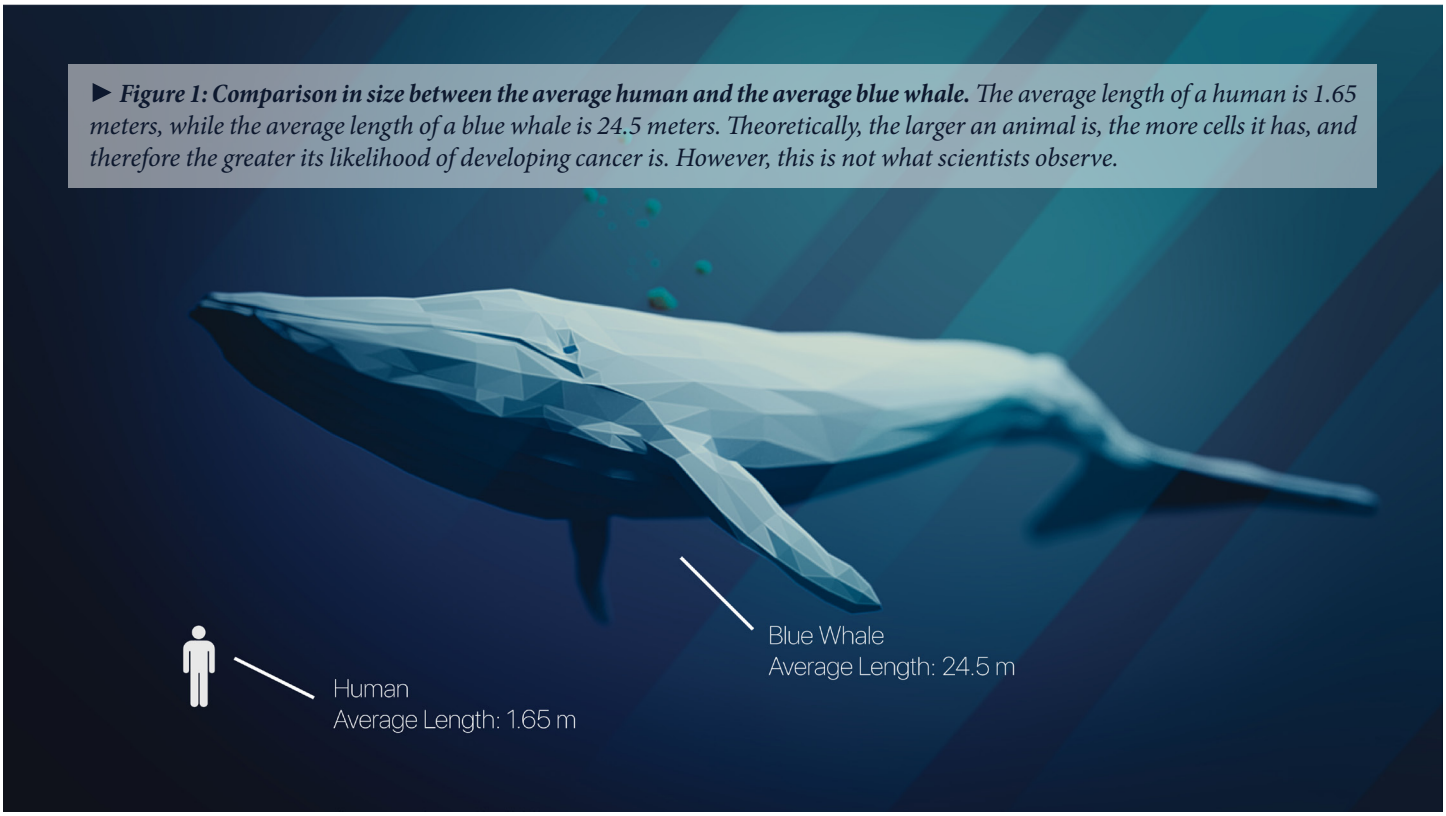
If every cell has the potential to become cancerous, then basic probability suggests that the more cells an animal has, the more likely it is to develop some form of cancer. This rings true for humans: a study from UC Riverside shows that a human who is 10 cm taller than the average is 10% more likely than average to develop cancer.[3] We should then expect large creatures to be riddled with tumors, while small animals like hamsters should develop cancer less frequently. However, this is not the case in nature. Research shows that large animals such as elephants actually have a lower risk of developing cancer than humans.[4] The lack of correlation between animal size and cancer risk summarizes the biological paradox that continues to puzzle researchers, named Peto's Paradox.

POTENTIAL SOLUTIONS

Ever since Peto's Paradox was first proposed by Richard Peto in 1977, researchers have been searching for potential answers to this perplexing question: Why do larger animals not develop cancer more often than humans, despite possessing a significantly greater number of cells? Peto's paradox intrigues many biological researchers, since a better understanding of cancer will aid efforts to prevent or cure the disease. Many solutions have been proposed so far, but none have conclusively provided an answer.

Competing Hypertumors

When a tumor cell forms, it begins competing against the rest of the human body for resources, such as nutrients and oxygen. As resources are brought to the tumor to support its growth, some tumor cells may become more aggressive and compete against the rest of the tumor for vital supplies. As this competition increases, it may form a tumor within a tumor, called by most researchers a "hypertumor." Studies suggest that larger animals may actually see increased rates of cancer than smaller animals, but the growth of hypertumors prevents tumors from reaching lethal sizes.[5]



► ***Figure 1: Comparison in size between the average human and the average blue whale.*** *The average length of a human is 1.65 meters, while the average length of a blue whale is 24.5 meters. Theoretically, the larger an animal is, the more cells it has, and therefore the greater its likelihood of developing cancer is. However, this is not what scientists observe.*

Ticking Telomeres

Telomeres are sequences of DNA that cap the ends of chromosomes. They shorten during cellular division, limiting the reproduction of DNA.[6] When telomeres become too short to protect the chromosome, the cell generally undergoes apoptosis, a form of cell death, in effect causing the telomeres to act as a timer for the cell's lifespan.[7] Researchers hypothesize that larger animals might have shorter telomeres, resulting in a shorter cellular lifespan and a greater tendency for cells to undergo apoptosis upon receiving damage to the DNA. This could potentially reduce the likelihood of cancer causing mutations forming in the cell.[8] The longer a cell lives and replicates, the more likely it is to develop potentially dangerous mutations. It's worth mentioning that telomeres can be elongated with telomerase. However, large animal cells usually suppress this enzyme from making telomeres longer because longer telomeres increase the chance of the cell developing mutations. One of the most common mutations in cancerous cells is the expression of telomerase, effectively making the cell immortal since the telomeres will never decrease in length.[9,10]

Natural Selection

Another possible solution proposed by researchers is that organisms must evolve cancer suppression or face extinction. Cancer is typically the result of genetic mutations in certain genes that control the growth and reproduction of the cell. These mutations can cause the cell to divide uncontrollably, producing a tumor.[11] In response, natural selection prompts animals to develop defenses against cancer. In nature, this defense is found in genetic mechanisms—a tumor suppressor gene given the name p53.[12] p53 triggers apoptosis after the cell detects an abundance of mutations in the cell's DNA. This is designed to prevent cells from accumulating enough mutations to become cancerous.

A study done at the Huntsman Cancer Institute notes that humans only possess one copy of p53 in their genetic code, which means that human cells are less likely to trigger apoptosis upon DNA damage, increasing the likelihood of cancer.[12] However, DNA sequencing has revealed that African savannah elephants contain 20 copies of p53, making apoptosis much more likely.[13] These pre-emptive cell implosions observed in larger animals like these African savannah elephants could be the evolutionary mechanism necessary to prevent these large animals from succumbing to cancer.[8]

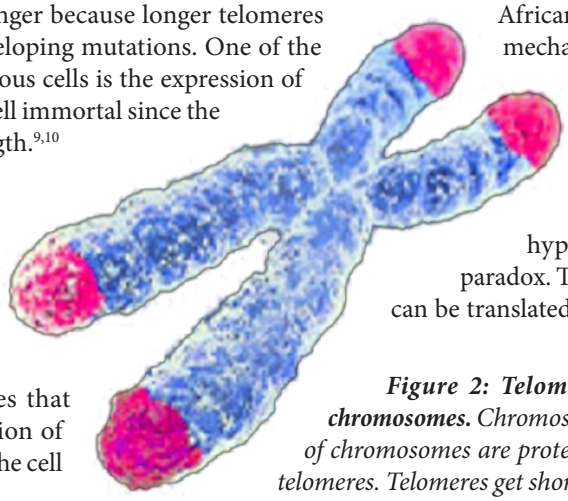


Figure 2: Telomeres marked in pink, found at the ends of chromosomes. *Chromosomes are tightly coiled strands of DNA. The ends of chromosomes are protected from damage by strands of DNA coded as telomeres. Telomeres get shorter and shorter with each successful replication.*

APPLICATION

These comparative studies and hypotheses suggest several solutions to Peto's paradox. The question then is how these possible solutions can be translated into cancer prevention strategies or remedies

Figure 3: Artist's rendering of a mother elephant looking after her child.

"Research shows that large animals such as the elephant actually have a lower risk of developing cancer than humans."

for humans. An evolutionary solution evident in one species may be difficult to incorporate in the human species due to the divergent trajectories of natural selection.

The most promising hypothesis to solving Peto's paradox looks to be genetic. As discussed earlier, certain larger animals have an abundance of p53 genes which potentially have cancer prevention effects. One early study decided to look deeper into this phenomenon. Researchers modified the genome of mice and inserted extra copies of the p53 tumor suppressor gene. These mice—so-called 'super p53' mice—displayed an enhanced response to DNA damage and cancer suppression compared to unmodified mice.[14] Modified mice cells were more likely to undergo apoptosis upon receiving DNA damage, preventing potential mutations into cancerous cells. However, a significant shortcoming of this study is that the modified mice experienced accelerated aging effects.

This study served as the foundation for many new discoveries and therapies for human cancer treatment. The importance of p53 has not gone unnoticed by cancer therapy researchers, and there is newly emerging research about the potential for cancer treatment options such as the "p-53 DC vaccine." This vaccine consists of an injection containing p53 bound to a carrier cell, which activates and strengthens an immune response to cancerous cells.[14]

Researchers noticed that roughly 50% of human tumors present mutated forms of p53 on the cell surface. In this form, p53 is classified as a tumor-associated antigen because it is a signal from a tumor that activates the immune cells specifically designed to kill cancerous cells.[15] Injecting more p53 should theoretically allow for a faster and more efficient response. This particular study confirmed that this vaccine could have strong, toxic effects on cancerous lung cells that present p53 on their surface in a laboratory setting. However, p53 vaccines as a treatment for human tumors are still undergoing clinical testing. This form of cancer treatment has completed Phase I trials with positive results and is currently undergoing Phase II testing, which examines any potential toxic effects that may occur after the injection.[16]

Peto's paradox presents many solutions to the age-old battle

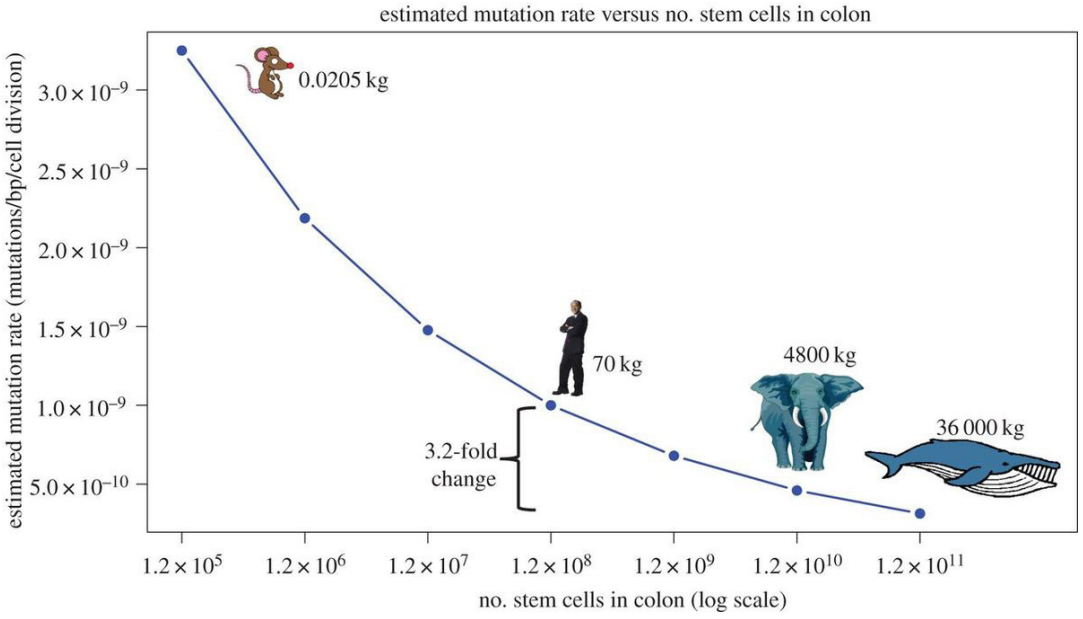


Figure 4: A graphic representation comparing mutation rates to the number of stem cells found in an animal. *The number of stem cells found in an area allows researchers to project the total number of cells that an animal possesses. Notice how larger animals actually see less mutation in their cells than humans do, despite being considerably larger. Licensed under CC BY 4.0.*

"These mice—so called 'super p53' mice—displayed an enhanced response to DNA damage and cancer suppression compared to unmodified mice."

against cancer. Since larger animals do indeed develop less cancer than they theoretically should, they must have some form of natural defense against cancer. Studying these natural defenses provides a great foundation for researchers to develop new cancer therapies for humans. The possibilities for better treatments to cancer are in the natural world, and Peto's paradox represents just one attempt to better our understanding of this mysterious disease.

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IMAGE REFERENCES

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