Why elephants almost never get cancer–and why that might save human lives

We've all heard the saying that quality is more important than quantity. The preference for quality over quantity applies in the human body as well. Cancer, for instance, is caused by malfunctioning cells that grow and divide uncontrollably, creating life-threatening health challenges for patients. It's easy to see that in the case of cancer, an individual should prefer a prescribed number of quality cells, cells performing their proper functions, over a large quantity of rogue cells, cells that are multiplying and wreaking havoc on the body.

The connection between quality and cancer is also clear in the causes of the disease; we frequently learn about mutations, or changes, in DNA that lead to cancer. But what is the role of gene quantity in cancer? Are there instances in which the number of copies of a gene could be just as important as how well a gene functions?

As it turns out, yes—gene copy number can affect cancer development in both directions, either by protecting an organism from potentially cancer-causing events or by pushing a cell over the edge from normal to cancerous. First, we'll explore what is meant by gene copy number, followed by examples of beneficial and harmful deviations from the normal number of gene copies.

It takes two: Gene copy number in human cells

The number of copies of each gene in each cell is important to the body's normal functioning, and in most cases, this number is tightly regulated from conception onward. Maintaining proper gene copy number starts with the germ cells—an egg and a sperm—when they combine to form a fertilized egg (Figure 1). All normal eggs and sperm carry one copy of each gene from the mother or father that produced them. After fertilization occurs, the resulting cell contains two copies of each gene, one from mom and one from dad. Through millions upon millions of cell divisions, that single cell divides to form every cell in the body, each of which should also contain two copies of each gene.

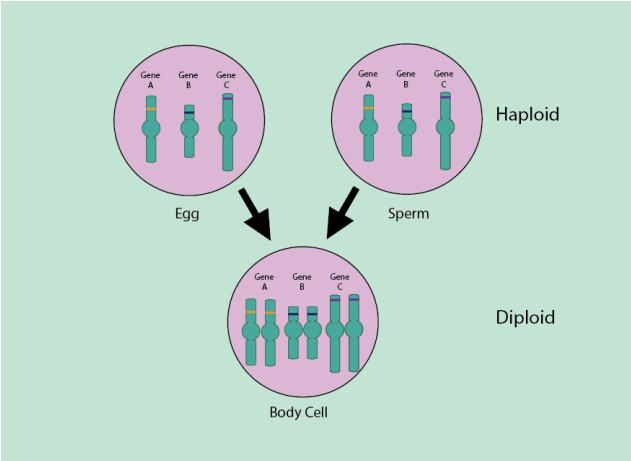

Figure 1: Normal Gene Copy Number in Human Cells. The number of copies of

each gene in human cells is tightly regulated even before conception. (Here, genes are represented as colored bands on green chromosomes.) Each egg or sperm contains one copy of each gene from the parent that produced it. Because these cells contain half the genetic information necessary to produce a whole organism, they are called haploid cells. When egg and sperm combine, the resulting fertilized egg contains two copies of each gene, one from the mother and one from the father. These cells are called diploid cells (di- meaning two). This first diploid cell undergoes billions of cell divisions to create every cell in the adult human, each containing two copies of each gene.

One notable departure from the “two gene copy” rule is called gene duplication. This phenomenon occurs when an extra copy of a gene is incorporated into a cell’s DNA (for example, through mistakes in DNA replication or repair). Such gains in gene copy number play an important role in several biological processes. For example, gene duplications rank among the genetic changes that can occur between species during the process of evolution; thus, some species have many more copies of certain genes than others do.

In addition to contributing to diversity among species, gene copy number gains can also affect human health and disease. For instance, individuals with an extra copy of the gene *MECP2* suffer from *MECP2* duplication syndrome, a moderate to severe neurodevelopmental disorder affecting movement, speech, and intellectual capabilities. Awareness of these deviations from the normal pattern of two gene copies per cell forms a foundation for understanding the effects of such deviations—both positive, like preventing cancer, and negative, like causing cancer.

Elephants never forget—And (almost) never get cancer?

One recent newsworthy example of gene copy number involves elephants’ resistance to cancer. Cancer results when cells accumulate changes in their DNA that cause them to grow and divide uncontrollably. Therefore, one would expect that the more cells an organism has or the longer it lives, the more opportunities it has to accumulate such changes in one or more of its cells, leading to tumor formation. Yet this is not the case: large animals, such as whales and elephants, do not have increased cancer rates compared to smaller animals (a finding known as Peto’s paradox).

So why don’t elephants die of cancer nearly as often as humans, even though they have about 100 times as many cells? Working independently, researchers from the University of Utah and the University of

Chicago recently discovered what may cause part of this phenomenon: elephants have an abnormally high number of copies of a key tumor suppressor gene, *TP53* (Figure 2). In fact, while humans have only 2 copies of this gene, the researchers found that Asian elephants have at least 30 copies, and African elephants have at least 40!

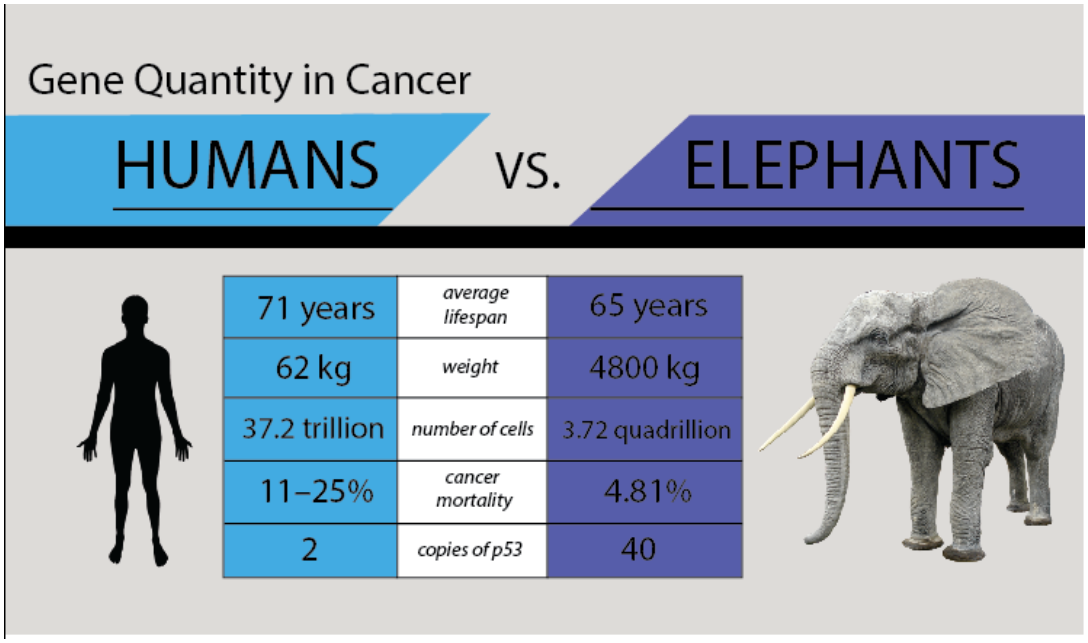

Figure 2: Humans vs. Elephants: Size, Lifespan, and Cancer Risk. Despite having about 100 times as many cells as humans do [8, 18], elephants die of cancer much less frequently. This difference may be due in part to elephants' increased copy number of the tumor suppressor gene TP53.

The *TP53*gene codes for a protein (p53) that is dubbed "the guardian of the genome". It oversees a cell's machinery for repairing damage to DNA, helping fix mutations before they cause cancer. If DNA damage is too severe, p53 can also stop a damaged cell from dividing or even trigger cell death. All of these processes prevent a damaged cell from passing on potentially cancer-inducing changes to its daughter cells.

Because elephants have so many copies of *TP53*, it seems likely that elephant cells are very good at repairing damaged DNA, stopping cell growth, or inducing cell death when the damage is too extreme to fix. To test this hypothesis, researchers dosed cells from an African elephant and a human with radiation, creating potentially cancer-causing DNA damage. The researchers found that the amount of DNA repair between the species was similar, but the elephant cells died almost twice as often as the human cells did [8].

These results suggest that elephants may escape cancer by more efficiently killing off potentially rogue cells before they have a chance to grow and divide into a life-threatening tumor. Researchers are currently following up on how this finding may inform the treatment of human cancers. Although these experiments indicate that high gene copy number can protect organisms from cancer, the same doesn't always prove

true in the case of other cellular genes.

Too much of a good thing: How gaining gene copies can cause cancer

While having more copies of the tumor suppressor *TP53* may help elephants evade cancer, increasing the number of some other genes can actually help cause cancer. These genes are known as proto-oncogenes (proto- meaning precursor): they have important functions in normal cells, but they also have the potential to cause cancer if altered.

One example of a gene that can cause cancer when too many copies are present is a gene called *HER2* (Human Epidermal growth factor Receptor 2), which codes for a protein of the same name. This protein is located at a cell's outer surface and receives signals from the surrounding environment that trigger the cell to grow and survive. However, this normal function becomes a problem if the cell gains additional copies of the *HER2* gene through errors in DNA replication or cell division, causing production of too much HER2 protein. Abnormally high levels of *HER2* cause the cell to receive an overload of growth signals, triggering it to grow and divide uncontrollably and leading to tumor formation. Such cancers driven by extra *HER2* gene copies actually comprise an entire class of breast cancers, known as HER2-positive cancers. This class accounts for up to 20% of all breast cancer cases, underscoring the potential negative impact of gene copy number changes in cancer development.

Therapeutic implications of gene copy number changes in cancer

Fortunately, like changes in gene quality, changes in gene quantity have also been identified as targets for anti-cancer drug development. For instance, breast cancers with *HER2* gene gains are currently treated with a drug called Herceptin (Figure 3). Herceptin binds specifically to the signal-receiving region of the HER2 protein. This binding has two effects: first, it signals the immune system to attack and kill the cancer cells bound by the drug; second, it prevents HER2 from receiving and relaying growth and survival messages into the cancer cell. One way to understand this second function is to imagine HER2 receptors as ears and Herceptin as a set of molecular "earplugs". Without earplugs, your ears can receive messages in the form of sound and relay them to your brain, where they are processed. With earplugs in place, however, sounds in your environment can't reach your ears and so are never transmitted to your brain. Herceptin bound to HER2 works in a manner similar to earplugs by blocking HER2 from "hearing" the growth and survival signals all around it. As a result, these signals never reach the cell. Deprivation of growth and survival signals caused by Herceptin therapy can cause a cancer cell to stop dividing or even die. When combined with traditional chemotherapy, Herceptin increases the long-term survival of patients with HER2-positive breast cancer.

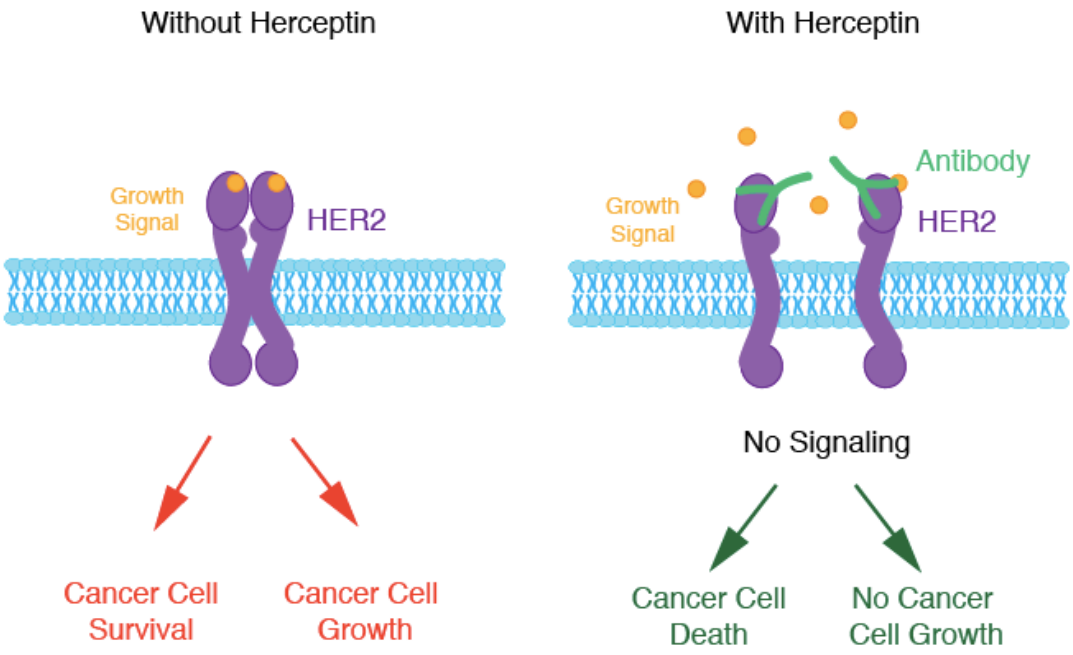

Figure 3: Herceptin and Treatment of HER2-positive Breast Cancer. In the absence of Herceptin, HER2 can receive growth and survival signals from the cell's environment and relay them to the cell. These signals lead to uncontrolled growth of HER2-positive breast cancer cells. Herceptin targets these cells by binding HER2 and preventing it from receiving and transmitting its normal signals. Cut off from growth and survival signals, HER2-positive breast cancer cells treated with Herceptin may stop dividing or even die.

Herceptin treatment of HER2-positive breast cancers provides an example of how gene copy number changes in humans can inform cancer therapy. But can the recently identified copy changes in our distant relatives, the elephants, also help advance the treatment of cancer? While the prospect is tempting, trying to use tumor suppressor genes such as *TP53* as avenues to attack cancer cells has proven difficult. This difficulty arises because tumor suppressor genes are typically mutated or deleted by abnormal cells en route to becoming cancerous. So far, broken or lost genes have proven very challenging to replace or fix (for example, by physically editing the cancer cell's DNA). However, future studies of genes like *TP53* could identify alternative ways to activate cellular processes that aid in fighting cancer, such as those regulating cell death.

Two heads are netter than one: Combining gene quality and gene quantity to fight cancer

Unfortunately, the complex molecular causes of most cancers will probably prevent any one therapy from

providing a cure. In the case of HER2-positive breast cancers, for example, many women treated with Herceptin eventually develop resistance to the drug and must be switched to a new treatment regimen. The same has proven true for other cancer therapies as well. This fact underscores the need for continued development of novel drugs that target a variety of cancer vulnerabilities. By focusing on drugs that target both cancer gene quality and gene quantity, researchers may be able to develop effective drug combinations to improve patient survival and quality of life.

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