How elephants evolved to become big and cancer-resistant

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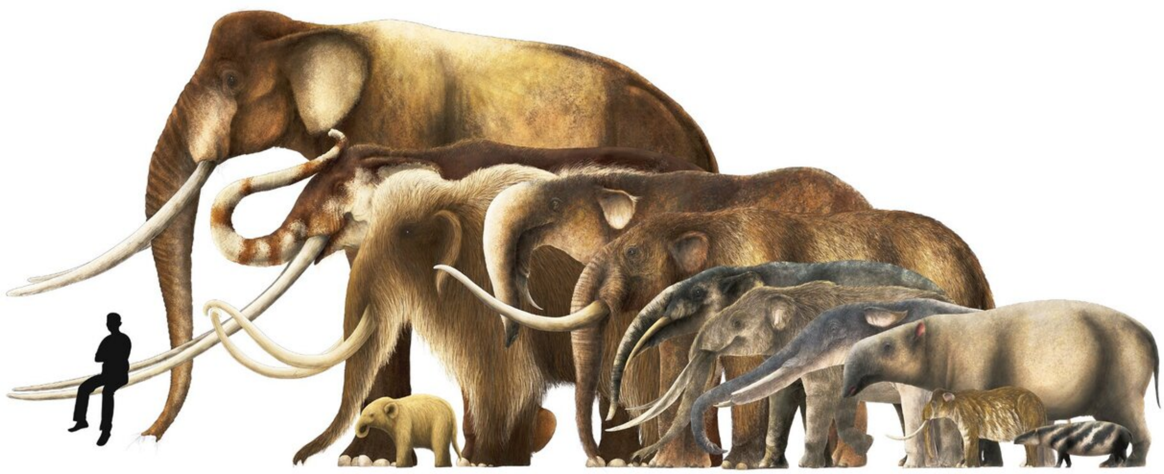

Artist's illustration of species within the taxonomic order Proboscidea, which includes elephants. Credit: Liam Elward

All things being equal, large, long-lived animals should have the highest risk of cancer.

The calculation is simple: Tumors grow when genetic mutations cause individual cells to reproduce too quickly. A long life creates more opportunities for those cancerous mutations to arise. So, too, does a massive body: Big creatures—which have many more cells—should develop tumors more frequently.

Why, then, does cancer rarely afflict elephants, with their long lifespans and gargantuan bodies? They are some of the world's largest land animals.

A new study delves into this sizeable mystery, showing that elephants possess extra copies of a wide variety of genes associated with tumor suppression.

But this phenomenon is not unique to elephants, scientists say: The research concluded that duplication of tumor suppressor genes is quite common among elephants' living and extinct relatives, including in small ones like Cape golden moles (a burrowing animal) and elephant shrews (a long-nosed insectivore). The data suggest that tumor suppression capabilities preceded or coincided with the evolution of exceptionally big bodies, facilitating this development.

The study was published on Jan. 29 in the journal *eLife* by biologists Vincent Lynch at the University at Buffalo and Juan Manuel Vazquez at the University of California, Berkeley.

"One of the expectations is that as you get a really big body, your burden of cancer should increase because things with big bodies have more cells," says Lynch, Ph.D., assistant professor in the Department of Biological Sciences in the UB College of Arts and Sciences. "The fact that this isn't true across species—a long-standing paradox in evolutionary medicine and cancer biology—indicates that evolution found a way to reduce cancer risk."

In the new study, "We explored how elephants and their living and extinct relatives evolved to be cancer-resistant," Lynch says. "We have past research looking at TP53, a well-known tumor suppressor. This time, we said, 'Let's just look at whether the entire elephant genome includes more copies of tumor suppressors than what you'd expect.' Is the trend general? Or is the trend specific to one gene? We found that it was general: Elephants have lots and lots and lots of extra copies of tumor suppressor genes, and they all contribute probably a little bit to cancer resistance."

Elephants do have enhanced cancer protections, compared with relatives

Though many elephant relatives harbor extra copies of tumor suppressor genes, the scientists found that elephant genomes possess some unique duplications that may contribute to tumor suppression through genes involved in DNA repair; resistance to oxidative stress; and cellular growth, aging and death.

"By determining how big, long-lived species evolved better ways to suppress cancer, we can learn something new about how evolution works and hopefully find ways to use that knowledge to inspire new cancer treatments," says Vazquez, Ph.D., a postdoctoral researcher at UC Berkeley who completed much of the project while earning his Ph.D. at the University of Chicago.

A related mystery: How did giant sloths and ancient mega-armadillos get so big?

Elephants are a great case study for understanding the evolution of cancer protection because they belong to a group of mammals—the Afrotherians—that are mostly small-bodied.

The study searched for extra copies of tumor suppressor genes in the

DNA of Asian, African savanna and African forest elephants, as well as in the genomes of a number of fellow Afrotherians, such as Cape golden moles, elephant shrews, rock hyraxes, manatees, extinct woolly mammoths, extinct mastodons and more. The team also studied certain species belonging to a group of mammals called Xenarthra that is closely related to Afrotherians, and found some extra copies of tumor suppressors in those animals' genomes as well.

Given the findings, Lynch wonders whether the duplication of tumor suppressors may have aided the evolution of other ancient large bodies within these groups.

"If you pick a weird mammal, there's a good chance that it will be in these groups, the Afrotherians and Xenarthrans: armadillos, aardvarks, sloths, anteaters, all of these weird mammals," Lynch says. "We found that within these groups of organisms, the ones we studied all seem to have extra copies of tumor suppressor genes. That may be why in the last Ice Age, there were giant sloths and ancient mega-armadillos. There's even an extinct species of manatee relative called the Steller's sea cow that was elephant-big. Extra copies of tumor suppressors may have helped all of these animals get really, really big."

More information: Juan M Vazquez et al, Pervasive duplication of tumor suppressors in Afrotherians during the evolution of large bodies and reduced cancer risk, *eLife* (2021). DOI: 10.7554/eLife.65041

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