Novel anti-cancer mechanism found in long-lived rodents

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Biologists at the University of Rochester have found that small-bodied rodents with long lifespans have evolved a previously unknown anti-cancer mechanism that appears to be different from any anticancer mechanisms employed by humans or other large mammals. The findings are published in today's issue of *Aging Cell*.

Understanding this mechanism may help prevent cancer in humans because many human cancers originate from stem cells and similar mechanisms may regulate stem cell division.

"We haven't come across this anticancer mechanism before because it doesn't exist in the two species most often used for cancer research: mice and humans," says Vera Gorbunova, assistant professor of biology at the University of Rochester, a principal investigator of this study. "Mice are short-lived and humans are large-bodied. But this mechanism appears to exist only in small, long-lived animals."

Gorbunova believes that cells of long-lived, small-bodied rodents are hypersensitive to cues from the surrounding tissue. If the cells sense that conditions are inappropriate for growth, they slow down cell division. Such a mechanism would arrest tumor growth and prevent metastases.

Gorbunova's team has worked at length investigating the links between body size and lifespan in rodents because rodents range in size from tiny field mice to the human-sized capybara of Brazil. She can use them to compare size and lifespan across several different-sized but closely

related animals. She discovered that telomerase—an enzyme that can lengthen the lives of cells, but can also increase the rate of cancer—is highly active in small rodents, but not in large ones.

Until Gorbunova's research, the prevailing wisdom has assumed that an animal that lived as long as we humans do needed to suppress telomerase activity to guard against cancer. Telomerase helps cells reproduce, and cancer is essentially runaway cellular reproduction, so an animal living for 70 years has a lot of chances for its cells to mutate into cancer. A mouse's life expectancy is shortened by other factors in nature, such as predation, so it was thought the mouse could afford the slim cancer risk to benefit from telomerase's ability to speed healing.

But Gorbunova and colleagues showed that it was not life expectancy, but body mass that regulated the expression of telomerase. Simply having more cells increases the likelihood that one will become cancerous. We humans, as large animals, would likely develop cancer much more often and much earlier if we didn't suppress our telomerase.

While the findings were a surprise, they revealed another question: What about small animals like the common grey squirrel that live for 24 years or more? With telomerase fully active over such a long period, why isn't cancer rampant in these creatures?

Gorbunova found that the squirrel, naked mole-rat, chipmunk, muskrat, and chinchilla express high levels of telomerase, which would be expected to increase their cancer risk over their long lifetimes. But these species have developed a mechanism to counteract the high telomerase activity and remain cancer free for the duration of their lifespans.

"Squirrels know a cure for cancer," says Gorbunova. "Short-lived small species display continuous rapid proliferation of their cells, but these long-lived rodents have somehow found a way to slow down that

proliferation when they need to."

Gorbunova thinks that squirrels and similar rodents have evolved a strict monitoring function within their cells that may be able to sense appropriate and inappropriate cell division—i.e., healthy reproduction and runaway cancerous reproduction—and slow or inhibit the division if necessary.

Gorbunova is now looking to isolate and understand this mechanism with the hope that it may be applicable to help human cells thwart the onset of tumor growth.

Source: University of Rochester