COMPARATIVE BIOLOGY

Looking for a master switch

Evolution can extend a species' lifespan by an order of magnitude. Can we learn the same tricks?

BY SARAH DEWEERDT

Lonesome George, the Galapagos tortoise famous for being the last of his subspecies, was thought to be about 100 years old when he died on 24 June 2012. That's a lifespan that fewer than 1 in 10,000 humans attain. But for his species, it was nothing special — giant tortoises can live for about 180 years, proving that slow and steady really can win the race.

To humans, contemplating a mortality that rushes up all too quickly, such long-lived creatures are fascinating. How do they last for so long — and could we learn to do the same?

So far, most research on the mechanisms of ageing has involved model organisms such as mice, roundworms and yeast. These studies have helped scientists uncover various ageing-related genes and biochemical pathways (see 'Live long and prosper', page S18).

But these species have become model organisms precisely because they don't live very long. They mature quickly, reproduce prolifically and soon die — all qualities that make scientific studies feasible. "We may be overlooking a whole category of tricks for long life that you're never going to see in short-lived animals," says Steven Austad, interim director of the Barshop Center for Longevity and Aging Studies at the University of Texas Health Science Center in San Antonio.

So researchers are looking for clues in other animals, including some with impressive lifespans in absolute terms and others that outlive related species.

The first strategy is to study animals that exhibit what Caleb Finch, director of the Gerontology Research Institute at the University of Southern California in Los Angeles, has dubbed 'negligible senescence'. Examples include deep-sea rockfish, which still produce a normal number of eggs at the age of 100; long-lived species of turtles and tortoises; and certain clams and oysters that live for nearly half a millennium (see 'Maximum lifespans').

Long-lived animals tend have one attribute in common: protection. Oysters and clams have tough outer shells, whereas bowhead whales, which can reach 200 years old, are protected by their size — larger species tend to live longer than smaller species. "There's no point building a mouse that can live 40 or 50 years, because they're all going to get eaten in the first year of life," says Richard Miller, who studies the biology of ageing in mammals at the University of Michigan in Ann Arbor. But that's not such a problem for a bat that can fly out of harm's way, a sea urchin that can deter enemies with its spines, or an elephant that is too powerful to be taken down by predators. "Nature makes long-lived species whenever there's an opportunity in the form of a low-hazard niche," Miller says.

And that opportunity has arisen over and over again. "Every kind of animal in every phylum has species that are short lived and species that are long lived," says Finch. "So lifespans can go in either direction, depending on the evolutionary pressures." In other words, evolution can extend the lifespan while keeping the same basic body plan and genetic heritage.

LEARNING TO LIVE LONGER

One result of surveying long-lived species is the realization that we are already members of that select group. "Humans are really sort of outliers," says Vera Gorbunova, professor of biology at the University of Rochester in New York. We have the longest lifespan of any primate, and live four times longer than similar-sized animals such as deer and cougars.

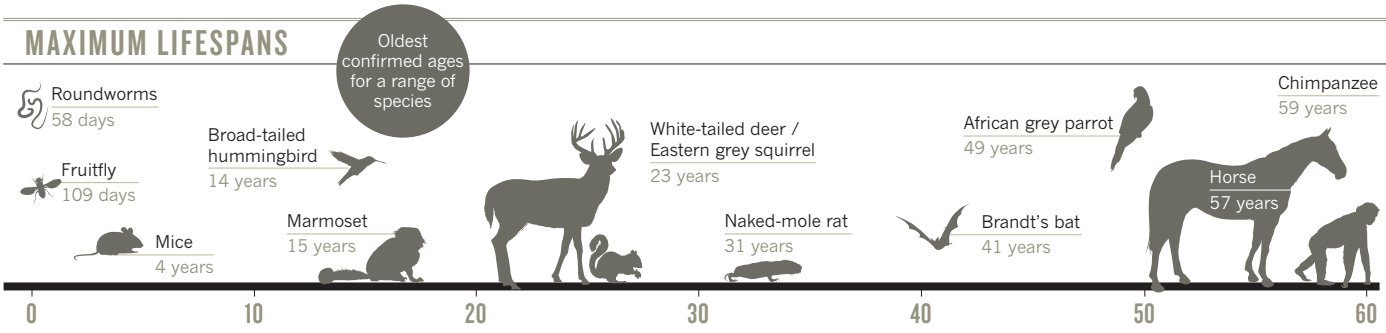
Even so, some researchers think we can still glean useful insights from species with even greater feats of longevity. Austad is studying hydras, small freshwater polyps related to jellyfish. "So far as we can tell, those things never age," Austad says. But hydras only achieve an indefinite lifespan if they reproduce asexually, budding off daughters from the mother's body wall. If environmental conditions turn harsh, the change can trigger each hydra to begin producing either sperm or eggs — and then it lives only as long as a fruitfly.

It's not clear how the hydra's genome is tuned to produce either extremely slow or extremely rapid ageing. But investigating this creature has great benefits: Austad points out that the hydra shares many genes with humans that have been lost in worms and fruitflies. "There's a universe of genes that we haven't been able to investigate in the traditional invertebrate models that may lead us to some new genetic pathways" involved in human ageing, he says.

Others are more cautious about extrapolating from long-lived species to humans. Many of these species are only distantly related to us and have very different lifestyles. Turtles, for example, have a low metabolic rate and live a slow, sluggish existence. They are "close to being dead most of the time, physiologically", says George Zug, curator emeritus of amphibians and reptiles at the Smithsonian Institution's National Museum of Natural History in Washington DC. Zug adds that evolution doesn't select for longevity directly, but for how long an organism takes to become reproductively mature, and for the length of its reproductive lifespan. So looking to evolution for insights on how to extend our post-reproductive lifespan might be a non-starter.

It might be better to compare species in the same taxonomic group with similar genetic material. For example, laboratory mice live for 4 years at most, but the longest-lived rodent, the naked mole-rat — a buck-toothed, wrinkly creature that dwells in colonies underground — can survive for nearly 30 years. Moreover, longevity has evolved in four different rodent lineages: porcupines, beavers and squirrels can also live for more than 20 years.

Even though none of these species lives as long as humans, we can learn a lot from them. Gorbunova points out that by manipulating single genes in a mouse, scientists have been able to extend their lives by 10–20%. "But compared to a mouse, a naked mole-rat lives ten



SOURCE: THE ANAGE DATABASE

TUI DE ROY/GETTY IMAGES

Lonesome George lived to about 100, which is merely middle-aged for a Galapagos tortoise.

times longer," she says. Clearly evolution is the superior experimentalist here.

MECHANICS OF AGEING

Comparative studies are beginning to give clues to the cellular and molecular mechanisms that enable some species to live longer than related species. Miller's team, for example, cultured skin cells from nine rodent species and exposed them to various stresses, including cadmium, hydrogen peroxide and heat[1]. Similar experiments[2] involved skin cells from 35 different bird species. Both studies showed that cells from long-lived animals are more resistant to stresses than those of short-lived species, says Miller.

Similar research also suggests one possible reason why birds tend to live longer than mammals of similar size, Miller adds. "Bird cells tend to be three- to ten-fold more resistant to many of these stresses than cells from rodents of the same size. We can't prove that's why birds live a long time, but it's a good guess."

Another possible mechanism of longevity comes from Austad's studies of protein stability[3] — the ability of proteins to remain properly folded when researchers try to disrupt them with chemicals or heat. "We've looked at protein stability in a number of long-lived organisms, and it seems to be the one thing that reliably associates with long life" in creatures as diverse as bats, naked mole-rats and clams, he reports.

Miller's and Austad's results don't necessarily contradict each other. "When an organism ages, so many things go wrong," Gorbunova says. To build an organism that lives substantially longer than related species, "you need to improve multiple maintenance mechanisms". Long-lived species might have better mechanisms of DNA repair, for example, something Gorbunova is currently investigating in cells from 20 different rodent species. Her team has shown[4] that naked mole-rat cells are hypersensitive to contact inhibition, the tendency to stop growing and dividing when they touch other cells. This characteristic makes the species extraordinarily resistant to cancer.

The naked mole-rat seems to have several potential protective mechanisms at its disposal. For example, a team of Israeli and US researchers recently reported[5] that the animals also have an unusually high level of NRG-1, a protein that protects nerve cells in the brain.

A more comprehensive approach to investigating the mechanics of ageing is provided by metabolomics, which attempts to identify the small molecules that comprise the metabolic profiles of cells. Daniel Promislow, a geneticist at the University of Georgia in Athens, investigated[6] the levels of about 2,500 different molecules in the bloodstream of young and old marmosets. This small monkey, native to South America, is becoming a popular model for studying ageing in primates because it is relatively short-lived and easy to keep in captivity. "All these metabolites and their interactions paint a portrait of the state of that individual," explains Promislow. "And that portrait changes with age."

Promislow's group is carrying out an even larger metabolomics study that will track the levels of more than 20,000 molecules over five years, charting differences between young and old marmosets, and in individual monkeys over time. He has also just finished collecting a similar data set in fruitflies.

So researchers are not short of anti-ageing mechanisms to investigate. For Miller the bigger question is whether these mechanisms are all separate or derived from a common 'master switch' for longevity. As he puts it: "When Nature wants to build a long-lived species, does she have more than one trick to do it?" ■

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