PHOTOTAKE/ALAMY

The naked mole rat has been extensively studied, but no cancer has ever been spotted in this species.

COMPARATIVE BIOLOGY

Naked ambition

A subterranean species that seems to be cancer-proof is providing promising clues on how we might prevent the disease in humans.

BY SARAH DEWEERDT

There is a lot not to envy about the life of the naked mole rat: imagine passing your days in a stuffy, pitch-black system of tunnels two or three metres underground with 100 of your closest relatives. But there is one thing that humans might covet: as far as anyone knows, the animal never gets cancer.

Native to the Horn of Africa, this small rodent (*Heterocephalus glaber*) is neither a mole nor a rat; it is actually more closely related to porcupines and guinea pigs. The animal's pale-pink, wrinkled skin is nearly hairless, the better to slip through those narrow burrows. But there is yet another more compelling fact: in all the thousands of naked mole rats that have lived and died in research labs and zoos over the past several decades, not a single instance of spontaneous cancer has been recorded[1].

So far, the animal provides little more than a footnote to the vast body of cancer literature based largely on studies of laboratory mice. But the species has a few fierce advocates in the scientific community, who say that to truly defeat cancer we need to pay a lot more attention to naked mole rats and species like them.

"If we want to learn what naturally occurring resistance mechanisms protect from cancer, we may not find them in mice because mice are even more prone to cancer than humans," says biologist Vera Gorbunova, who co-leads naked-mole-rat studies at the University of Rochester in New York. In some strains of mice, for example, cancer kills 90% of animals.

In other words, although mice are an excellent model for cancer development, progression and treatment, naked mole rats may be better for prevention. "We have to study species that are more resistant," Gorbunova explains.

Researchers have found it tough to induce cancer in naked mole rats. Working in culture, they have infected cells from the creatures with a genetically engineered virus that contains a pair of oncogenes, or cancer-promoting genes, that reliably turns mouse cells malignant[2,3]. "This common oncogenic cocktail had no effect on the naked-mole-rat cells," says Rochelle Buffenstein, a physiologist at the University of Texas, San Antonio, and a pioneer of naked-mole-rat research. "They did not become tumorigenic, they didn't rapidly proliferate, they didn't invade tissues."

Naked-mole-rat cells also seem to be highly sensitive to their neighbours. Normally when cells are grown in culture dishes, they stop proliferating when they touch neighbouring cells; the end result is a smooth, uniform layer covering the surface of the dish. This property, called contact inhibition, is absent in cancer cells. But Gorbunova's team observed that naked-mole-rat cells stop proliferating after just a few cell-to-cell contacts, rather than when all the spaces on the culture plate have been filled in.

The researchers dubbed this hypersensitivity early contact inhibition, and found that it

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is regulated by two genes: *p16* and *p27* (ref. 2). If *p16* is disabled, they showed, *p27* stops cell growth — but at higher cell densities. In humans and mice, *p27* is the main player in contact inhibition, with *p16* taking a minor supporting role. But in naked mole rats, the two genes have become decoupled, resulting in two layers of protection against runaway growth.

In trying to understand what was activating *p16*, Gorbunova's team noticed that naked-mole-rat cells were secreting something into the growth medium that was making it viscous. "We spent some time trying to isolate the goo, and identify what kind of chemical it is," Gorbunova says.

The goo turned out to be hyaluronan, a long polymer of sugars that occupies the spaces between cells in the skin and connective tissues of vertebrates. But in naked mole rats, hyaluronan production is in overdrive: the animals make a large quantity of an unusually large type of the polymer, and break it down more slowly than do other species[4].

That extra dollop of hyaluronan seems to be key to early contact inhibition, because adding enzymes that degrade it to the culture dish blocks the phenomenon[4]. So does blocking CD44, a receptor found on the surface of cells that binds to hyaluronan. How *p16* and CD44 are functionally connected is unknown, Gorbunova says. "We know the beginning point and the end point of the pathway, but we don't understand what's in between."

Others disagree with this interpretation of the results. "We don't see early contact inhibition in our lab," says Buffenstein, who uses a different protocol for growing naked-mole-rat cells. Under optimal culture conditions, she says, the cells will grow to cover a culture dish.

WEIRD AND WONDERFUL

But the cells behave unusually in other respects, Buffenstein has found. They can survive remarkably high doses of heavy metals and carcinogens, although such agents do stop the cells proliferating. By contrast, a high proportion of mouse cells die at low doses — and those that survive continue to proliferate. These multiplying, damaged cells may be the ultimate source of cancers[5].

In a sense, these results parallel Gorbunova's, Buffenstein believes. "We think it's the same mechanism," she says. "When things aren't exactly the way the cell thinks they should be, the cells just sit tight and stop proliferating."

The recognition that something isn't right probably involves *p53*, a tumour-suppressor gene found in many species, including humans. In most species, *p53* is activated only when cells are stressed, but naked-mole-rat cells produce high levels of the protein even under normal conditions. They also express high levels of another protein — nrf2, a master regulator of hundreds of cell-protection genes[6].

All of this suggests that naked mole rats rely on many of the same cancer-protection mechanisms as do humans, just kicked into high gear. "They've upregulated the system to really be extra careful about changes in the cell and when to replicate and when not to," Buffenstein says.

Applying the model of the naked mole rat to human cancer resistance is unlikely to be as simple as upregulating existing anticancer genes. Too much activity of *p16*, for example, can cause cell ageing and death. "My bet would be to try to somehow manipulate turnover of hyaluronan," Gorbunova says. After all, she points out, hyaluronan is already used as a cosmetic treatment for wrinkles, so it may be a relatively feasible target.

Further research may pinpoint other resistance mechanisms in the naked mole rat. "Perhaps many pathways are involved," says Vadim Gladyshev, a cancer biologist at Harvard Medical School in Boston, Massachusetts, who helped to sequence the animal's genome in 2011. "The problem," he adds, "is that the naked mole rat is quite distant from other organisms with completely sequenced genomes." For precisely this reason, he is now sequencing the genome of the Damaraland mole rat (*Fukomys damarensis*). This close cousin of the naked mole rat also lives underground in groups but does develop cancer, so differences between the species could help to identify genomic regions relevant to resistance.

> ***"To some degree we still lack the molecular tools to study them."***

Another challenge in working with such an unexplored model is that "to some degree we still lack the molecular tools to study them", says João Pedro de Magalhães at the University of Liverpool, UK, who specializes in the genomics of ageing. But DNA sequencing and gene-expression technologies can be applied across species, so his lab is surveying how gene expression changes in cells from mice, rats and naked mole rats after exposure to DNA-damaging chemicals. Such patterns may shed more light on exactly how damaged naked-mole-rat cells decide when to stop proliferating.

The naked mole rat is not the only cancer-resistant animal. Scientists are increasingly focusing their attention on the blind mole rat (*Spalax* spp.). These are furry brown torpedoes of rodents that are agricultural pests in the Mediterranean region. "In none of the *Spalax* we've raised, thousands of individuals, have we ever found any cancer," says Eviatar Nevo, founder of the Institute of Evolution at the University of Haifa in Israel.

Despite their similar names, blind mole rats are not closely related to naked mole rats (they are more closely related to rats and mice). The two animals evolved their resistance independently, making for intriguing similarities and differences in the underlying mechanisms.

For example, blind mole rats produce hyaluronan in a form similar to that of naked mole rats, but their cells do not show early contact inhibition when grown in the lab. However, the contact inhibition they do show is not normal: instead of filling a culture dish and then holding steady, blind-mole-rat cells undergo mass cell death when they reach high densities[7].

But the species have in common a *p53* tumour-suppressor gene that functions in an unusual way. In the blind mole rat, this gene has a sequence almost identical to a mutated form of *p53* found in many human cancers, and it seems to encourage cells to stop proliferating rather than to self-destruct[8].

DIRECT ATTACK

Researchers at the University of Haifa have also discovered a tantalizing clue that anticancer mechanisms in the blind mole rat may involve selective destruction of malignant cells. When placed in the same laboratory dish as cells derived from human breast or liver cancers, blind-mole-rat cells reduce survival of the cancer cells[9] — suggesting that they secrete an anti-proliferation factor into the medium.

Many researchers believe that these species' cancer resistance is related to their ability to tolerate the oxygen-poor environment of underground burrows, which is similar to the oxygen-poor environment experienced by cells in rapidly growing tumours. "The idea that an animal living in a cancer-like environment would be able to generate adaptations against cancer is very, very natural," Nevo says. "There are 200 species of subterranean mammal," he adds, suggesting that additional anticancer mechanisms may be found by studying this group of species more thoroughly.

Other researchers are looking more broadly across the animal kingdom, plumbing the genomes of long-lived, cancer-resistant species such as Brandt's bat (*Myotis brandtii*) and the bowhead whale (*Balaena mysticetus*). "Harnessing the power of natural selection to increase our knowledge of cancer and hopefully develop therapies against cancer or for cancer prevention is a very unexplored area," says de Magalhães. The end of cancer may yet prove to be underground — or in the seas or in the air. ■

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1. Delaney, M. A., Nagy, L., Kinsel, M. J. & Treuting, P. M. *Vet. Pathol.* **50,** 607–621 (2013).
2. Seluanov, A. *et al. Proc. Natl Acad. Sci. USA* **106,** 19352–19357 (2009).
3. Liang, S., Mele, J., Wu, Y., Buffenstein, R. & Hornsby, P. J. *Aging Cell* **9,** 626–635 (2010).
4. Tian, X. *et al. Nature* **499,** 346–349 (2013).
5. Lewis, K. N., Mele, J., Hornsby, P. J. & Buffenstein, R. *Gerontology* **58,** 453–462 (2012).
6. Lewis, K. N., Mele, J., Hayes, J. D. & Buffenstein, R. *Integr. Comp. Biol.* **50,** 829–843 (2010).
7. Gorbunova, V. *et al. Proc. Natl Acad. Sci. USA* **109,** 19392–19396 (2012).
8. Ashur-Fabian, O. *et al. Proc. Natl Acad. Sci. USA* **101,** 12236–12241 (2004).
9. Manov, I. *et al. BMC Biol.* **11,** 91 (2013).