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Biology

Advanced

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Scientific Article for use with Question 7

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Naked and ugly: The new face of lab rats



1. In a small room in the lab-animal wing of the University of Illinois at Chicago, biologist Thomas Park peers into a plastic box full of naked mole rats. "You guys are so cute," he says softly, in a voice usually reserved for babies or puppies.
2. Park is mistaken. Naked mole rats are not cute. They are bald, wrinkled and purply pink, with tiny near-blind eyes and huge yellow teeth. Ranging from the size of a large mouse to that of a small rat, these odd rodents are among the strangest looking mammals on the planet. But don't judge a naked mole rat by its unfortunate appearance. These bizarre creatures could help us tackle all sorts of human maladies, from cancer and stroke to pain relief and ageing.






Naked Mole Rat

Magnification $\times 0.3$

3. A dozen species of mole rat exist, all native to sub-Saharan Africa. Naked mole rats stand out, though, not least because they appear completely bald. They are also extremely social, living underground in elaborate networks of tunnels and chambers in groups of up to 300. Here in the lab, Park mimics their burrow system by connecting several dozen plastic boxes with long tubes. The animals spend their days pushing bedding around the tubes and nibbling on bits of sweet potato.
4. "Naked mole rats are a really odd mammal species," Park tells me. "Their social structure is like that of insects." Akin to bees and ants, they live in a eusocial society in which a single breeding queen churns out all the offspring, with help from between one and three kings. The rest of the animals work for a living: soldiers defend the colony against predators and rivals, while housekeepers forage for root vegetables and tidy up the tunnels.
5. Many features of the skin of the naked mole-rat, such as the lack of an insulating layer and the loosely folded morphological arrangement contribute to poikilothermic responses to changing temperatures of this mammal. Further evidence for poikilothermy in the naked mole-rat is indicated by the presence of pigment containing cells in the dermis, rather than the epidermis, as commonly occurs in homeotherms. Lack of fur is compensated by a thicker epidermal layer and a marked reduction in sweat glands.

6. This unusual social arrangement is what first drew scientists to study the wrinkled rodents. "For many years, most of the studies were on their behaviour," says Rochelle Buffenstein, a physiologist at the University of Texas Health Science Center in San Antonio. In time, though, researchers couldn't help but notice another intriguing aspects of naked mole rat biology. "They are incredibly long-lived creatures," she says. 
7. In general, lifespan tends to correlate with body size. Large animals, on average, live longer than small ones. However, while mice and rats are lucky to survive three years in captivity, similar-sized naked mole rats live three decades, making them the longest-lived rodents on Earth. That's not all. They also maintain excellent health well into their sunset years. Their bones remain strong, their bodies stay fit and they don't show signs of heart disease or mental decline. Breeding females continue to produce pups right up to the end and, to top it off, naked mole rats don't even get cancer. 
8. Naturally, scientists are eager to understand the secrets of this small, bald Methuselah. Buffenstein, who has been studying naked mole rats for 30 years, is among those looking for molecular explanations for their astounding longevity. She began by investigating their response to oxidative stress, one of the leading theories of how the ageing process works.
9. According to this theory, oxygen-containing free radicals damage the molecules of the body, causing them to deteriorate over time until they stop functioning altogether. This oxidative damage, as it is known, is apparent as extra molecules that attach to DNA and proteins "like chewing gum stuck to the bottom of a shoe", Buffenstein says. If oxidative stress is truly an important mechanism of ageing, she predicted, naked mole rats should have lower rates of oxidative damage than more short-lived species.
10. To her surprise, Buffenstein found the opposite: more telltale oxidative damage in 6-month-olds than in mice of the same age. Remarkably, however, the damage had no obvious impact on their well-being.

Keeping in shape

11. Why is this? To find out, Buffenstein took a closer look at the 3D structure of proteins, which is critical to their functioning. Mouse proteins begin misfolding very quickly after suffering oxidative damage – a kind of anti-origami that causes them to stop working properly. But naked mole rat proteins can withstand significantly more damage before they lose their shape (*Proceedings of the National Academy of Sciences*, vol 106, p 3059). "We think [protein stability] is a very important component of their extraordinary longevity," she says. "If your proteins maintain their integrity, if they have the mechanisms to protect themselves, it doesn't matter what stress comes along." 

12. Another factor that helps naked mole rats reach an advanced age is their remarkable ability to avoid cancer. Nearly all mice have cancerous cells lurking in their bodies by the time they die but cancer has never been seen in a naked mole rat. "Every time one of our animals die, we try to figure out what they die of," Buffenstein says. "We haven't seen a tumour, we haven't seen lesions, we haven't seen signs of lymphoma. We know they don't get age-related cancer."
13. To understand why, Buffenstein and her colleague Peter Hornsby introduced cancer-causing genes into cells from rats, mice, humans and naked mole rats. They then inserted the altered cells into immune-compromised mice. In two to four weeks, the mice injected with modified cells from rats, mice and humans developed highly invasive tumours. "In the case of naked mole rats, six months lapsed and there were still no tumours," Buffenstein says. 

14. The abnormal cells were still alive but had stopped replicating. "We think mole rats have better surveillance mechanisms to assess what's going on in their DNA," she says. When things go awry, the deviant cells are essentially locked away, unable to replicate and cause tumours (*Aging Cell*, vol 9, p 626).
15. This is probably just one of several tricks that allow these animals to avoid cancer. Another possible mechanism being investigated centres on how cells multiply. When cultured in a Petri dish, cells from both mice and humans multiply until they form a single dense layer. At that point, they stop dividing, halted by a process called contact inhibition. In cancerous tissues, however, the abnormal cells continue to multiply, piling up and growing out of control.
16. "We think we've found the reason these mole rats don't get cancer, and it's a bit of a surprise," says Vera Gorbunova, associate professor of biology at the University of Rochester and lead investigator on the discovery.
17. Naked mole rats can live up to 30 years, which is exceptionally long for a small rodent. Despite large numbers of naked mole-rats under observation, there has never been a single recorded case of a mole rat contracting cancer, says Gorbunova. Adding to their mystery is the fact that mole rats appear to age very little until the very end of their lives.
18. Over the last three years, Gorbunova and Andrei Seluanov, research professor of biology at the University of Rochester, have worked an unusual angle on the quest to understand cancer: Investigating rodents from across the globe to get an idea of the similarities and differences of how varied but closely related species deal with cancer.
19. In 2006, Gorbunova 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.
20. Until Gorbunova and Seluanov's research, the prevailing wisdom had 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, says Gorbunova. 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.
21. 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?
22. Gorbunova sought to answer that question, and in 2008 confirmed that small-bodied rodents with long lifespans had evolved a previously unknown anti-cancer mechanism that appears to be different from any anticancer mechanisms employed by humans or other large mammals.
23. At the time she was not able to identify just what the mechanism might be, saying: "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. Mice are short-lived and humans are large-bodied. But this mechanism appears to exist only in small, long-lived animals."
24. Now, Gorbunova believes she has found the primary reason these small animals are staying cancer-free, and it appears to be a kind of overcrowding early-warning gene that the naked mole rat expresses in its cells.

25. When Gorbunova and her team began specifically investigating mole rat cells, they were surprised at how difficult it was to grow the cells in the lab for study. The cells simply refused to replicate once a certain number of them occupied a space. Other cells, such as human cells, also cease replication when their populations become too dense, but the mole rat cells were reaching their limit much earlier than other animals' cells.
26. "Since cancer is basically runaway cell replication, we realized that whatever was doing this was probably the same thing that prevented cancer from ever getting started in the mole rats," says Gorbunova.
27. Like many animals, including humans, the mole rats have a gene called *p27* that prevents cellular overcrowding, but the mole rats use another, earlier defense in gene *p16*. Cancer cells tend to find ways around *p27*, but mole rats have a double barrier that a cell must overcome before it can grow uncontrollably.
28. "We believe the additional layer of protection conferred by this two-tiered contact inhibition contributes to the remarkable tumor resistance of the naked mole rat," says Gorbunova in the *PNAS* paper.
29. Gorbunova and Seluanov are now planning to delve deeper into the mole rat's genetics to see if their cancer resistance might be applicable to humans.
30. This finding could be an important step towards new cancer therapies. Gorbunova and her colleagues are now trying to decipher the extracellular signals that prompt early contact inhibition. In theory, such a signal might be co-opted to stimulate the process in human cells, and prevent tumours from forming. "If this is some kind of extracellular molecule, then we could actually apply it to people as an injection or a drug," she says.
31. Exciting as that research may be, cancer and ageing are only the tip of the iceberg as far as the naked mole rat's peculiar biology is concerned. The rodent's neurobiology is also of interest, as Park is discovering. Setting out to better understand their sense of touch, he stumbled across something surprising: they lack a receptor that transmits messages about chemical pain. Inject lemon juice or the essence of chilli pepper, capsaicin, beneath the skin of a mouse's paw, and it will shake and lick it like crazy. "If you do that with naked mole rats, they don't do anything," Park says. "They couldn't care less." Naked mole rats do feel acute pain such as cuts and burns, he says, but they are impervious to chemical pain (*PLoS Biology*, vol 6, p e13).
32. This finding is particularly significant because the nerve fibres associated with chemical pain are also involved in post-traumatic pain in people – precisely the type of discomfort researchers would like to eliminate. "It's OK to have pain sensation to tell you to get your hand off the stove, or to stop exercising because your knee is in trouble," says Park. "But post-surgical pain, or joint pain after a knee injury, those types of pain we could do without. The naked mole rats are laying the groundwork for potentially finding new ways to treat the kinds of pain we don't want."
33. Though the applications are intriguing, Park's own interests are more basic: why would naked mole rats lack this type of pain? The answer, he suspected, stemmed from their unusual habitat. Although many animals live underground, few live in such close quarters and in such large numbers as naked mole rats. The air in their burrows is rank, with low oxygen levels and extremely high levels of carbon dioxide. While normal air is about 0.03 per cent CO₂, levels in naked mole rat burrows can easily reach 5 per cent or more – an intensity that would sting our eyes and noses and leave us gasping for air. The rodents, however, are unaffected. "They will stay away from 10 per cent CO₂, but they're perfectly happy to wallow around in 5 per cent," Park says. "It turns out that high levels of CO₂ affect the types of nerves that the naked mole rats have disconnected," he says. "I think that's the evolutionary driving force to disconnect these pain nerves."



34. This isn't the only effect the naked mole rat's burrows have on their physiology. The low oxygen levels are just as important. Fresh air contains about 21 per cent oxygen, whereas levels in the burrows can be as low as 12 per cent in captive colonies, and are probably much lower in the wild. Park has found that naked mole rat brains are incredibly resistant to oxygen deprivation, with their brain tissue able to bounce back after 30 minutes without the gas (*NeuroReport*, vol 20, p 1634).
35. Two University of Illinois at Chicago researchers report that adult naked mole rat brain tissue can withstand extreme hypoxia, or oxygen deprivation, for periods exceeding a half-hour – much longer than brain tissue from other mammals.
36. The findings may yield clues for better treatment of brain injuries associated with heart attack, stroke and accidents where the brain is starved of vital oxygen.
37. John Larson, associate professor of physiology in psychiatry, and Thomas Park, professor of biological sciences, studied African naked mole rats – small rodents that live about six feet underground in big colonies of up to 300 members. The living is tight and the breathing even worse, with the limited air supply low in oxygen.
38. But naked mole rats studied were found to show systemic hypoxia adaptations, such as in the lungs and blood, as well as neuron adaptations that allow brain cells to function at oxygen and carbon dioxide levels that other mammals cannot tolerate.
39. "In the most extreme cases, naked mole rat neurons maintain function more than six times longer than mouse neurons after the onset of oxygen deprivation," said Larson.
40. "We also find it very intriguing that naked mole rat neurons exhibit some electrophysiological properties that suggest that neurons in these animals retain immature characteristics."
41. All mammal fetuses live in a low-oxygen environment in the womb, and human infants continue to show brain resistance to oxygen deprivation for a brief time into early childhood. But naked mole rats, unlike other mammals, retain this ability into adulthood.
42. "We believe that the extreme resistance to oxygen deprivation is a result of evolutionary adaptations for surviving in a chronically low-oxygen environment," said Park.
43. "The trick now will be to learn how naked mole rats have been able to retain infant-like brain protection from low oxygen, so we can use this information to help people who experience temporary loss of oxygen to the brain in situations like heart attacks, stroke or drowning," he said.
44. Larson said study of the naked mole rat's brain may yield clues for learning the mechanisms that allow longer neuronal survival after such accidents or medical emergencies, which may suggest ways to avoid permanent human brain damage.



Sociable by nature

45. Medical benefits may even arise from continuing research into naked mole rat behaviour. Previous studies in voles and other mammals have shown that behaviours such as monogamy and maternal performance can be explained, in part, by genetic differences that influence the patterns of certain hormone receptors in the brain. To find out whether naked mole rats' sociability has a genetic factor, Chris Faulkes at Queen Mary, University of London and colleagues compared their brains with those of the solitary cape mole rat. They were looking for receptors that bind to the "cuddle chemical" oxytocin. The team found that the naked mole rat has far more of these receptors in several brain regions including the nucleus accumbens, an area known as the brain's pleasure centre, and assume this is under genetic control (*Journal of Comparative Neurology*, vol 518, p 1792). "It's a good example of a change in a gene giving a change in complex behaviour," says Faulkes. Changes in the oxytocin receptor in humans are associated with certain kinds of autism, he adds, so the finding could have direct implications for humans.
46. The possibilities don't end there. Naked mole rats do not experience menopause or osteoporosis, so perhaps they could help researchers develop osteoporosis treatments without the side effects of hormone replacement therapy. And, as they spend 24 hours a day in the dark, naked mole rats don't follow normal circadian rhythms. Studies of their sleep patterns could feasibly help treat disordered sleep in humans.
47. Even their incisors are fascinating. Instead of staying put in their mouths, they grow right through the skin of the lips, something of great interest to prosthetics designers. Traditional prosthetics put pressure on delicate soft tissue causing sores and cell death, so a team led by Gordon Blunn and Catherine Pendegrass at University College London are testing new prosthetics that are attached directly to the bone of an amputated limb. To avoid infection, however, there needs to be a permanent seal where the skin meets the metal implant. This is where naked mole rats come in. Understanding the interface between their teeth and skin may help in the development of new coatings or structures that can be applied to the prosthetics.
48. Our current hypothesis is that behavioural interactions between the queen and non-breeders are translated into a suppression of gonadotrophin-releasing hormone in the hypothalamus, which in turn suppresses the release of gonadotrophins from the anterior pituitary. This results in a suppression of ovulation in non-breeding females, while in non-breeding males testosterone concentrations and sperm numbers are lower, and in most males sperm are non-motile. Not only does the queen suppress reproductive function in the non-breeders, but she also apparently exerts some control over the breeding male(s), such that concentrations of testosterone in the latter are suppressed except around the time of ovulation in the queen. Despite these endocrine deficiencies in non-breeders that may persist for many years, the block to reproduction is reversible. Non-breeding males and females will rapidly become reproductively active if they are removed from the suppressing influences of their colony and housed singly or in male-female pairs, or if the queen in a colony dies.
49. Patterns of genetic structure in naked mole-rat populations were quantified within and among geographically distant populations using DNA fingerprinting. Individuals within colonies were genetically almost monomorphic, having coefficients of band sharing estimated from DNA fingerprints ranging from 0.93 to 0.99.

50. Prolonged inbreeding is usually associated with lowered fitness, and it has been shown that most highly inbred small mammals have inbreeding-avoidance mechanisms that promote some degree of outbreeding. Although rare, a dispersive morph exists within naked mole-rat colonies that may occasionally promote outbreeding. These dispersers are morphologically, physiologically and behaviourally distinct from other colony members. They are laden with fat, exhibit elevated levels of luteinizing hormone, have a strong urge to disperse, and only solicit matings with non-colony members.
51. Kin recognition and female mate choice using a series of choice tests in which the odour, social and mate preferences of females were determined. Discrimination by females appears to be dependent on their reproductive status.
52. Reproductively active females prefer to associate with unfamiliar males, whereas reproductively inactive females do not discriminate. Females do not discriminate between kin and non-kin suggesting that the criterion for recognition is familiarity, not detection of genetic similarity *per se*. In the wild, naked mole-rats occupy discrete burrow systems and dispersal and mixing with non-kin is thought to be comparatively rare. Thus, recognition by familiarity may function as a highly efficient kin recognition mechanism in the naked mole-rat. A preference by reproductively active females for unfamiliar males is interpreted as inbreeding avoidance. These findings suggest that, despite an evolutionary history of close inbreeding, naked mole-rats may not be exempt from the effects of inbreeding depression and will attempt to outbreed should the opportunity arise.
53. With so much to offer science, it is no surprise that naked mole rats are becoming more common in labs. Unlike mice, the naked mole rat hasn't yet had its genome sequenced yet. "With naked mole-rats, we have to start from scratch with many things," Gorbunova says. "It's not very convenient, but I think it's definitely worth it."

Acknowledgements

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