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Why Naked Mole Rats Don’t Get Cancer *by* Ed Yong

The problem with writing about the [naked mole rat](http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/naked_mole_rats_can_they_help_us_cure_cancer_.html) is the long list of bizarre traits that you don’t have space to talk about. For this post, let’s  forget that they look like a wrinkled finger with teeth. Put aside their inability to feel pain in their skin, their tolerance for chokingly low oxygen levels, their[bizarrely rubbish sperm](http://phenomena.nationalgeographic.com/2011/12/04/the-rubbish-sperm-of-the-naked-mole-rat/) or their poor temperature control. Don’t even think about how they live in ant-like colonies, complete with queens and workers. Ignore their ability to live for more than 30 years—an exceptional lifespan for a rodent of their size.

Instead, let’s talk about the cancer angle.

They don’t get it.

No one has ever seen a naked mole rat with a tumour. Scientists have raised[large colonies of these rodents](http://www.ncbi.nlm.nih.gov/pubmed/18180931) and watched them for many years. They’ve never seen an individual spontaneously develop cancer.

Now, Xiao Tian, Jorge Azpurua and Christopher Hine from University of Rochester have discovered one of the secrets behind this exceptional resistance. The team were trying to grow skin cells from naked mole rats in laboratory flasks, when they noticed something weird. The liquid that the cells were growing in would get viscous and syrupy within a few days.

This was because the cells secreted a sugar called hyaluronan, which was thickening the liquid. Hyaluronan is common in the skin, cartilage and other connective tissues of mammals. Like mortar in a wall, it’s one of many molecules that fill [the spaces between cells](http://en.wikipedia.org/wiki/Extracellular_matrix) and provide them with support. The naked mole rat makes an exceptionally large version of the sugar that’s over five times bigger than ours. And it has a *lot*of it.

There are two innovations behind the naked mole rat’s hyaluronan-fest—ineffective versions of the enzymes that digest hyaluronan, and altered versions of the protein that makes it. This hyaluronan-maker, known as HAS2, is made of 552 amino acids. The naked mole rat has altered just two of these, which are always the same in other mammals. These tiny changes were enough to allow it to make a monster hyaluronan.

[Andrei Seluanov](http://www.rochester.edu/College/BIO/professors/seluanov), who led the study, suspects that the larger hyaluronan physically cages potential cancer cells, preventing them from breaking free and growing into tumours. But it also allows cells to stop each other from growing if they become too crowded. This is called ‘[contact inhibition](http://www.ncbi.nlm.nih.gov/pubmed/19858485)’—it’s why healthy cells form a flat layer if they’re grown in a dish but cancerous ones pile on top of each other.

[Based on an earlier study](http://news.sciencemag.org/sciencenow/2009/10/26-02.html), Seluanov’s team suspected that naked mole rat cells are protected against cancer because they’re especially sensitive to contact inhibition. Now, they’ve shown that large hyaluronan is responsible. The rodents’ cells are very receptive to the sugar; as they get close, hyaluronan sticks to their surface and triggers a genetic programme that stops them from growing.

As a final test of their ideas, the team switched on a couple of cancer genes in naked mole rat cells and transplanted them into mice. Normally, nothing would happen—the cells are *that*resistant to cancer. But when the team also interfered with hyaluronan, either by stopping its production or boosting its destruction, the naked mole rat cells finally did the unthinkable—they formed tumours.

Seluanov thinks that hyaluronan is probably the naked mole rat’s “primary anti-cancer mechanism”. After all, disrupting it makes the rodent’s cells as cancer-prone as those of a mouse. Not so fast, cautions [Rochelle Buffenstein](http://physiology.uthscsa.edu/new/research/faculty_view.asp?id=57)from the University of Texas Health Science Center, who discovered the naked mole rats’ cancer resistance. “This is now the third study to provide a potential mechanism,” she says. “Clearly there are multiple anti-cancer defenses employed in the naked mole rat.” Others might include [mass suicide](http://www.ncbi.nlm.nih.gov/pubmed/23129611)of overgrowing cells, and a [tolerance for DNA-damaging oxygen molecules](http://www.ncbi.nlm.nih.gov/pubmed/23025341).

So why did this animal evolve its super-sized hyaluronan? The answer might have nothing to do with cancer.  Seluanov says that the large sugars are slightly elastic and surround themselves with water molecules—two properties that make the naked mole rat’s skin very loose and stretchy. This allows it to move through tight underground tunnels without ripping its flanks as it rubs against dirt, rocks or tubers. Perhaps the large hyaluronans evolved as an adaptation for underground life, and a cancer-free existence was just a neat bonus!

Does this discovery mean anything for humans? It’s tempting to think that hyaluronan holds the secret to stopping cancer, but we have to tread carefully. In the early days of hyaluronan research, scientists were confused by the fact that the molecule seemed to both prevent and cause cancer (the Daily Mail would have loved it).

Since then, we’ve discovered that the sugar’s size is responsible for its dual nature. [Bryan Toole](http://regmed.musc.edu/Faculty/TooleB.htm) from the Medical University of South Carolina, who studies hyaluronan, says that high concentrations of the large versions can stop cells from turning cancerous, while smaller versions can actually promote cancer. In a similar way, the large forms tamp down inflammation while the small ones exacerbate it, which may relevant to cancer since inflammation is tied to several tumours. “It’s not clear how the cell distinguishes between the two,” adds Seluanov. That’s something the team still needs to find out.