

an unexpected turn of events

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Life depends on exchange. To this end, and on the cellular level, molecules are continuously secreted for the purposes of signalling, strengthening, transporting, protecting... Sometimes, the primary role of a molecule can bring about an unforeseen consequence which – if positive – is gladly preserved for the benefit of the species. This seems to be the case for a particular form of a polysaccharide known as hyaluronan: high molecular mass hyaluronan, or HMM-HA. The polymer is secreted in large quantities in a rather peculiar animal – the naked mole rat, or *Heterocephalus glaber* – and is thought to be responsible, at least in part, for the animal's exceptionally long life span, because of the total absence of any form of cancer. Consequently, understanding how HMM-HA achieves this – and particularly the enzyme which synthesizes it, hyaluronan synthase 2 – could pave the way to therapies able to fight off the formation of malignant tumours.



"Naked mole bat", by Dominick Rabrun

courtesy of the artist

Naked mole rats are peculiar creatures that live in the plains of East Africa. They were first described by Eduard Rüppell (1794-1884), a German naturalist and explorer, who thought he had come across a diseased or mutated rat. The species does, indeed, seem to be one of Nature's freaks. They are one of the very rare mammals who live in colonies that are organised like those of ants. There is one queen and two or three sexually active males, while the rest of the colony is busy burrowing away or fighting off

predators. They are very short-sighted, move backwards and forwards with equal ease, are unable to regulate their body temperatures and spend their whole life underground, squeezing their way through dark narrow tunnels in oversized elastic skin, as though they were all wearing handed down sweaters. And, last but not really not least, they have a lifespan of about 30 years – 20 times longer than that of other rodents, and the equivalent of 600 years for a human being...

The elasticity of the rats' skin is important for the surroundings in which they live and is the makings of the polysaccharide HMM-HA. HMM-HA is a very large version of hyaluronan (HA), which is secreted by fibroblasts into the extracellular matrix, and coats the outer plasma membrane along with other extracellular macromolecules such as collagen. HA participates in giving tissues their shape, and skin its elasticity, but also regulates fundamental cell behaviours such as cell adhesion, cell migration and cell differentiation. Naked mole rat fibroblasts synthesize a very long and large (5 to 6 times larger than in mice) version of HA – or HMM-HA – by building a thick cushion of goo around the cell's surface. It is thought that this special form of HA evolved in naked mole rats to help them squeeze more easily through their narrow tunnels. It is this

thick protective layer that prevents tumour cells from replicating by literally nipping would-be cancers in the bud.

HA is synthesized by three different hyaluronan synthases in mammals – each of which produce HA of a different size, with different properties. HA which coats the cells' membranes are synthesized by hyaluronan synthase 2, or HAS2. It is a transmembrane protein; its product, HA, is synthesized inside the cell and then secreted. In naked mole rats, HAS2 has a unique sequence change: two asparagine amino acids – which are conserved 100% in all other mammals – are replaced by two serine amino acids. These two Ser are located in the middle of the cytoplasmic loop which contains the enzyme's active site. The exchange of asparagine for serine is enough to direct the production of HMM-HA, which gives the extra goo to the naked mole rats' cells.

In what way does HMM-HA protect naked mole rats from cancer? HA has a role in the regulation of cell proliferation. When the level of polysaccharide is high, cells stop multiplying. And when it is low, they don't. This is the consequence of a phenomenon known as contact inhibition, i.e. when cells come into contact with each other or the extracellular matrix. When HMM-HA is secreted, it binds to receptors on cell surfaces which, in turn, trigger off anti-mitotic signals, thus preventing the cell from multiplying. It is then easy to understand that contact inhibition is a powerful anticancer mechanism – which malignant tumour cells

have lost. The accumulation of HMM-HA in naked mole rats is caused by an overexpression of HAS2, weak expression of HA-degrading enzymes and good binding affinity. The result is a mass of hyaluronan in the rats' tissues, which – though first meant for elasticity and viscosity – acts as a barrier to cancer almost as an afterthought.

Rats and mice are used as laboratory models because of their relatively short life span of about 4 years due, in part, to their tendency to develop cancer. Hence, rats and mice must have fewer anticancer mechanisms than naked mole rats. This is why it would be informative to inspect these creatures more closely.

HA is already administered by injection to treat arthritis and wrinkles. But how would you administer HMM-HA to every tissue? Engineering each cell type in a human body would be problematic. Therapies could also target HMM-HA's receptor or the downstream signalling pathway. Besides anticancer remedies, in the future it may be possible to modify human skin, brain, eyes and blood vessels – tissues in which HA production decreases with age, making them lose their elasticity. A greater knowledge of HMM-HA and its accidental role in preventing cancer and extending life may well help lengthen the lives of humans in the future. But there is more to a long life than molecules. Bestowed with infinite patience and a peaceful social organisation, naked mole rats go through life under – what seems to be – little stress...

Cross-references to UniProt

Hyaluronan synthase 2, *Heterocephalus glaber* (Naked mole rat) : G5AY81

Hyaluronan synthase 2, *Mus musculus* (Mouse) : P70312

References

1. Tian X., Azpurua J., Hine C., Vaidya A., Myakishev-Rempel M., Ablaeva J., Mao Z., Nevo E., Gorbunova V., Seluanov A.
High molecular mass hyaluronan mediates the cancer resistance of the naked mole rat
Nature 499:346-349(2013)
PMID: 23783513
2. Itano N., Sawai T., Yoshida M., Lenas P., Yamada Y., Imagawa M., Shinomura T., Hamaguchi M., Yoshida Y., Ohnuki Y., Miyauchi S., Spicer A.P., McDonald J.A., Kimata K.
Three isoforms of mammalian hyaluronan synthases have distinct enzymatic properties
The Journal of Biological Chemistry 274:25085-25092(1999)
PMID: 10455188