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Natural Cancer Immunity in Naked Mole Rat: A Review

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ABSTRACT: The present understanding of naked mole rat which is cancer resistant is examined in this research paper. The review will examine the crucial issue of cancer resistance in naked mole rat and concentrate on the reasons why people are more susceptible to cancer than this animal. Studying their genes that are resistant to cancer in order to treat human cancer sickness involves the proliferation, tumour growth and development of cancer in humans. The review specifically discusses cancer in the first section before moving on to why naked mole rat are resistant to the disease and outlining the mechanisms involved. Modern techniques detect cancer in early stages which decreases the death rate and increases the recovery of cancer patient. The review will then examine the cancer treatment from the perspective of the gene present in naked mole rat that fight cancer utilised in pharmacological treatment.

Keywords: Contact inhibition, Sand puppy (naked mole rat), Subterranean mole rat, Fibroblastic cells.

INTRODUCTION

Cancer is among the leading causes of death worldwide. In 2022, there were almost 20 million new cases and 9.7 million cancer-related deaths worldwide or one in every six fatalities. Women are more likely than men to have breast, colorectal, lung, cervical, and thyroid cancer. Men are more likely to acquire stomach, liver, lung, prostate, and liver cancer. Cancer is a serious problem.

Modern techniques detect cancer in early stages which decreases the death rate and increases the recovery of cancer patient.

Not only in human cancer also spread in animals while some animals are resistant to cancer. In developed countries, cancer is still the second biggest killer. There are numerous remedies available nowadays for various types of cancer, but the majority have negative effects and harm the body's healthy tissues.

Creating a therapeutic or preventative approach that is effective and harmless is one of cancer research's key objectives. Given the stark differences across animal species in their rates of cancer and the ages at which diseases first manifest themselves, such naturally-occurring methods have in fact undergone several evolutionary iterations. For instance, cancer kills 50 to 90 percent of old mice when compared to around 23% in humans.

Wild animal cancer is a topic that receives little research. However a few species have a reputation for having high levels of cancer resistance which include naked mole rat. According to the species' longevity, the age at which cancer first appears also varies substantially. Long-lived species experience cancer development over decades, compared to a mouse's two-year average.

The disease affects not just people but also animals. Humans and animals differ slightly in that some animals have a mechanism for resistance to cancer.

Since these creatures have mechanisms, we need to conduct research to understand them. Elephants, howling whales, naked mole rats, blind mole rats, and great white sharks are just a few of the animals that are resistant to cancer. Because of their huge bodies, these animals are more resistant to cancer than smaller animals, but they also have tumour suppressor genes or other mechanisms or genes that are already present in their bodies.

Although the sand puppy has a long lifespan of 30 to 200 years, he has a gene that makes him resistant to cancer and since mice are more closely related to humans, more research is being done on them. The primary goal of the research paper is to develop a treatment for cancer that will prevent future cancer epidemics.

CANCER RESISTANCE MECHANISM THE SAND PUPPY

The mouse-sized *Heterocephalus glaber* lives in underground tunnels in East Africa. Because there is no need for insulation underground due to the consistent temperature, Heterocephalus shed its fur, giving them their odd moniker look. The fact that this particular rat is nude is not its most intriguing trait. The greatest longevity in captivity for naked mole rats is 32 years (although they spend shorter lives in the wild) (Buffenstein and Jarvis 2002).

They also have very high levels of cancer resistance (Buffenstein, 2008; Liang *et al.,* 2010). Only six incidences of malignancies, two of them possibly benign (Delaney *et al.,* 2016), have been discovered during decades of monitoring thousands of individual

animals in zoo colonies and biomedical research labs (Delaney *et al.,* 2013).

The six documented neoplasms were all found in zoos. The sand puppy exhibits excellent cancer resistances is caused by a number of ways. In fact, a single mechanism would not be adequate to prevent cancer during a 10-fold longer lifespan than that of a mouse.

A class of tiny, long live animal species including the sand puppy, that depends on anti-hyperplastic tumour suppressor systems and don't experience replicative senescence. Inhibition of early contact (ECI) a phenomenon, causes the sand puppy's fibroblasts to multiply very slowly in culture (Seluanov *et al.,* 2009). The majority of typical adherent cells have a trait called contact inhibition. Normal cells stop reproducing when they are in close proximity to one another and dense monolayer was formed.

On the other hand, cancerous cells lose the ability to prevent contact and grow continuously. Contact inhibition in sand puppy's cells is more prone as compared to other species and they also arrest cell proliferation sooner before creating a denser fibroblastic cells monolayer.

Instead of p27 there is stimulation of p16INK4A, these are the proteins that shows contact inhibition often involves in species like the human or mouse causes ECI to occur. Normal contact inhibition is induced by inducing p27 if Cdkn2aINK4A (encoding p16INK4A) is silenced or altered in sand puppy's fibroblasts (Hanahan and Weinber 2000).

It takes the removal of both the Cdkn2aINK4A and Cdkn1b genes to entirely abolish contact inhibition in the sand puppy (encoding p27). Due to the fact lost in majority of tumors due to contact inhibition, two levels of defence promotes cancer resistance (Weinberg *et al.,* 2001).

It's interesting to note that the Cdkn2a-Cdkn2b locus in sand puppy have a distinct structure and is under positive selection (Kim *et al.,* 2011). The important tumour suppressor genes Cdkn2a and Cdkn2b are located in a region that is rapidly evolving (Sharpless, 2005). It encodes the CDK inhibitors p15INK4B and p16INK4A in both humans and mice, ARF is the activator protein of p53 shared coding sequence with p16INK4A. The first exon of p15 is fused with the second and third exons of p16INK4A in the naked mole rat, however, as a result of alternative splicing (Tian *et al.,* 2015).

The resulting new compound, pALT, functions as a powerful CDK inhibitor, providing the sand puppy's cells with another degree of controlled cell cycle (Tian *et al.,* 2013). It has been demonstrated that a particular extracellular signal that activates ECI is produced by naked mole rat cells and consists of HMM-HA.

The Cdkn2a-Cdkn2b gene is activated through a signalling pathway that needs the CD44 receptor. But it is uncertain what happens during the intermediary signalling stages. The main non-protein element of extracellular matrix is hyaluronan, a linear glycosaminoglycan (ECM). Longer hyaluronan molecules possess anti-metastatic, anti-proliferative as well anti-inflammatory properties (Toole, 2004).

In shorter molecules, on the other hand linked to metastasis, faster proliferation and inflammation. The molecules of hyaluronan are 6–10 times smaller than human and mouse than they are in the sand puppy. The high levels of HMM-HA in sand puppy are caused by two different causes. The enzymes that degrade hyaluronan known as hyaluronidases are only moderately active in the tissues of sand puppy. The first is that the naked mole rat has a special sequence in its hyaluronan synthase 2 (Has2) gene that may help to boost hyaluronan production. When Tp53 and Rb1 are inactivated and HrasG12V is activated in sand puppy's cells, HMM-HA is abrogated. This can be accomplished by either silencing the gene or overexpressing a hyaluronan-degrading enzyme (Tian *et al.,* 2013).

Hence, for fibroblasts from naked mole rats to convert into cancer four hits are necessary. Four of them are unique to the sand puppy, although three of them are linked to other rodents and the fourth is linked to HMM-HA.

Another distinctive characteristic In the case of deactivation of Tp53 and Rb1, consider the sand puppy. If just one of these tumour suppressors is deactivated, sand puppy's experience apoptosis (Seluanov *et al.,* 2009). The opposite is true for mouse or human cells, which multiply more quickly when TP53 or RB1 is deactivated (Hong *et al*., 2004). Similar to this, it has been demonstrated that Cdkn2aARF inactivation causes p53 function to decline, which promotes senescence in cells from naked mole rats (Miyawaki *et al.,* 2016).

This proves that the mole rat was exposed to have developed mechanisms to "detect" the absence of the tumour suppressors Tp53 or Rb1 and to cause apoptosis or senescence. For the cells to remain cancerous, both of these tumour suppressors must be deactivated concurrently (Seluanov *et al.,* 2009). Induced pluripotent stem cell reprogramming shares several characteristics with malignant transformation (Folmes *et al.,* 2011).

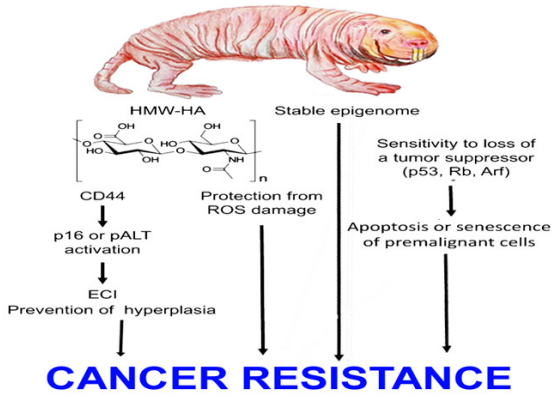
It's interesting to note that Even after reprogramming, sand puppy iPSCs are only moderately successful at developing teratomas (germ cell tumours made up of cells derived from the three germ layers) (Miyawaki *et al.,* 2016). Sand puppy cells are resistant to iPSC.

It is possible that the more stable epigenome of sand puppy's cells, in which the reprogramming gene (Klf4,Myc,Sox2,Oct4) are reprogramming genes more tightly suppressed than in mouse cells, is to blame for the lower success rate of reprogramming (Toole, 2004). The improved cancer resistance in the sand puppy is most likely made possible by a more stable epigenome. Sand puppy cells have an intriguing trait called fructose-driven glycolysis, evolved in response to living in anoxic environments (Park *et al.,* 2017). Tumors also have Fructose-driven glycolysis (Liu *et al.,* 2010).

As a result of this of the multiple tumor-suppressive adaptations already mentioned, it must have been balanced out by the evolution of this trait, which would have made sand puppy's cells more susceptible to cancer (Azpurua *et al*., 2013). Antioxidant pathways process that may contribute to the sand puppy's

resistance to cancer include high-fidelity protein synthesis (Lewis *et al.,* 2015) more active antioxidant response pathways, enhanced activity of the proteasome and autophagy in proteolysis (Rodriguez *et al.,* 2014).

THE NAKED MOLE RAT PATHWAYS

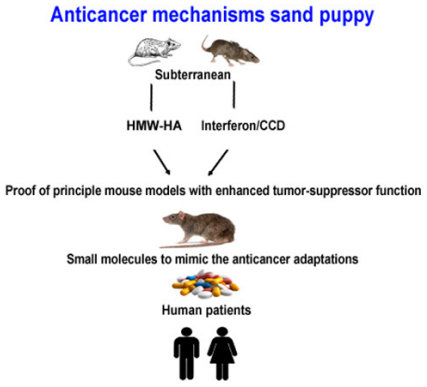


Large amounts cells and tissues from naked mole rats (HMM-HA) are capable of producing high molecular mass hyaluronan. By activating either p16INK4A or pALT, the INK4 locus's product that is exclusive to naked mole rat fibroblasts, HMM-HA interacts with CD44 receptors and produces early contact inhibition (ECI) in naked mole rat fibroblasts.

ECI guards against cancer by stopping the cell cycle at low cell density and preventing hyperplasia. HMM-HA may help stop metastasis by maintaining a thicker extracellular matrix.

HMM-HA works as an antioxidant to prevent the damage that reactive oxygen species (ROS) can do to proteins and nucleic acids. The epigenome of naked mole rat cells is likewise more stable than that of mouse cells, making them resistant to the Yamanaka factors (Oct4, Sox2, Klf4, and Myc) and perhaps even the reprogramming brought on by malignant transformation.

The potential of naked mole rat cells to detect the loss of a single tumour suppressor, such as p53, RB, or p19ARF, and then go through apoptosis or senescence, is a special trait of these cells.



Importance of Cancer Resistance. Because cancer resistance has the potential to drastically lower the cancer burden worldwide, it is an important topic of study in medical research. Increased survival rates were the result. The body's ability to fend off the start or spread of cancer could lessen the need for harsh therapies like radiation and chemotherapy, which come with a long list of negative side effects. Improving cancer resistance may result in early detection and treatment, which would lower the overall cost of cancer care. Hospital stays, extended therapy, and late-stage treatments come at a high expense. It lowers the cost of medical care. Comprehending the underlying reasons behind certain people's inherent resistance to cancer helps advance tailored therapy. Personalised treatments could be created for various individuals by identifying genetic, lifestyle, or environmental factors that contribute to cancer resistance. Finding out about creatures that are naturally resistant to cancer, including some animals (like elephants that have extra copies of the tumor-suppressor gene p53), can help us understand how cancer is prevented. Enhancing human preventive measures can be possible with this understanding. We can create novel medicines to assist people either prevent cancer or fight it more successfully when it is detected if we can identify or imitate natural cancer resistance mechanisms. This can involve immune system stimulation, gene therapy, or cutting-edge drugs. Tumour resistance can directly contribute to strengthening life expectancy and enhancing the quality of life. The financial, emotional, and physical impact that cancer takes on patients and their families is lessened when it is prevented. Research on cancer resistance plays a critical role in developing cancer treatments and enhancing public health.

CONCLUSIONS

Many cancer-resistant species share some of the same evolvable processes, whilst other evolvable mechanisms are unique to specific clades of cancer-resistant species. HMM-HA, which limits cell division and slows the formation of premalignant cells, has evolved in sand puppy. Independently, the demand for more potent anticancer defences has emerged. In many evolutionary groupings which explains why tumor suppressor mechanism are so diverse. Simply said, mice do not have additional anticancer defences that people do not. The possibility for accelerating the creation of antitumor medicines is significantly greater with regard to animals that are naturally cancer-resistant.

Humans may lack the anticancer characteristics that these species have developed and if these adaptations were added to human cells, cancer resistance may grow. As humans do not live a subterranean lifestyle, they did not evolve HMM-HA, hence it may be advantageous to activate analogous systems in humans. The body naturally contains HA, which is well tolerated. Finding methods significantly increase HMM-HA levels in human beings could therefore be used to cure cancer or prevent it in people who are at risk of developing it.

There are numerous naturally cancer-resistant animals outside of the conventional laboratory inventions which means nature has a lot to give in the quest for novel tumor suppressor strategies. In addition to the elephants mentioned here, the subterranean mole rat, the

microbat, the sand puppies and the cows were also discovered to be very resistant to breast cancer.

For example, it is possible to produce mice that overexpress the hyaluronan synthase gene from naked mole rats. The development of pharmaceutical therapies to imitate the cancer-resistant animal adaptations for use on humans is possible if these mice models go on to demonstrate enhanced tumour resistance. Anticancer adaptations with a question mark indicate those for which the precise molecular mechanisms are not known.

FUTURE SCOPE

With the involvement of the advance technology in medical science we can target the tumor cells and suppress the infected cell or by correcting the gene with the help of advance bio technology and Nano technology by knowing their genetic and molecular profile so that tailored treatment should be given to individual patient. It reduces the chance of mortality and increase the chance of survival with the help of effective treatment.

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Conflict of Interest. None.

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