Elephant's deterrence to cancer decoded

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Russian scientist Theodosius Dobzhanski, once said: 'Nothing in biology makes sense except in the light of evolution'. Cancer and the phenomenon of cancer resistance are no exception to this rule. It is interesting to note that evolution has solved the problem of cancer, at least in few species. Understanding why and how of this phenomenon could help us treat or prevent this catastrophe of cellular disobedience. Among the documented species which defy cancer, naked mole rats[1], blind mole rats[2], larger animals such as whales[3] and elephants[4,5] are well studied. Patients with Laron syndrome are the only human examples of cancer resistance[6]. Laron syndrome is an autosomal recessive disorder characterized by insensitivity to growth hormone (GH), which causes short stature, resistance to diabetes (mellitus type 2) and surprisingly cancer. A series of elegant experiments has revealed that cancer resistance in naked mole rats is derived from their cells exhibiting high, early contact inhibition and abundant production of high molecular weight hyaluronic acid. Hyaluronic acid accumulates within the extracellular matrix, stimulates an intracellular pathway that induces expression of $p16^{ink4a}$ and suppresses oncogenic transformation. The cells of blind mole rats on the other hand, when grown to confluence, commit collective suicide by releasing a type of interferon IFN-β, mediated by p53 and Rb pathways. Humans also produce hyaluronic acid, but the structure is subtly different from that of the mole rats. Scientists are now exploring different avenues to simulate the production of naked mole rat version of hyaluronic acid in humans[7].

Human war on cancer is far from being won. Humanganous effort and money is being spent to combat this curse on humanity. All individuals aged above 60 years or older have microscopic cancer lesions in the body; but most of these micro-tumours never develop into cancer. Some form secondary tumours, while the rest is kept under check by the body's own immune system[8]. Thus cancer is not a rule, but an exception. Dwelling into the molecular mechanism of this exception is an aggressive area of research. DNA repair, suppression of oncogene activation, activation of tumour-suppressor genes, epigenetic stabilization of chromatin structure and apoptosis are the known mechanisms which provide a potential roadmap for cancer resistance[9]. Our understanding of biology of cancer resistance is at its infancy and much research is warranted in this arena to win over this neoplastic disease. The underlying mechanism of cancer resistance in larger animals, such as blue whales and elephant, is an intrusive mystery. In theory, cancer genesis is a simple numbers game. The more cells an organism has and the longer it lives, the more likely it is that one of its cells will succumb to a random cancer-causing mutation. But it turns out that not all cells are equally prone to cancer. In nature, body size and cancer are not correlated and this disconnect is called the Peto's paradox[10], after epidemiologist Richard Peto, who noted the phenomenon in the 1970s.

In an attempt to understand Peto's paradox at the molecular level, two recently published studies delve into the mechanism of cancer resistance in elephants. The studies show that elephants have evolved extra copies of the tumour suppressor gene *TP53*, which helps them to stay free of cancer to a large extent (Figure 1). *TP53* is the convoy of the cellular world. If a cell with faulty DNA is replicating, the *TP53* gene encodes a protein called p53, which can arrest the process of replication until the DNA is repaired, or if the damage is irreparable, P53 leads the cell on the path of apoptosis or self-destruction[11].

Abegglen *et al.*[4] presented evidence that elephants have at least 20 copies of the *TP53* and their cells also favour apoptosis over DNA repair when subjected to DNA-damaging agents. The authors sought to confirm the increased cancer resistance in large and long-lived animals, by investigating the necropsy data of 36 mammalian species spanning from mouse which weighs 51 g and has a life span of 4.5 years, to the elephant which weighs 4800 kg, and lives 65 years on an average. As expected, cancer mortality did not increase with body size, and elephants were estimated to only have a 4.8% cancer mortality rate, whereas in humans, it is 25%. Next, the team analysed the elephant genome and found something remarkable. Unlike humans with one copy of *TP53*, elephants have 20 copies, i.e. 40 alleles of *TP53*. When the researchers examined these alleles further, they found that 38 of them were retrogenes, duplicates of the original gene. The team then exposed cells isolated from humans and elephants to DNA-damaging radiation and observed the difference in the effects. It was observed that elephant lymphocytes underwent p53-mediated apoptosis at higher rates than healthy human controls. Then they compared the results with cells isolated from patients with Li-Fraumeni syndrome – a disorder in which a missing working copy of *TP53* leads to a dramatically increased cancer

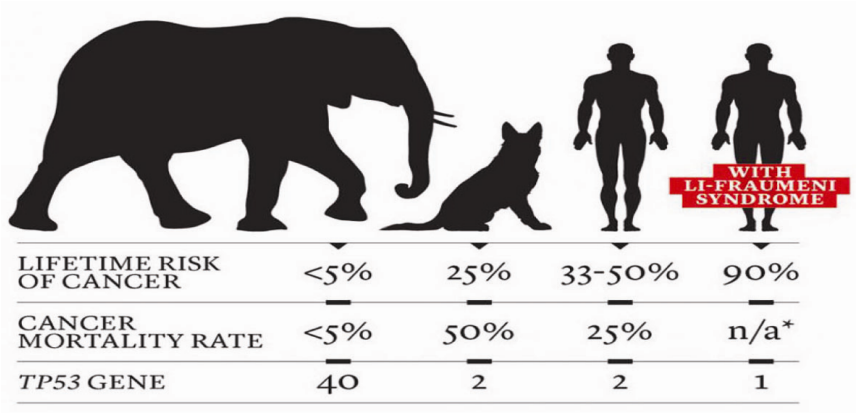

Figure 1. *TP53* copy number is linearly correlated. Courtesy: Joshua-Schiffman, 2015.

risk. Thus compared with human cells, elephant cells demonstrated increased apoptotic response following DNA damage. Thus in elephants, the extra copy of the *TP53* gene seems to be a by-product of selective pressure to suppress cancer.

In a separate study, Lynch *et al.*[5] reported similar results. They discovered increased copy number of *TP53* retrogenes (*TP53RTG*) in elephants. Using whole genome sequencing data and phylogenetic analysis, the authors showed that the increase in copy number of *TP53RTG* is directly proportional to body size. From RNA sequencing data of elephant dermal fibroblast, they found that among the 19 retrogenes of *TP53*, *TP53RTG12* is transcribed and translated into a functional protein. Therefore, they investigated the functionality of the *TP53* retrogenes. It was seen that elephant cells up-regulate TP53 signalling, and therefore apoptosis, in response to lower levels of DNA damage than other species. Thus, in elephants, the *TP53* gene seems to do two things. First, it stops the cell from proliferating; giving it the time it needs to repair itself. Second, if the cell cannot be fixed, it is prompted to commit suicide. These unique features in elephants are a complete detour from the way human DNA with a single copy of *TP53* responds to cancer. Scientists hypothesized that if this can be replicated in humans, it may be used in treating or even preventing cancer. To examine this hypothesis, the team inserted *p53* genes from elephants into mouse cells and found that those cells mimicked the cancer resistance of elephants and self-destructed when exposed to DNA-damaging drugs. This observation, though at its primitive stage, is worth further exploration/investigation.

Though increasing the *TP53* copy number seems to be an exciting option to prevent and treat cancer in humans, translational research would have a few hurdles. Our genetic make-up has evolved to be different from that of elephants; hence extra copies of a gene that helps fight cancer in elephants might produce undesirable effects. The speculation is that *TP53* might not be the only candidate selected for imparting cancer resistance. Sluggish metabolism and environmental factors may also make a contribution. So, though at this stage, the molecular reasons for immunity of elephants to cancer are intriguing, they are not instructive. Nonetheless, it is indeed a revelation that evolution has provided us, and other animals, with multiple mechanisms to stop cells from going into uncontrolled division. Understanding evolutionary-driven cancer resistance can help us appreciate its impetuous behaviour and how we can piece together therapeutic armamentarium to fight this malady called 'Cancer'.

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