Mètode Science Studies Journal
ISSN: 2174-3487
ISSN: 2174-9221
metodessj@uv.es
Universitat de València
España

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Mètode Science Studies Journal, vol. 10, 2020, pp. 201-205
Universitat de València
Valencia, España

DOI: https://doi.org/10.7203/metode.10.14593

MONOGRAPH
MÈTODE SCIENCE STUDIES JOURNAL, 10 (2020): 201-205. University of Valencia.
DOI: 10.7203/metode.10.14593
ISSN: 2174-3487. eISSN: 2174-9221.
Submitted: 5/04/2019. Approved: 09/07/2019.

DIVERSE WAYS TO THINK ABOUT CANCER

What can we learn about cancer by studying it across the tree of life?

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When asked about cancer, most would first think of it as a devastating disease. Some might add that lifestyle (e.g., smoking) or environmental pollution has something to do with it, but also that it tends to occur in old people. Cancer is indeed one of the most common causes of death in humans, and its incidence increases with age. Yet, focusing on our own species, we tend to overlook something very elementary: cancer is not unique to humans. In fact, it is a phenomenon that unifies diverse branches of the tree of life. Exploring the diversity of ways in which different organisms cope with it can lend us novel insights on cancer. In turn, by acknowledging cancer as a selective pressure, we can better understand the evolution of the biodiversity that surrounds us.

Keywords: cancer, Peto's paradox, life history, multicellularity, ageing.

WHAT IS CANCER?

A skin cell will never meet a liver cell, but they come from the same fertilized egg and work together to ensure that the body functions well. Unless a cell is specially geared towards reproduction, it will die when the organism does so. What then makes it work so hard? An answer is the shared interest in the fate of shared genes, and organisms have various ways to ensure the cooperation between their cells (reviewed in Aktipis et al., 2015). However, occasionally some cells escape these control mechanisms: if a cell divides faster than its neighbour in the short term it is, from a numerical perspective, at an advantage. Cancer is the uncontrollable division and spread of these cells within an organism.

At a molecular level, cancer results from the accumulation of mutations in the lineage of cells on their way from the fertilized egg to a tissue: a cell stops listening to the rules dictating when it should divide and when not. Because the «anti-cancer» mechanisms are themselves genetically encoded, mutations that disrupt the functioning of these genes can initiate cancer. Mutations are not rare: the DNA in our cells tend not to be fully identical copies of what was there at fertilization. If a mutation occurs in a key cancer-related gene, cells can become malignant. Taking colorectal cancer as an example, the process might start with a mutation in a tumour-suppressor gene (e.g., *APC* gene), which results in the uncontrolled growth of the cells into a mass (Vogelstein et al., 2013). Subsequent mutations in other key genes (e.g., *KRAS* or *TP53*) can allow cells to divide faster, let this mass grow larger, and eventually invade the surrounding tissue as well as distant parts of the body (Vogelstein et al., 2013). Although the genes involved differ between cancer types and organisms, as well as within one single tumour itself, the problem is a general one: keeping the genetic content of all cells unchanged across numerous cell divisions is impossibly difficult. We would therefore expect all multicellular organisms to be susceptible to cancer.

«Cancer is an underappreciated factor in natural selection and evolution»

This expectation is confirmed: cancer is widespread across the tree of life. Within the animal kingdom, essentially all vertebrates can get cancer (Aktipis et al., 2015). If we expand the definition of cancer to include any uncontrollable growth and cover the tumours that do not spread (i.e., metastasize), cancer-like phenomena are almost ubiquitous. From invertebrates like famous *Drosophila* flies to more simple animals like hydra, cancer tends to be found once we care to look for it (Aktipis et al., 2015). Even plants cannot

escape it, though the plant way of keeping cells inside cell walls, without circulating blood, limits the spread of any one tumour.

We believe that cancer is an underappreciated factor in natural selection and evolution. Cancer in the wild might remain undetected. If, for example, a sparrowhawk attacks a flock of feeding birds, being the slowest of the flock to take off is bad news for survival. If one bird is not in prime condition (due to the initial stages of cancer), it will become a sparrowhawk's breakfast. In this case, one might simply categorize the cause of death as predation, but what natural selection actually ended up doing here was to remove genes that made an individual prone to getting cancer. This problem makes it hard to collect data to compare cancer incidences across wild species. Zoos are therefore valuable sources of cancer data: since animals in captivity are not exposed to predation and may also have a reduced parasite burden, their intrinsic cancer proneness is easier to measure, fuelling the burgeoning field of comparative oncology (e.g., Abegglen et al., 2015).

PETO'S PARADOX: WHO EXCELS AT CANCER AVOIDANCE?

Comparing cancer incidences across species results in some counter-intuitive insights: large-bodied and long-lived animals are not as cancer prone as we would expect. Before explaining why, let us consider why one would expect cancer risk to increase with body size and lifespan in the first place. Take a step back and, again, consider cancer as an outcome of multicellularity. Multicellular organisms start from a single cell and require cell divisions to reach their «target» body size. Once fully grown, one might think dividing could stop, but no: cell divisions are still needed, with the reasons ranging from wound healing to the gut's inability to distinguish between food and its own lining when digesting organic material. Each cell division comes with a risk of a cancer-inducing mutation happening, and if this remains undetected, it will be passed on to all descendants of this cell. Purely by chance, we would therefore expect a larger number of cells to translate into a higher probability of dangerous mutations per animal. Likewise, long-lived animals would have more time to accumulate these mutations.

Cancer data from humans support this expectation: being 10 cm taller increases one's cancer risk by about 10% (Nunney, 2018). This is a modest change in body size, if we consider the full extent of body size variation within animals. In fact,

Leslie Seaton

extrapolating from this, one could argue humans, having 1,000 times the size and 30 times the lifespan of mice, should routinely succumb to cancer (Peto, 1977) and elephants and whales should be so cancer-prone that they should not even reach reproductive age. But… they do, an observation known as «Peto's Paradox». To be precise, the paradox refers to a lack of increase of cancer incidence with lifespan and body size across species (Abegglen et al., 2015). This lack of correlation has far-reaching implications: large and long-lived animals must have evolved ways to combat an *a priori* higher cancer risk.

WHAT CAN OTHER SPECIES TEACH US ABOUT CANCER SUPPRESSION?

Intrigued by Peto's Paradox, researchers have set out to explore the relative cancer-robustness of large-sized and long-lived animals. Although one cannot easily argue for replacing lab rats and mice with

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Cancer-like phenomena are observed across the diversity of life. Plants may be better than animals in coping with the uncontrolled growth of their cells, as a result of their cell walls and modularity. Due to this, they stand to prove pervasiveness of cancer-like phenomena, as seen here in these specimens of saguaro (left) and daisy (right), both with an abnormal growth (also known as *fasciation* in plants).

populations of lab whales, gentler methods of genomic analyses have led to the discovery of possible mechanisms these animals might have evolved on their way to a «large» life. Elephants, for example, have 19 extra copies of *TP53* gene, which is a crucial tumour suppressor gene that coordinates various DNA damage responses from halting cell division to programmed cell death (Abegglen et al., 2015). Experiments hint that these extra copies really do help: when treated with DNA damaging agents, elephant cells had a higher rate of programmed cell death (so-called apoptosis) compared to human cells (Abegglen et al., 2015). In other words, elephant tissues might be «more alert» than humans' when it comes to judging the health of their cells; elephant bodies kill their damaged cells faster, recycling the material as food for other cells, rather than letting a potentially dangerous cell lineage participate in the future of the tissue.

Naked mole rats provide another curious case of cancer evasion. Their strikingly long lifespan (up to 32 years in captivity) with extremely low cancer incidence (six known cases) has long puzzled ageing and cancer researchers (Seluanov, Gladyshev, Vijg, & Gorbunova, 2018). Or so until a team working on naked mole rat cells noticed an important clue: naked mole rat cells divided very slowly in the laboratory conditions (Seluanov et al., 2018). Normal cells in a tissue stop dividing when they reach a given density. This mechanism, called «contact inhibition», is employed by multicellular organisms to keep cell divisions under control. Losing contact inhibition is one of the characteristics of cancer cells, allowing them to continue dividing even when they reach high density. Naked mole rat cells secrete a unique molecule that increases their sensitivity to contact inhibition (Seluanov et al., 2018) – one of the mechanisms they might be employing against cancer. Another way naked mole rats keep their cells under check is via increased sensitivity to DNA damage: their cells go through programmed cell death upon losing only one of the tumour suppressors (specifically: p53, RB, or $p19^{ARF}$), while the same loss results in an increased cell division in humans or mice (Seluanov et al., 2018).

A variety of genomic changes, such as copy number variations in cancer-related genes (as described above for elephants), have become established in long-lived and/or large-sized animals, including e.g., bats and whales (Tollis, Schiffman, & Boddy, 2017). Comparing genetic sequences and the functions of those genes have already led to the discoveries of cancer risk management in elephants and naked mole rats, and therefore highlight promising research avenues that might nourish clinical cancer research as well. The study of cancer across species offers intuition about where to look; the beauty of this research program is that it begins with an appreciation of features of life that have existed since multicellularity first arose, then scans observations that do not match expectations (a similar incidence of cancer across species of varying size and lifespan) to pinpoint species that could be particularly interesting (large ones like whales, or outliers who live longer than expected based on body size alone, such as bats).

«Body size is actually a key trait that influences many aspects of species' ecology and evolution»

CAN CANCER AFFECT THE EVOLUTION OF BIOLOGICAL DIVERSITY?

Even a superficial look at nature reveals that species vary in size and, as highlighted above, this has implications for cell division management. Size differences do not only matter for cancer risk and tumour suppression mechanisms; body size is actually a key trait that influences many aspects of species' ecology and evolution. For instance, larger


John Brighenti

animals typically live longer, while smaller animals tend to reproduce earlier and have more offspring. Within a species, being larger than one's conspecifics tends to yield a competitive edge, and species indeed tend to evolve towards larger body sizes over time – the so-called Cope's rule (Kingsolver & Pfennig, 2004). Why some species remain small is therefore a conundrum of evolutionary biology (Blanckenhorn, 2000). One inevitably wonders whether cancer risk can prevent lineages from increasing in size, if they aren't lucky enough to have acquired the elephant-like innovations discussed above.

Evidence from various large-sized organisms suggests that adaptations to an increased cancer risk could be a prerequisite for a larger body size. Using a mathematical model, Kokko and Hochberg (2015) showed that an increase in body size can translate into a reduction in lifespan due to cancer. However, the organism may still enjoy a net benefit if the other advantages of being large sufficiently compensate such costs (e.g., a large animal of either sex might outgrow some of its predators, or a big male might win fights over access to mating opportunities with females), or, of course, if cancer suppression is adequately elevated. Some support for the latter comes from a recent study, which reported that a gene involved in cell death response (*LIF6*) in elephants appears to have evolved around the same time as this lineage increased in body size (Vazquez, Sulak, Chigurupati, & Lynch, 2018). The authors suggest that this adaptation might have been «permissive» for body size evolution in the elephant lineage (Vazquez et al., 2018). Even when increased cancer suppression is theoretically achievable, if an organism has a high probability of dying due to extrinsic causes it may not live long enough to benefit significantly from its improved cancer defences (Kokko & Hochberg, 2015). Accordingly, both the cancer risk and the ecological context need to be factored in when studying the evolution of biological diversity.

«In humans, there may be a mismatch between how long our genes "expect" our bodies to live for and how long they can do so now»

CAN ORGANISMS ADAPT TO A CHANGING CANCER RISK?

While the evolution of cancer suppression mechanisms allows species to become larger and live longer, organisms may also experience changes in cancer risk compared with their ancestors (Hochberg & Noble, 2017). Humans are a prime example of this. We enjoy a longer average lifespan than our ancestors, largely thanks to a better control of infectious diseases and improved diets. We are also larger, though with much interpopulation variation. If the circumstances that prevailed during much of our evolutionary past differ from the current ones, there may be a mismatch between how long our genes «expect» our bodies to live for and how long they can do so now (Brown, Cunningham, & Gatenby, 2015; Hochberg & Noble, 2017). As a result, modern humans might lag behind their currently optimal levels of cancer suppression (Brown et al., 2015). This, of course, does not mean that we cannot do anything about it. Healthy lifestyles can reduce cancer risk, and research into treatments has greatly improved survival odds once a tumour is discovered (Brown et al., 2015; Hochberg & Noble, 2017).

Zooming out from ourselves, humans are not the only species suffering from such a mismatch: human-mediated environmental changes can increase cancer risk for all the populations exposed to them (Giraudeau, Sepp, Ujvari, Ewald, & Thomas, 2018; Hochberg & Noble, 2017). From various sources of pollution (e.g., toxic industrial waste, light and noise pollution) to diet-associated changes (e.g., human food waste that potentially has carcinogenic toxins), wild organisms face novel cancer-related

John Brighenti

Each cell division comes with a risk of a cancer-inducing mutation happening. This should mean that a larger number of cells involves a higher probability of dangerous mutations per animal, especially if they are long-lived animals. However, species like elephants (both large and with a long lifespan) or naked mole rats (which can live up to 32 years in captivity) seem to have evolved cell risk management strategies that translate into a really low cancer incidence.

pressures due to human activity (Giraudeau et al., 2018). Obviously, cancer is not the sole problem of flora and fauna trying to survive the Anthropocene; it might not even be in the top ten. Yet, the fact that evolutionary adaptations tend to happen more slowly than ecological changes suggests that an increasing cancer risk could become a conservation issue.

A FEATHERY END

Most ecological and macroevolutionary «rules» are there to be broken, and Cope's rule is no exception. Not every lineage evolves towards larger sizes. Dinosaurs were immensely large, but not all of them; some actually became miniaturized after having spent some evolutionary time in the mid-size range (for a dinosaur). This theropod lineage also survived the meteoritic event that killed off the large ones; the descendants of these survivors are the birds that fly, hop and sing on our planet today (Lee, Cau, Naish, & Dyke, 2014). Do modern birds show traces of their dinosaurian past, with anti-cancer adaptations still there from their large-bodied history? Data suggest that birds might be more cancer-robust compared to mammals (Effron, Griner, & Benirschke, 1977). This opens the doors for many exciting questions like whether birds can have different cancer suppression mechanisms compared to those already found in mammals, further highlighting the importance of the diverse ways to think about cancer.

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Acknowledgements: This work was supported by the University Research Priority Program (URPP) «Evolution in Action» of the University of Zurich (Switzerland).

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