Cancer without end? Discovery yields fresh insights

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CTVT first emerged in a dog that lived 4-8.5 thousand years ago. All CTVT tumours carry the DNA belonging to this 'founder dog'. By counting and analysing the mutations acquired by CTVT tumors around the world, researchers can piece together how and when CTVT emerged and spread. Artist's impression of the 'founder dog' that first gave rise to CTVT. This dog's phenotypic traits were interpreted from the genetic variation found in the DNA of the cancer that

it spawned. Credit: Emma Werner

If there is any consolation to be found in cancer, it may be that the devastating disease dies with the individual carrying it. Or so it had long been assumed. Recent research however has uncovered some forms of cancer that are transmissible, jumping from one host to another. Indeed, one such contagious cancer, known as canine transmissible venereal tumor (CTVT), has managed to persist in dogs for thousands of years.

In a new commentary appearing in the August 2nd issue of the journal *Science*, Carlo Maley and Darryl Shibata describe the dynamics of this sexually transmitted disease, which arose in a single ancient animal, living as much as 8.5 millennia ago.

Intriguingly, the exploration of long-term, multi-generational cancer evolution in CTVT may shed new light on how human cancers evolve during the typical course of the disease and may inspire new approaches to treating cancer, which remains the second leading cause of death worldwide.

"Cancers evolve, and our strategies for managing cancer need to take that into account," Maley says. In the future, we hope to maintain long-term control over these evolving tumors. CTVT is fascinating because it shows us how cancers might evolve over the long term."

Maley is a researcher in the Biodesign Center for Biocomputing, Security and Society, the Center for Immunotherapy, Vaccines and Virotherapy and the Center for Mechanisms of Evolution at Arizona State University, as well as ASU's School of Life Sciences. He is the director of the newly established Arizona Cancer and Evolution Center (ACE). Shibata is a professor in the Department of Pathology at USC

and the co-director of the ACE Center.

Ominous signs emerge

Examples of contagious cancers in humans exist, but they remain exceedingly rare and have never spread beyond a second host. Other animals however are less fortunate and may fall prey to a range of transmissible cancers, which vary in the severity of their impact.

In 1996, a mysterious illness began sweeping through animal populations in the central highlands of Tasmania. The island's Tasmanian devils were dying from a gruesome facial tumor. At first, a virus was the suspected culprit in the rapidly spreading epidemic. But when the DNA fingerprints of afflicted devils were examined, researchers made a remarkable discovery. The tumor cells were genetically distinct from the devil's own healthy cells, yet they matched tumor cells taken from other Tasmanian devils with the facial tumor disease. It was as though the tumor cells had been cloned and transplanted into each stricken animal. The disease was positively identified as an aggressively lethal, transmissible cancer.

The current commentary concerns CTVT, which causes grotesque, oozing tumors that afflict the genital area in dogs. When researchers sequenced cells from these tumors, the results mirrored those observed in the Tasmanian devils. All of the cancer cells shared a suite of genetic variants that did not appear in the dogs' healthy cells. This led to a startling conclusion: CTVT is not simply a disease that occasionally develops in dogs. It arose only once, in a single dog and has been transmitted through the ages from one animal to the next ever since.

When two dogs with CTVT were examined, one in Brazil and another in Australia, each belonging to a different breed, their tumor cells shared nearly 2 million mutations that were not found in normal canine DNA.

While the CTVT genome diverged considerably from the original dog genome, it remained remarkably stable over time.

Dog years

Unlike the pitiless cancer devastating the Tasmanian devils, CTVT is rarely lethal. Instead, it typically persists for a matter of months before being cleared by the dog's immune system. (See drawing based on genetic sequencing of what the first dog carrying CTVT may have looked like.)

Recent investigations of CTVT, carried out by Adrien Baez-Ortega and colleagues, advance the unusual story of this disease. Their findings appear in the current issue of *Science* and are the focus of Maley and Shibata's commentary.

Baez-Ortega, a researcher at the University of Cambridge, sequenced tumors from 546 dogs around the world. The results showed the great antiquity of CTVT, which has been transmitted by dogs for 4000 to 8500 years. For evolutionary biologists like Maley and Shibata, the findings are revelatory, in part because CTCV appears to have stopped evolving long before it spread around the world.

New directions

The study of cells derived from transmissible cancers like CTVT provides valuable clues for biologists interested in the development of human cancers. Examining somatic cell evolution around the world and over significant spans of time helps researchers understand the subtle dynamics of the evolutionary processes involved in cancer. (In contrast, observing the life and death of cells over time in an individual patient is very difficult.)

Perhaps the most critical observation resulting from the genome sequencing of CTVT is that cancer is not an inevitably progressive disease. Rather, tumors may reach an optimal state that can stabilize over time, exhibiting little or no additional gains in biological fitness—the ability to survive and reproduce.

Typically, tumors persevere and wreak havoc by generating numerous mutations. While most of these have no effect on cancer cell survival, or are even harmful, a few convey an adaptive advantage to cells, increasing their survivability. These are known as driver mutations and as the name implies, they are responsible for a successful cancer's relentless expansion. Driver mutations generate the cells that are able to resist cancer treatment.

It appears that CTVT has been evolving neutrally after its inception, accumulating mutations that do not affect fitness. The successful development of CTVT in dogs therefore seems to require only a few minor adjustments to the genome. The lack of ongoing natural selection in CTVT also suggests that the disease has not had a significant impact on dog survival and reproduction.

The stability of CTVT over time offers hope that certain slow-growing human cancers resistant to conventional therapy, for example prostate cancer, could be tamed and controlled. This might be achieved through so-called adaptive therapies, which seek to limit tumor growth as opposed to aggressive treatments aimed at total eradication, which invariably select for resistant and often lethal cell variants. A pilot clinical trial to test this approach in metastatic breast cancer will soon start at the Mayo Clinic's Arizona campus, in collaboration with ASU.

It seems likely that ongoing explorations of cell evolution in CTVT will provide further insights into complex cell trajectories and genetic transformations in a range of human cancers and inspire innovative

methods of addressing the disease.

"Most cancers can only evolve for a few decades before they die with their host," Maley says. "CTVT is an incredible natural experiment, which showed us that it doesn't take much for a cancer to reach an optimal state. It is amazing that it did not discover additional adaptations over thousands of years, even as it infected all different breeds of dogs in all different environments around the world."

More information: A. Baez-Ortega el al., "Somatic evolution and global expansion of an ancient transmissible cancer lineage," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aau9923

C. Maley el al., "Cancer cell evolution through the ages," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aay2859

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