As cancer grows old: tracing the evolution of an ancient tumour lineage

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Cancers are the product of a process of somatic evolution at the cellular level, and their cells may be regarded, in a Darwinian sense, as the fittest in the body. Paradoxically, however, cancers are short-lived, self-destructive entities, governed by a proliferative nature that makes their survival incompatible with that of their hosts. The path of malignancy is therefore a cul de sac; evolution steers cancers toward an unsustainable existence from which there is seemingly no escape.

But must this always be the case? Or could a tumour find a way to overcome these barriers, to unlock its fate from that of its host, to balance relentless proliferation with a stable existence, and perhaps even to aspire to that immortality which is the preserve of germ lines? And what changes would such a tumour undergo as it lives through the decades, centuries and millennia?

Hypothetical as these questions may seem, they are nonetheless quite real, for there are indeed cancers that reach for immortality. These are known as transmissible cancers, and their approach to survival is that of parasites: parting from the body which first spawned them, the tumour cells have gone on to infect new hosts, in an unbroken chain of cancer transmission which may extend for thousands of years. Only ten instances of this phenomenon are known at present, affecting dogs, Tasmanian devils and marine bivalves (*1*).

The oldest and most widespread of transmissible cancers is the canine transmissible venereal tumour (CTVT). This cancer arose in a dog that lived several thousand years ago, and survived the death of this original host by developing the ability to infect other dogs via transfer of living cancer cells, usually during coitus (see Figure). In this way, CTVT has subsisted as a canine parasite until the present day, and continues to thrive in the form of genital tumours in dogs around the world (*2*). As the oldest and most prolific somatic cell lineage, CTVT not only exemplifies the potential for indefinite survival of malignant cells, but also grants us an opportunity to understand how cancer genomes evolve over long time-scales, and to explore the biological consequences of the remarkable transition from somatic mammalian cell to asexual unicellular parasite. During my PhD, I investigated the somatic mutations found in the protein-coding genomes of 546 globally distributed CTVT tumours, with a view to charting the life history, genomic diversity, and somatic evolution of this seemingly immortal cancer (*3,4*).

Like a historical travel journal inscribed in DNA, the mutations in these tumours compose an organic record of CTVT's past. Reconstructing the somatic phylogeny of the CTVT lineage yielded fascinating insights into this cancer's history of geographic expansion (see Figure).

Analyses by myself and colleagues suggest that CTVT originated 4000–8500 years ago in Central or Northern Asia, and probably journeyed into Europe along the Silk Road. Sixteenth-century Europeans subsequently introduced CTVT into the Americas, from where it spread to dogs worldwide in an unfettered sweep enabled by the transoceanic trade routes of the eighteenth and nineteenth centuries.

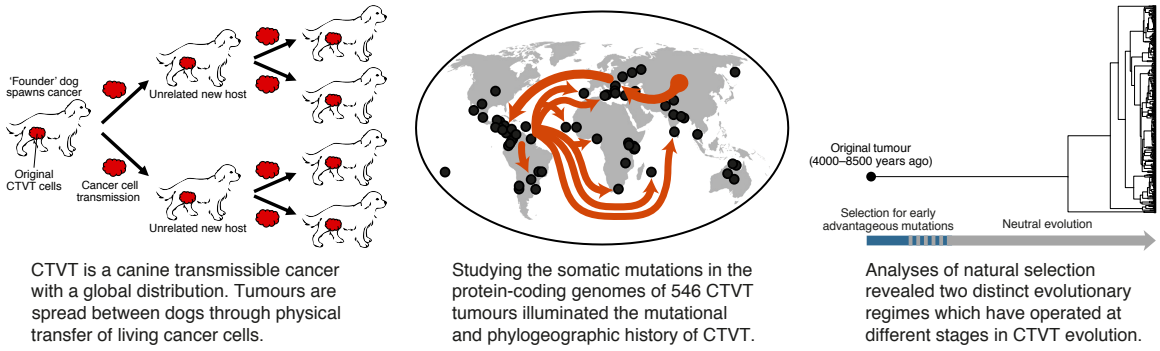
The mutations in CTVT not only chronicle its geographic history, but are also molecular fingerprints of the mutagenic processes that have acted on its cells over millennia. I explored these processes and their spatiotemporal distribution across the tumour lineage, discovering a previously undescribed process which battered the CTVT genome with a distinctive fusillade of mutations before suddenly dissipating ~1000 years ago. This likely reflects exposure to an unknown mutagen that was present in CTVT's original environment, and may thus be the first detailed characterisation of the genomic imprint of a carcinogen from the distant past. Additionally, I uncovered an association between the degree of ultraviolet-light-mediated DNA damage in each tumour and its collection latitude, providing quantitative evidence that sunlight-induced DNA damage is exacerbated in low-latitude regions. These findings highlight the potential for long-lived clonal lineages to document shifting mutagenic environments.

The uncommon phenotypes of CTVT emanate from both the action of its genes and the features of its microenvironment. To illuminate these largely unexplored dimensions of CTVT biology, I developed a statistical model that leverages mutation and gene expression data to disentangle the gene expression contributions from tumour and host cells in CTVT biopsies (*4*). This enabled the identification of genes which are respectively in use by tumour and host cells, revealing that, while a variety of immunity-, inflammation- and angiogenesis-related genes are expressed by host cells, expression in CTVT is mainly centred on genes involved in DNA organisation, replication and repair. These results shed some early light on the molecular priorities of CTVT cells, and on the roles of tumour-infiltrating host cells in promoting and suppressing tumour growth.

Lastly, I evaluated the contribution of natural selection to CTVT evolution. Despite the identification of five potential early cancer-causing mutations, my analyses revealed no evidence of ongoing selection for more recent mutations. This stands in contrast to observations of sustained positive selection in human cancers, suggesting that tumour evolution proceeds differently over short and long time-scales. Furthermore, detectable signals of selection acting against deleterious mutations were confined to essential genes, indicating that mutation accumulation has proceeded largely unopposed in CTVT. Altogether, these findings imply that the long-term evolution of CTVT has been dominated by neutral processes such as genetic drift,

rather than natural selection. Intriguingly, mutation accumulation is expected to induce a progressive decline in fitness over time (*5*), suggesting that the continued existence of CTVT may be evolutionarily unsustainable.

From its origins as a single, unremarkable dog cell, CTVT has grown to challenge its own somatic disposability, revealing the potential for cancers to thrive as independent life forms. In the process, evolution has crafted something unique: a unicellular mammalian species. Yet the CTVT genome, unlike those of immortal germ lines, is mostly unguarded against mutation. Its mode of evolution remains a somatic one, possibly rendering it vulnerable to the mutation-driven dysfunction which likely contributes to the ageing of tissues. It may be that the immortality of CTVT, while sustainable in appearance, has come at a fatal genomic cost.



Cancer evolution through the millennia. The information encoded in hundreds of thousands of somatic mutations enabled an investigation of the life history, genomic diversity and somatic evolution of the ancient CTVT tumour lineage.

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