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The cancer which survived: insights from the genome of an 11 000 year-old cancer

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The canine transmissible venereal tumour (CTVT) is a transmissible cancer that is spread between dogs by the allogeneic transfer of living cancer cells during coitus. CTVT affects dogs around the world and is the oldest and most divergent cancer lineage known in nature. CTVT first emerged as a cancer about 11 000 years ago from the somatic cells of an individual dog, and has subsequently acquired adaptations for cell transmission between hosts and for survival as an allogeneic graft. Furthermore, it has achieved a genome configuration which is compatible with long-term survival. Here, we discuss and speculate on the evolutionary processes and adaptions which underlie the success of this remarkable lineage.

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Introduction

The canine transmissible venereal tumour (CTVT) (Figure 1a) is a cancer that first emerged as a tumour affecting an individual dog that lived about 11 000 years ago [1••,2••,3••]. Rather than dying together with its original host, the cells of this cancer are still alive today, having been passaged between dogs by the transfer of living cancer cells during coitus (Figure 1b). The genome of CTVT, which has recently been sequenced, bears the imprint of the evolutionary history of this extraordinary cell lineage [1••]. Furthermore, the genome variation captured in global CTVT populations has highlighted some of the unique adaptations that have driven this lineage to become the longest-living and most prolific cancer known in nature. This 'cancer which survived' is a remarkable biological entity which illustrates that evolution can drive a transition from mammalian somatic cell to obligate colonial parasite.

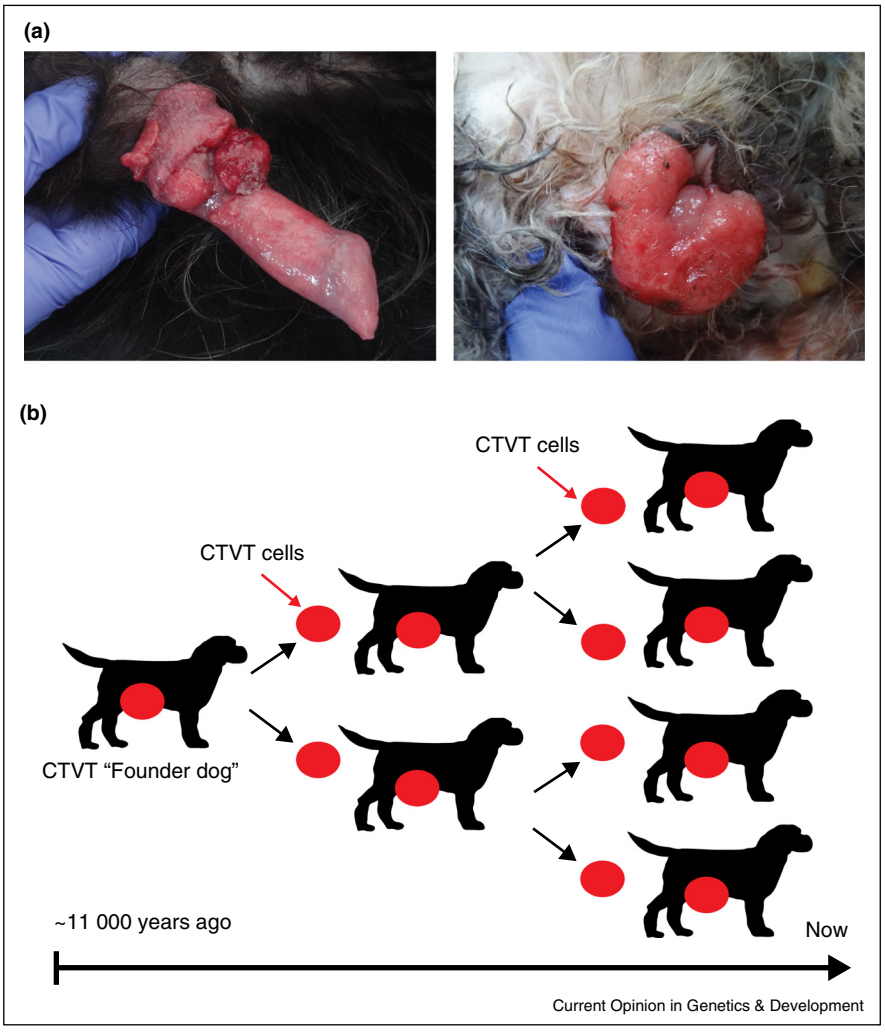
The canine transmissible venereal tumour: origins of a global parasite

CTVT is a sexually transmitted cancer that affects dogs and usually manifests clinically with tumours associated with the external genitalia of both male and female animals (Figure 1a). Although CTVT first appeared in the veterinary literature at least two hundred years ago [4], its uniqueness as a transmissible cancer was not noted until much later [2••,3••,5–7]. CTVT is endemic in at least ninety countries worldwide across all inhabited continents and its distribution is linked to the presence of free-roaming dogs [8].

Although CTVT is found worldwide, the patterns of genetic identity detected in tumours located on different continents indicate a single clonal origin for the disease [2••,3••]. Analysis of a mutational process with clock-like features, as well as comparison of microsatellite variation between tumours and between tumours, dogs and wolves, suggest that the lineage first arose as a cancer several thousand years ago [1••,2••,3••]. By searching for genetic variation present in the CTVT genome and comparing it with genotypes associated with specific traits in modern canids, a picture of the 'founder dog' that first spawned CTVT has emerged [1••,2••,3••]; it appears that this individual was more closely related to modern dogs than modern wolves and had relatively low levels of genomic heterozygosity. This animal was probably of medium or large size with an agouti or solid black coat. The XO karyotype and genotype found in CTVT tumours precludes conclusions about the founder animal's gender [1••,9].

CTVT probably first arose from a somatic cell, possibly a tissue macrophage or a dendritic cell [10,11], of this 'founder animal' via evolutionary processes that are common between all cancers. The life-history of a cancer is generally characterised by successive waves of clonal outgrowth, driven by the acquisition of positively selected 'driver' mutations [12]. The molecular processes promoted by driver mutations can shed light on the biological pathways underlying cancer, such as proliferative autonomy, resistance to cell death and genomic instability [13]. CTVT shares a number of putative driver mutations with human cancers, some of which possibly occurred in the original CTVT tumour. These include a rearrangement involving *MYC*, homozygous deletion of the *CDKN2A* locus, homozygous loss of *SETD2* and a rearrangement involving *ERG* that creates a potential in-frame *NEK1-ERG* fusion gene [1••,5]. There is, however, no evidence

Figure 1



Canine transmissible venereal tumour (CTVT). **(a)** CTVT causes tumours most often associated with the external genitalia of both male (left) and female (right) dogs. **(b)** CTVT first emerged from the somatic cells of the 'founder dog' about 11 000 years ago. Since then, it has been transmitted between individual dogs by the allogeneic transfer of living cancer cells.

to suggest that the original CTVT or its host were particularly extraordinary; we cannot know if the original CTVT was metastatic in its founder dog, or even if the original CTVT was the cause of its founder's death. Nevertheless, we presume that a series of highly improbable events next triggered CTVT to become a transmissible cancer (Table 1).

Crossing the gaps

Cancers frequently acquire features that cause cells to depart from a primary tumour and establish new tumours in distant sites of the body via a process of metastasis. CTVT, however, has acquired adaptations for the transmission of cancer cells to new hosts. The family Canidae may have been particularly at risk for the establishment of a sexually-transmitted cancer due to the existence of the long-lasting coital tie that is peculiar to this group. The coital tie may last for up to 30 minutes, and may lead to injuries to the genital mucosa; such conditions may thus provide an exceptional opportunity for the exchange of cancer cells between individuals [14]. Despite the potential for mating between dogs and wild canids, including wolves and coyotes, CTVT has not been reported within wild canid populations [8]. CTVT tumours are also occasionally found affecting non-genital regions, most commonly skin, nasal cavity, lymph node, eye and mouth [8]. As these sometimes occur without genital involvement [15–17], this suggests that there may be non-coital routes of CTVT transmission, possibly involving licking, sniffing or parturition.

Transmissibility has presumably had consequences for CTVT genome evolution. Direct transmission of cancer cells may select for loss of cell adhesion; indeed, CTVT