Mitochondrial Capture by a Transmissible Cancer

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Canine transmissible venereal tumor (CTVT) is a highly adapted cancer, transmitted as an allograft during coition. Nuclear DNA sequences indicate that this asexual mammalian unicellular pathogen originated ~10,000 years ago, perhaps when dogs were first domesticated, although the common ancestor of extant tumors existed no more than a few hundred years ago (*1*, *2*).

We sequenced two regions of the mitochondrial (mt) genome that are most informative about canine relationships (*3*) plus the highly variable control region [D-loop (*4*)] in 37 CTVT samples originating from seven countries on four continents (*2*). We also sequenced mitochondria from 15 hosts, and in all cases the tumor haplotypes were distinct from that of their hosts. The level of nucleotide polymorphism among CTVT samples was high, with 28 polymorphic sites in 2265 examined in the coding regions (1.2%) and 14 of 666 in the control region (2.1%) (*1*), only one order of magnitude less polymorphic than nuclear microsatellite loci in the same samples (*2*), despite an expected mutation rate five orders of magnitude smaller [10^{-8} versus 10^{-3} (*5*, *6*)].

This high polymorphism may be due to occasional transfer of mitochondria from host dogs into CTVT. We constructed a phylogeny for a combined data set of CTVT and host sequences, including published sequences from 43 dogs, wolves, and coyotes. In all analyses, we excluded the control region sequences as containing too many parallelisms and reversals masking the phylogenetic signal. Both likelihood and parsimony analyses consistently divide the CTVT samples into two clades and three isolated samples (Fig. 1). Constraining the CTVT sequences to form a single clade results in a significantly worse phylogeny (parsimony analysis $P = 0.034$; likelihood analysis $P = 0.006$). Additionally, the mitochondrial phylogeny of CTVT samples is significantly different from the nuclear microsatellite phylogeny of the same samples (parsimony analysis $P = 0.096$; likelihood analysis $P = 0.017$). These results cannot be explained simply by a high mutation rate in the CTVT samples and suggest that CTVT lineages periodically acquire the mitochondria of their hosts.

The scattered placement of CTVT samples on the phylogeny suggests multiple events since the common ancestor of the CTVT samples. Because the time back to this common ancestor is only about 1% of the time back to the origin of the tumor (*2*), there may well have been many transfers in the history of CTVT.

We suggest that CTVT cells periodically acquire mitochondria from their hosts because a high metabolic rate (and thus mutation rate) and absence of a bottleneck to allow for between-cell selection cause their own mitochondria to accumulate deleterious mutations. Consistent with this idea, the tips leading to the two large clades of CTVT samples extend further than other tips on the tree (Fig. 1), suggesting a higher mutation rate and/or reduced purifying selection. Moreover, the proportion of mutations that change an amino acid is higher in these two clades than in the dog sequences (75% versus 40%, $n = 20$ and 25, $P = 0.034$, Fisher's exact test), suggesting that purifying selection is less effective in the CTVT samples. Thus, host mitochondria may simply be more fit than CTVT mitochondria, with transfer events rescuing CTVT mitochondrial function. If CTVT is derived from a histiocyte (*7*), it could be preadapted to engulf foreign material. Rescue of mitochondrial function by horizontal transfer has been demonstrated in mammalian cell culture (*8*).

The nuclear genome of CTVT may also have degenerated, because of its asexual life-style and the likelihood that many dog genes are no longer necessary in this pathogen. Because sporadic cancers often show mitochondrial mutations and have an unusual metabolism of aerobic glycolysis that may be due to accumulated defects in oxidative phosphorylation (*9*), mitochondrial transfer may occur in many cancers as they seek to optimize, or at least repair, their metabolic machinery.

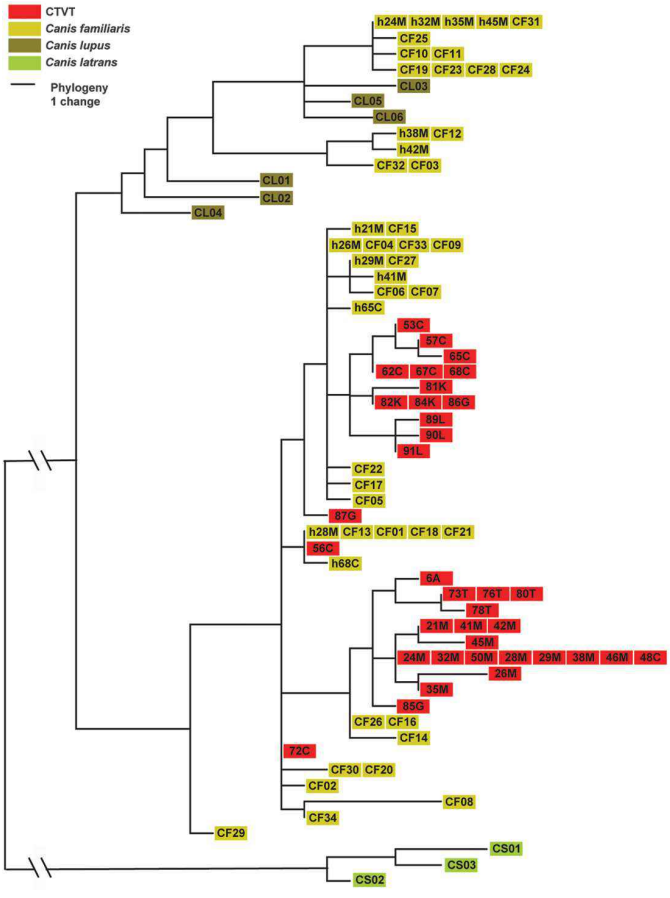

Fig. 1. Maximum parsimony phylogeny of CTVT mitochondria ($n = 146$ parsimony-informative characters; consistency index = 0.91, retention index = 0.97).

References and Notes

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Supporting Online Material

www.sciencemag.org/cgi/content/full/331/6015/303/DC1
Materials and Methods
Table S1
References

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