It is highly likely that there are integrin-dependent and -independent mechanisms that control transformation induced by oncogenes. Inhibition of signaling by β4 integrin significantly delayed the mammary tumorigenesis induced by ErbB2, but did not block it. Although the activation of Ras/MAPK mediated by ErbB2 could account for the proliferation observed in tumors formed in the absence of the β4 integrin signaling domain, it is not known whether there are β4-independent mechanisms that mediate ErbB2-induced disruption of tight junctions and epithelial organization. Further investigations are needed to answer questions such as: what are the pathways used by oncogenes to disrupt cell polarity? Are these pathways selective for deregulation of cell architecture (Figure 1)?

Such questions lead us to a hypothesis. Pathways that deregulate cell organization and disrupt cell polarity are promising targets for cancer therapeutics. Unlike cell proliferation, disruption of cell polarity and organization is never observed under normal physiological conditions in adult tissue and is unique to disease states such as cancer and inflammation. If oncogenes disrupt epithelial cell polarity using pathways that are distinct from those involved in the control of proliferation, further understanding of how oncogenes disrupt cell polarity and organization can lead to identification of new targets for therapeutic intervention. Such targets may have limited effects on normal cells and hence have minimal general toxicity. Thus, a comprehensive understanding of the molecular mechanisms by which oncogenes disrupt polarity and epithelial organization may open doors for a new class of drug targets.

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The Singular History of a Canine Transmissible Tumor

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In this issue of *Cell*, Murgia et al. (2006) confirm that the infectious agent of canine transmissible venereal tumor is the cancer cell itself and that the tumor is clonal in origin. Their findings have implications for understanding the relationship between genome instability and transmissible cancer and for conservation biology, canine genomics, and companion animal medicine.

Canine transmissible venereal tumor (CTVT, also called Sticker's sarcoma) is a contagious venereal tumor found in the domestic dog (*Canis familiaris*) and potentially in other social canids, such as the gray wolf (*Canis lupus*) and coyote (*Canis latrans*). It has been proposed that the tumor cells themselves—rather than another agent such as a virus—constitute the contagious agent of this disease. In this issue of *Cell*, Murgia and colleagues (2006) address the key issue of whether CTVT indeed represents a "contagious cancer."

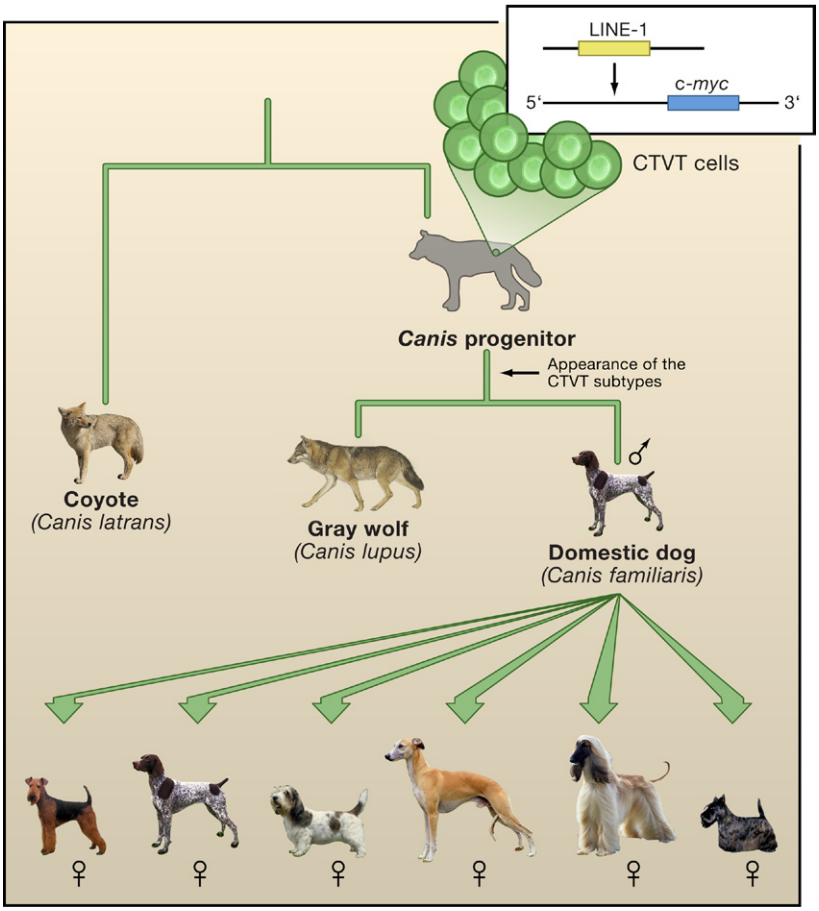

Figure 1. Ancestry of the Canine Transmissible Venereal Tumor Lineage
The canid phylogeny depicts the origins of canine transmissible venereal tumor (CTVT). The LINE-1 element was inserted upstream of c-*myc*, a proto-oncogene, in the cells of a wolf/dog progenitor. CTVT lineage divergence occurred soon after its emergence. The subtypes do not necessarily correspond to species. Once the CTVT tumor enters the dog lineage, an infected individual can rapidly transmit it (green arrows) by coitus. The tumor can potentially be transmitted among *Canis* species. Scottish terrier photo courtesy of the American Kennel Club (AKC); other dog photos courtesy of Mary Bloom, AKC. Wolf photo courtesy of Priscilla Barrett (D.W. MacDonald and P. Barrett, Mammals of Europe [Princeton University Press, Princeton, NJ, USA, 1993]). Coyote photo courtesy of Dr. Robert K. Wayne.

Proponents of the "contagious cell line" hypothesis argue that CTVT is passed through the population by allografts, with the tumor cells from one animal directly seeding tumor formation in the next, usually during coitus (Cohen, 1985; Katzir et al., 1987). This is supported by the fact that CTVT can only be transmitted experimentally using living cells, not cellular filtrates or killed cells. In addition, although the tumor is always aneuploid, tumors from distinct geographic regions feature unique chromosomal patterns of gain and loss, arguing for local lineages. Finally, all tumors are marked by the presence of a diagnostic long interspersed nuclear element (LINE-1) inserted near the c-*myc* gene. The LINE-1 element is absent at the corresponding position in the germline (Liao et al., 2003). Skeptics, however, cite multiple reports of virus-like particles found in CTVT tissue. In their new study, Murgia et al. (2006) analyze microsatellite markers, mitochondrial DNA (mtDNA), and major histocompatibility (termed dog leukocyte antigen [DLA] in dogs) genes in order to elucidate the natural history of this unusual tumor.

Using both recently collected and archival tissue from dogs in locations spanning five continents, the authors first established the clonal origin of the tumors. All tumors contained the tumor-specific LINE-1 element, even samples collected two decades apart. In addition, whereas DLA analysis revealed a large number of variants in germline DNA, only two major haplotypes appeared in the tumors, suggesting the existence of just two tumor subtypes. Results were supported by mtDNA analysis, which grouped tumors into two distinct clusters within a single clade, clade A, of the canine phylogeny. Germline mtDNA from the same dogs was distributed among three clades (Murgia et al., 2006).

The authors then investigated the origin of the tumors. Both DLA polymorphism and microsatellite data indicated that all tumor samples were closely related to DNA from wolves and East Asian dog breeds, providing convincing evidence for a common origin (Figure 1). Microsatellite analysis of the two CTVT subgroups revealed an equivalent degree of variation, implying a divergence event soon after the emergence of the original tumor. Assuming about the same mutation rate in canine microsatellite DNA as in human microsatellite DNA (10^{-3} to 10^{-4}), divergence between the two CTVT subgroups is estimated to have taken place 200 to 2500 years ago.

How does CTVT evade the host's immune system? One possibility is that the tumor suppresses the DLA antigen activity of the host. Indeed, Murgia et al. (2006) observed that CTVT tumors downregulated expression of class I molecules and that class II activity was completely absent, generating a mechanism for avoiding detection. In CTVT, tumor cells decrease DLA activity by secreting the inhibitory factors TGF-β1 and interleukin 6. This is a unique evolutionary adaptation that rarely results in death for the infected animal, thus guaranteeing tumor transmission during the next breeding cycle. Further characterization of CTVT adaptations may

provide clues to the more familiar problem of understanding how viruses escape host surveillance.

The success of this single cell lineage, believed to be the longest continually propagated cell lineage in the world, can be attributed to the tumor's mode of transmission in a specific host system. Although direct contact is generally not a highly efficient mode of transfer, CTVT takes advantage of the "popular sire" effect of domestic dogs. A single male can produce dozens of litters over his lifetime, allowing the tumor to affect many more females than it could if a monogamous species were the host. Understanding the epidemiology of CTVT will provide insights for populations that may experience CTVT exposure and information about disease prevalence. CTVT is more often found in temperate climates where there are large populations of stray dogs, but little is known about the details of transmission. Is male-to-female transmission more effective, or vice versa? Can tumors be transmitted via artificial insemination (Moulton, 1978; Cohen, 1985)? The latter is a particular concern as many canids, both domestic and wild, are impregnated via artificial methods. Learning more about the details of tumor transmission is key for understanding how more aggressive forms of the tumor, should they evolve, will spread through the population.

As a result of this work, both oncologists and evolutionary biologists must now question why allografting is not a more common mode of transmission both for tumors and for viruses. Consistent with this possibility, genomic insertions of LINE-1 have the potential to disrupt transcriptional regulation of downstream genes, possibly initiating oncogenic activity, as is the case with CTVT, where LINE-1 inserts close to the c-*myc* gene. Thirty-four percent of the dog genome consists of repetitive elements. Indeed, Bentolila et al. (1999) have described a particular 3′ open reading frame (ORF) that shares sequence homology with a viral reverse transcriptase, providing a plausible mechanism for genome jumping. However, despite its many specialized adaptations, CTVT rarely becomes disseminated in an immunocompetent animal, highlighting the importance of the host immune response in susceptibility to a transmissible cell lineage. Moreover, other nonviral transmissible tumors have been described, but they tend to be aggressive, such as the Tasmanian devil facial tumor and the Syrian hamster tumor, both of which result in rapid tumor growth and host death (Pearse and Swift, 2006).

In addition to their implications for tumor biology and companion animal medicine, these findings have implications for conservation biology and genome evolution. At present, CTVT can enter the wild canid population through physical contact between individuals (licking and biting) or mating between closely related species such as gray wolves, coyotes, and domestic dogs. For highly endangered canids, exposure to CTVT could theoretically create an immediate threat to the population's survival. Virtually nothing is known about the immune response to CTVT in wild canids.

Despite the above concerns, CTVT can prove useful for studies of population dynamics, serving as a molecular proxy for the host. Proxy (parasite, virus, tumor) genomes generally evolve at a faster rate than host DNA, providing an accurate measure of host gene flow and migration when other genetic markers are uninformative (Whiteman and Parker 2005; Biek et al., 2006). For example, analysis of feline immunodeficiency virus (FIV) genes indicated strong genetic separation between populations of North American mountain lions (*Puma concolor*) within a defined geographic region when host microsatellite DNA and mtDNA data were uninformative (Biek et al., 2006). Similar applications would be beneficial for elucidating host species demography, especially when hosts are highly mobile and social, as are most *Canis* species.

The prospect of a contagious cancer cell is at once intriguing and frightening. Important directions for future study include expression profiling of DLA antigens during tumorigenesis and regression. Also important will be investigations into the origins of the LINE-1 transposition and evolutionary pressures that conserve the aneuploid genomic structure of CTVT. At any rate, if and when a more toxic contagious cancer emerges, we should not be surprised. Ever vigilant, man's best friend has warned him of dangers to come.

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