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Review

Transmissible Tumors: Breaking the Cancer Paradigm

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Transmissible tumors are those that have transcended the bounds of their incipient hosts by evolving the ability to infect another individual through direct transfer of cancer cells, thus becoming parasitic cancer clones. Coitus, biting, and scratching are transfer mechanisms for the two primary species studied, the domestic dog (*Canis lupus familiaris*) and the Tasmanian devil (*Sarcophilus harrisii*). Canine transmissible venereal tumors (CTVT) are likely thousands of years old, and have successfully travelled from host to host around the world, while the Tasmanian devil facial tumor disease (DFTD) is much younger and geographically localized. The dog tumor is not necessarily lethal, while the devil tumor has driven the population to near extinction. Transmissible tumors are uniform in that they have complex immunologic profiles, which allow them to escape immune detection by their hosts, sometimes for long periods of time. In this review, we explore how transmissible tumors in CTVT, DFTD, and as well as the soft-shell clam and Syrian hamster, can advance studies of tumor biology.

Types of Transmissible Tumors

Transmissible tumors are, by definition, spread directly by transfer of cells between individuals. They are clonal in origin, suggesting an ancient, singular event from which all modern tumors evolved. The most-well studied transmissible tumor is CTVT, dubbed the 'oldest continuously propagated cell lineage' [1,2]. Originally termed 'Sticker's sarcoma', it has been observed for over 200 years and is spread primarily by coitus and oral contact [3,4]. It was initially defined as a histocytic tumor by Novinski in 1876, who demonstrated its transmissibility by rubbing an excised tumor from one dog onto the genital mucosa of another [5,6]. CTVTs feature strong genetic identity with one another, but are markedly distinct from their extant, transient host [1,2,7,8]. CTVT is endemic in more than 90 countries and believed to be the most widely disseminated tumor in existence [6,9–12].

DFTD is a much younger tumor, first diagnosed in 1996 in the Tasmanian devil (*Sarcophilus harrisii*), the largest marsupial carnivore [13,14]. Originating in the northeast corner of Tasmania, DFTD has reached epidemic proportions. Between 1996 and 2006, it was observed in 41 locales, encompassing 50% of the island [13]. In contrast to CTVT, DFTD is not a venereal tumor; instead, it is spread by biting, often during mating or feeding [15–17]. The tumor forms around the face and neck [18], ulcerating and causing death within 6 months of onset by asphyxiation or starvation [19]. This underscores a very real concern that current rates of infection may drive the Tasmanian devil population to extinction [13,20,21]. In this review, we compare and contrast available genomic data from these two transmissible tumors. Specifically, we consider how genomic advances have changed our view of these two tumors. Finally, we briefly discuss additional manifestations of transmissible tumors in two other species, the Syrian hamster (*Mesocricetus auratus*) and the soft-shell clam (*Mya arenaria*).

Trends

Recent whole-genome sequencing (WGS) of CTVT has provided the first detailed glimpse into mechanisms allowing transmissibility.

Evaluation of CTVT against 186 canine whole genomes drastically increased the ability to distinguish between somatic and germline variants, leading to accurate classification of single nucleotide variants (SNVs), insertions and deletions (indels), and structural variants (SVs).

This evaluation, as well as a more accurate depiction of tumor evolution, has resulted in a better understanding of the underlying immunology that facilitates the characteristic transmissibility of transmissible tumors.

DFTD shows evidence for convergent evolution with the much older CTVT within class I MHC molecule presentation, indicating an essential hurdle for host immune evasion.

Additional transmissible tumor models in the Syrian hamster and soft-shell clam may further highlight commonalities and divergences between tumor transmissibility mechanisms.

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CTVT

CTVT Is a Parasitic Tumor

Several lines of evidence support CTVT as a naturally transmissible allograft. It can only be induced in a naïve individual by transplanting living tumor cells; neither frozen, heated, desiccated, killed, nor filtered cells transmit the tumor [5,22–24]. In addition, karyotypes of tumors collected from different regions are more divergent than those from the same region, which are themselves highly similar, confirming cellular transfer as well as clonality [24,25] (Box 1). Finally, oncogenic viral particles have not been not detected in tumor cells, further supporting this paradigm [26–28]. The tumor clone is demonstrably long-lived and stable [29], with experimental passaging for 40 generations (564 dogs) over 17 years producing no changes in its histopathology [30].

The epidemiology of CTVT suggests no sex bias [12] or breed barrier [9,10,22]. Many canids, including dogs, wolves, foxes, and coyotes, can be infected [24,29]. However, there is no evidence for transfer between distant species, because inoculation into rats, mice, hamsters, and cats has been unsuccessful [31].

The tumor generally remains localized to the external genitalia [9] (Figure 1). Histologic staining shows it to be characterized by large diffuse masses of compact, round or polyhedral neoplastic cells [24]. Canid sexual intercourse entails a long (up to 30-min) 'tie', where the male and female genitalia are in direct physical contact, often resulting in abraded tissue, likely contributing to the spectacular success of the tumor. Based on morphology and histologic staining patterns, CTVT was originally proposed to be histiocytic [24,25], lymphatic, or reticuloendothelial [32]. Subsequent immunohistochemistry has since assigned it to be in macrophage origin [33,34].

Tumor Dissemination

Early cytogenetic support for the clonality of all CTVTs was demonstrated by extensive conservation of genomic imbalances across tumors (Figure 2) [26,29,35,36]. Analysis of microsatellites, mitochondrial DNA (mtDNA), and the MHC locus in 40 dogs from five continents also showed that worldwide CTVT is derived from a single neoplastic clone [1]. Two major tumor clades were proposed, one in coyote and another encompassing the gray wolf and domestic dog (*Canis lupus familiaris*) lineages. This data suggested that CTVT originated in the pre-domestication *Canis lupus* lineage [37]. However, these findings would later be refuted using modern genomic methods [2,8].

Epidemiologic studies of CTVT, done using mtDNA, identified a close relation among tumor haplotypes from Mexico, the USA, Chile, and Brazil. Asian haplotypes were more divergent, although were most closely related to American haplotypes, suggesting that tumors in the USA, although rare, originally disseminated from Asiatic lineages [38].

Box 1. Key Features of CTVT

CTVT is a transmissible tumor believed to have originated hundreds or thousands of years ago.

The tumor is clonal, meaning that tumors from all infected canids share strong genetic identity.

Distinguishing somatic mutations, which drive tumor growth, from those found in the original or transient host is important for understanding how the tumor evades host immunity.

The tumor evades immune detection by accumulating mutations in all pathways related to recognition of self versus nonself.

Genomic approaches, including large catalogs of variation found in modern canids, are critical for identifying somatic drivers of tumor growth.