

DFTD: A Contagious Fatal Cancer that Threatens the Tasmanian Devils

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Editorial

The Tasmanian devil (*Sarcophilus harrisi*) (Figure 1), similar to its infamous animated cartoon character, Taz, is a ferocious carnivore with a notoriously short temper and little patience. However, future survival of Tasmanian devils in the wild is endangered by a fatal cancer disease that has wiped out ~60% of Tasmanian devils within just two decades [1].



Figure 1: Tasmanian Devil (*Sarcophilus harrisi*).

The fact that Tasmanian devils are prone to a bizarre type of contagious facial cancer disease was first noted in 1996 in the far north east of Tasmania, and since then, the disease has spread south and west and now affects devils in over 85% of their distribution territory [1,2]. The disease, termed devil facial tumor disease (DFTD), is spread by biting, causing the appearance of tumors on the face, jaws and in the oral cavity. The tumors often become very large and in ~60% of the cases, metastasize to internal organs, including regional lymph nodes, lungs, spleen, heart and kidneys [3]. The tumors kill the host within 6 months of the emergence of first lesions, due to starvation, secondary infection and metastases formation [3].

In contrast to other transmissible cancer diseases, such as the human Burkitt's lymphoma and adult T-cell leukemia, which are spread by viruses (Epstein-Barr virus (EBV) and adult T-cell leukemia/lymphoma (HTLV-I), respectively), the DFTD which is spread by

biting, appears to be transduced by the cancer cells themselves being passed from one animal to another [4]. Whole genome sequences of DFT cells from two geographically distant individual subclones did not produce evidence for exogenous viruses which might have contributed to DFTD pathogenesis and/or dissemination [5]. However, substantiation of the non-viral nature of the DFTD spreading hypothesis awaits experiments whereby healthy devils injected with DFTD tumor-cell-free filtrates, remain free of the disease.

Considering the genetic heterogeneity that exists in Tasmanian devils, as demonstrated by the acute skin allograft rejection responses observed between individual devils [6], it was surprising to discover that tumor cells that appeared to be of an allogeneic origin, were not rejected by genetically non-matched hosts.

In an attempt to solve this puzzle, Pearse and Swift performed a cytogenetic study on tumor samples from 11 different animals from various locations across Tasmania. They found that all devil facial tumor (DFT) cells tested had a distinctive aberrant karyotype with an identical aneuploidy observed in all samples. All DFT cells were missing both sex chromosomes, both chromosomes 2 and one chromosome 6, and had a deletion of the long arm of one chromosome 1. In addition, all DFT cells had four additional unidentified marker chromosomes [4]. In general, the genetic studies provided support for the clonal nature of the tumor [7-9], and further demonstrated that DFT cells are of a Schwann cell origin [8,10]. A thorough study that included chromosome painting and gene mapping of different DFTD cell lines showed minimal cytogenetic differences between tumor strains [5,9].

These findings supported the hypothesis that DFT cells are transmitted between devils as an allogeneic tissue, raising questions regarding the mechanism(s) by which the tumor cells evade the immune surveillance [3].

The possibility that Tasmanian devils are somewhat immune compromised and therefore cannot mount strong T cell-mediated or humoral anti-tumor immune responses have been ruled out by several independent studies showing that the devils' immune system is fully competent [11-13]. More specific analyses demonstrated that Tasmanian devils with DFTD have almost no anti-DFT cell antibodies, and their peripheral blood mononuclear cells (PBMCs) exhibited no cytotoxic activity towards DFT cells [14]. However, *in vitro* stimulation of PBMC with mitogens or interleukin 2 induced PBMC-mediated cytotoxic activity towards DFT cells [14], suggesting that proper immunization might be useful in evoking an *in vivo* anti-DFT cell cytotoxic response.

Another possible explanation for the ability of DFT cells to grow across allogeneic barriers might be due to insufficient diversity of major histocompatibility (MHC) antigens among devils [7,15,16].

Indeed, mixed lymphocyte reactions (MLR) revealed low or complete lack of alloreactivity between lymphocytes of different individuals in the affected population [7,13]. This was despite their ability to mount strong proliferative responses to the T cell mitogens, concanavalin A (ConA) and phytohemagglutinin (PHA), and the T cell/B cell mitogen, pokeweed mitogen (PWM) [7,13]. An additional study demonstrated that MLR between individual devils varies in responses, from complete lack to a relatively strong response, where highest responses were obtained when lymphocytes from devils from the east of Tasmania were mixed with lymphocytes from devils from the west of Tasmania [6]. Furthermore, despite the limited MHC diversity observed among devils [6], five out of five skin allografts were rejected within 14 days after transplantation, and an extensive T cell infiltration into the graft supported an immune-mediated graft rejection [6]. It was therefore concluded that the devil's immune system is capable of mediating a strong allogeneic graft rejection, and although DFT cells appear to express MHC class I and class II mRNA [7], it was unclear whether they express functional and immunogenic MHC proteins on their outer membrane.

This ambiguity has recently been resolved by Siddle et al. [17], who found a marked reduction in MHC class I protein expression on the surface of DFT cells, both *in vitro* and *in vivo*. DFT cells expressed almost no β 2-microglobulin, which is essential for stabilizing MHC class I α -chain protein on the cell surface, and were devoid of transporter associated with antigen processing 1 (TAP1) and TAP2 proteins, which are critical for cytosolic peptide delivery into the endoplasmic reticulum (ER) to enable peptide antigen binding to nascent MHC class I proteins. Down regulation of MHC genes was not due to gene loss or mutations, and as suggested, it might have occurred as a result of a regulatory defect that is associated with epigenetic regulation of histones [17].

The possibility that DFT cells grow across allogeneic barriers due to loss of expression of MHC or other transplantation antigens is currently the favored hypothesis, since a similar mechanism has already been found in other types of cancer diseases in dogs and mice [18,19]. Thus, the canine transmissible venereal tumor (CTVT) is a naturally occurring contagious non-fatal tumor in which low or high expression levels of MHC molecules correlate with progression or regression of the tumors [20,21]. In an additional experimental model of the murine metastatic Lewis lung carcinoma (3LL), transplanted tumor cells grew in all mouse strains tested, irrespective of their genetic background [19]. Further studies revealed that 3LL cells are devoid of immunogenic cell surface H-2K Class I MHC proteins [22,23]. However, lung metastases developed only in strains that shared H-2D Class I MHC proteins and the entire non-MHC genetic background with the syngeneic host of origin, the C57BL/6 mouse [24]. These studies indicate that individual MHC proteins might differ in their biological activity and/or immunogenicity, and that partial expression of certain MHC proteins may be sufficient for the induction of an effective immune response against lung infiltrating tumor cells, but insufficient for mounting an effective response leading to complete rejection of the primary tumors.

Until recently, the DFTD has been linked to a single cancer cell lineage, also designated DFT1. A recent study revealed a distinct devil's transmissible cancer, called DFT2, which was observed in five devils from southeastern Tasmania [25]. The DFT2 causes facial tumors indistinguishable from those caused by DFT1, and microscopic examinations revealed only minor differences. However, DFT2 carries a Y chromosome, in contrast to DFT1, which is of female origin. Thus,

the Tasmanian devils have given rise to two distinct and independent transmissible cancers, which are rarely observed in other species.

The ability of DFT cells to grow across allogeneic barriers poses a puzzle for scientists. However, the clonal nature of this tumor provides hope that once an efficient vaccine is developed, it could provide an ultimate solution that will help eradicate the DFTD epidemic.

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