**Cancer as a contagious disease**

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*Abstract*

Contagious cancers are malignant cells that are physically transferred between individuals as a natural allograft, forming new clonal tumours. These cancers are highly unusual, but have emerged in two mammalian species, the dog and the Tasmanian devil, as well as four species of bivalve. The transfer of malignant cells in mammals should initiate a robust immune response and although invertebrates have a less complex immune system, these species still have mechanisms that should prevent engraftment and protect against cellular parasitism. Here the naturally occurring contagious cancers are reviewed to determine what features are important and necessary for the emergence and spread of these types of cancer, with a focus on the mammalian contagious cancers and how they successfully cross histocompatibility barriers.

Keywords: Contagious cancer, Tasmanian devil, DFTD, MHC*Introduction*

Cancer is not usually an infectious disease, but in some cases tumour cells can acquire the ability to pass between individuals in a population. There are seven naturally occurring contagious cancers found in two mammalian species and four bivalve species. In mammals, Canine Transmissible Venereal Tumour (CTVT) passes between dogs (*Canis lupus*) (1) and two further examples are found in the Tasmanian devil (*Sarcophilus harrisii*), Devil Facial Tumour 1 (DFT1) (2) and Devil Facial Tumour 2 (DFT2) (3). Most recently, four genetically distinct contagious cancers have been identified in bivalves, known as Bivalve Transmissible Neoplasms (BTNs) (4, 5). In each of these examples malignant cells have the ability to physically transmit between individuals.

In mammals, transmission of cells between individuals should primarily be prevented by an allogeneic response targeted against foreign Major Histocompatibility Complex (MHC) molecules and bound peptides. Allografts can be rejected within 7-14 days when host CD4+ and CD8+ T cells are exposed to foreign MHC molecules on the surface of donor cells (6). Alternatively, T cells can be primed to graft-derived peptides (minor antigens) that are taken up by host antigen presenting cells (APCs) and presented by MHC class I and/or class II molecules to host T cells, also causing rejection of the graft (7). Although bivalve species do not have a histocompatibility system comparable to mammals, these species may be able to reject non-self cells using an alternative locus, as has been found in colonial chordates (8, 9). Thus, the ability of these malignant cells to passage between individuals implies that the histocompatibility system has broken down, challenging our understanding of how the immune system responds to foreign cells.

For a cancer to successfully transfer between individuals, the cancer cells and the host individuals must have specific characteristics. Here these characteristics are reviewed, to address the question, how does a cancer become contagious? This review focuses primarily on the mammalian contagious cancers and the role of MHC molecules, but with reference to the contagious cancers of bivalves. Understanding how these cancers have become contagious is essential to assess how likely these tumours are to arise in other species, including humans.

*Canine Transmissible Venereal Tumour (CTVT)*

The oldest known contagious cancer, CTVT, is found in dogs, and is thought to have arisen over 10,000 years ago in an ancient species of dog or a wolf, making CTVT the oldest continually passaged cell line (1, 10). The original transformed cell remains obscure but a histiocytic origin has been suggested (11, 12). CTVT cells are passed during coitus, sniffing or licking behaviour and cause tumours primarily around the genetalia, forming firm nodules before becoming multilobed and up to 10 cm in diameter (13) (Figure 1). CTVT has spread to every continent and during its long evolution has diverged into unique subtypes, although any functional differences between these strains (such as growth rate or transmissibility) are not known. Interestingly, CTVT has repeatedly acquired mitochondria from host cells, perhaps allowing the tumour to maintain genome integrity throughout its evolution (14).

CTVT is generally not fatal to host dogs and a tumour specific immune causes regression of the tumour and protective immunological memory (15). In an experimental setting CTVT progresses through predictable stages. Once cells are transferred to a new host, a tumour forms during a growth phase, followed by a stationary phase where growth stabilizes before regression of the tumour (16, 17). In outbred dogs where CTVT circulates the length of these phases appears to be highly variable and the stationary phase may not always be followed by complete regression (18, 19). Thus, CTVT can also exist as a stationary tumour in dogs, providing additional opportunities for the tumour cells to be passed to a new host.

*Devil Facial Tumours (DFT1 and DFT2)*

The Tasmanian devil is the only vertebrate species in which two genetically distinct contagious cancers have arisen, DFT1 and DFT2. DFT1 was first identified in 1996, in the north east corner of the island of Tasmania and has now spread across most of the geographic range of the species (2, 20). This tumour is highly aggressive and has caused a sharp decline in devil numbers (21). In contrast, DFT2 was identified in 2014 and preliminary studies indicate that its range is restricted to the south east of the island (3). Currently, DFT2 has been reported in only five individuals, all of which are male, and the epidemiology and potential immune response to the tumour has not been studied. Interestingly, the ultrastructural characteristics of DFT1 and DFT2 are similar, they are both characterised by the development of tumours around the face and neck of animals and can grow to beyond 10 cm in size (2, 3). These tumours become necrotic and infected over time and can severely affect the jaw structure and teeth of affected individuals (Figure 1). In contrast to CTVT, DFT1 has a high mortality rate, only recently have six animals been identified in which there is evidence of an immune response against the tumour (22). At present, the mortality rate of DFT2 is thought to be similar to DFT1, but due to the small number of cases this is difficult to determine. Despite the gross similarity of DFT1 and DFT2, analysis of genetic markers and karyotypes has shown that they have distinct genetic origins, ie that they derived from different host devils (3). In addition, the tumours have different MHC genotypes. DFT1 has been shown to have derived from a Schwann cell (23), while the cell type of origin of DFT2 is unknown.

*Bivalve Transmissible Neoplasms (BTN)*

Most recently, four contagious tumours have been identified in four bivalve species (soft shell clams (*Mya arenaria*), mussels (*Mytilus trossulus*), cockles (*Cerastoderma edule*) and golden carpet shell clams (*Polititapes aureus*)), these are collectively known as Bivalve Transmissible Neoplasms (BTNs) (4, 5). Although these tumours have existed for many years, their contagious nature has only recently been established due to the discovery that each tumour shares the same copy number of retrotransposons and identical integration sites (4). These cancers cause high levels of mortality and have negatively affected populations. Three of the four BTNs are species specific and experimental transmission across species is not possible (5). However, the BTN defined in *P. aureus* originally derived from a second species, *V. corrugate*, which means this cancer has crossed a species barrier. Interestingly, this cancer is now only found in *P.aureus*, perhaps implying an acquired resistance in *V. corrugate*, the species in which it derived (5). Although the DFTs and CTVT require physical contact for transmission, the BTNs are thought to transfer between individuals through release into sea water as bivalves are filter feeders. The immunological consequences of the emergence of BTNs are somewhat different to the contagious cancers in vertebrates due to absence of a histocompatibility system similar to HLA. However, invertebrates such as colonial chordates are known to have a gene system that prevents or allows colony fusion in these species (8). Although graft rejection has not been studied in bivalves it is likely that this species also have a similar system that needs to be overcome for a contagious cancer to emerge.

*What makes a tumour contagious?*

All cancers evolve under a Darwinian process, with tumour cells acquiring mutations that are the subject of selection pressures in a given environment (24). An important selection pressure is applied by the immune system, which can destroy immunogenic tumour cells through a process of immunosurveillance (25). In single organism cancers, tumour cells can change their environment when they metastasise, a process that is usually associated with the acquisition of mutations that facilitate immune escape and survival in a new environment or tissue. The process of metastasis has some similarities to the spread of contagious cancer cells between individuals, where each transmission to a new individual is a metastatic event. Given the ability of cancer cells to transmit to new tissues and survive in new environments, it is perhaps surprising that contagious cancers do not emerge more regularly. Interestingly, tumour cells that pass between individuals have been documented in humans, but these instances are usually where cells have passed across the maternal/fetal interface or during clinical transplants (reviewed in (26)). Thus, the emergence of a contagious cancer must require a number of characteristics of the host and/or of the tumour cells themselves. If these characteristics are specific to the host it would imply that contagious cancers are simply ‘opportunistic’ spreaders, ie. they have characteristics common to many single organism tumours, but have taken advantage of ‘deficiencies’ in their host to become transmissible. Alternatively, contagious cancer cells may have characteristics in common that are not found in single organism cancers, providing them the ability to transfer regardless of the host. If this is the case then a contagious cancer could emerge in any species. A third possibility is that the emergence of a contagious cancer is dependent on the interplay of host and tumour characteristics.

*Tumour cell characteristics*

DFT1 and CTVT both transiently down-regulate MHC molecules (27, 28), removing the potential for T cells to recognise foreign peptide/MHC complexes, as well as potential tumour specific antigens presented by class I molecules. DFT1 cells have only trace amounts of MHC class I expression on the cell surface due to down-regulation of the genes that allow peptide processing and presentation, β2m, TAP1 and TAP2 (Transporters for Antigen Processing) transcripts (27). This explains the loss of the MHC class I protein, as without β2m and peptides (pumped into the endoplasmic reticulum (ER) by the TAP heterodimer) the MHC class I molecule is not stable and will be retained in the ER. There is no evidence for haplotype loss or structural mutations in the coding regions of β2m, the TAP genes or the promoter regions of these genes. However, changes in the acetylation state of the promoter regions of these genes affect transcription. Similarly, during the growth period of CTVT the tumour cells do not express MHC molecules, most likely due to loss of β2m expression (28, 29). Due to the recent emergence of DFT2, it is no yet known whether these cells express MHC molecules.

Both DFT1 and CTVT cells retain the ability to express MHC molecules, which in both cancers is associated with an immune response from the host (27, 30). We have shown that treatment of DFT1 cells with recombinant devil interferon gamma (IFNγ) results in a significant upregulation of MHC class I protein on the cell surface of DFTD cells *in vitro* indicating that the antigen processing and presentation pathway of DFTD cells is intact. We also observed instances of β2m expression in primary DFTD biopsies where tumour cells were adjacent to clusters of CD3 positive lymphocytes (27). In addition, Pye et al have recently identified six wild Tasmanian devils with antibodies against MHC positive DFT1 cells and in two of these individuals DFT1 tumours have spontaneously regressed (22). In one of these animals CD4+ and CD8+ T cells are observed infiltrating the tumour and β2m positive tumour cells are present. While direct evidence of an MHC restricted response is lacking, this data implies that any protective immune response requires the expression of MHC molecules and elicits both a CD4+ and CD8+ T cell response, resulting in circulating antibodies. Whether this immune response sustains immunological memory has not been determined.

Similarly, regression of CTVT is characterised by an increasing proportion of tumour cells that express both MHC class I and class II molecules (28). The expression of MHC molecules occurs along with the infiltration of CD4+ and CD8+ T cell (Tumour Infiltrating Lymphocytes (TILs)) into the tumour mass, which have been shown to be cytotoxic to CTVT cells. The pro-inflammatory cytokines, IL6 and IFNγ have been detected in *ex vivo* cultures of TILs from regressing tumours and most likely play a role in the switch from growth to regression (30).

The down-regulation of MHC molecules appears to be important in allowing both DFT1 and CTVT cells to transmit between individuals. However, in CTVT the expression of MHC class I molecules is consistently associated with a protective immune response, whereas a protective immune response in DFT1 is a rare occurrence. However, it has not been conclusively shown in either tumour that the immune response is MHC restricted. An interesting area for further research is to determine if these immune responses are truly MHC restricted and if so to determine the specific MHC class I/II/peptide complexes that drive them. We are currently investigating the peptide/MHC class I complexes that drive the immune response to DFT1, these peptides have the potential to be used as a peptide vaccine against this disease.

Although down-regulation of MHC molecules is most likely necessary for tumour cell transmission, this characteristic is not unique to contagious cancers. Many single organism tumours lose expression of MHC molecules, particularly tumour cells that have metastasised (reviewed in (31)) but these tumour cells typically do not gain the ability to transmit. Antigen loss occurs in a number of different ways, either through ‘hard’ mutations in the DNA, such as Loss of Heterozygosity (LOH) or through ‘soft’ epigenetic mutations that affect transcription (32).

*Immunosuppressive factors*

The absence of MHC class I molecules means that DFTD and CTVT cells should be susceptible to lysis by NK cells. In CTVT, this may be prevented by the expression of immunosuppressive cytokines, such as Tumour Growth Factor β (TGFβ) (30). TGFβ is secreted by CTVT cells during the growth stage and is still present when the tumour becomes stationary. However, the release of IL6 and IFNγ by TILs during the stationary and regression phase has been shown to antagonise TGFβ, allowing IL6 and IFNγ to promote a more general inflammatory response. Only one study has investigated the expression of immunosuppressive cytokines by DFTD cells. It was reported that TGFβ and IL10 mRNA levels in DFTD biopsies are not significantly higher than that of spleen and nerve tissue suggesting that this type of immunosuppression is not playing a role in DFT1 growth (33). It is also possible that the ability of both CTVT and DFT1 cells to express MHC class I molecules may protect the tumour cells from NK cells at different stages of transmission and tumour growth.

*Host characteristics*

There is no evidence that dogs, Tasmanian devils or the bivalve species affected by contagious cancers have a compromised immune system. In dogs, CTVT does not readily metastasise, except in cases where the dog is already immunocompromised (34). Similarly, Tasmanian devils can reject skin grafts from both MHC matched and mismatched individuals (35) and devils have been shown to have a competent cellular and humoural immune response (36). However, there is some evidence that characteristics of the host may contribute to the emergence of contagious cancers, specifically the level of genetic diversity present in a host population (37).

The DLA genotype may impact the ability of CTVT to spread among host dogs. When inoculated with CTVT, sib pairs with identical MHC haplotypes have similar CTVT growth patterns, while sib pairs that differ by 2 DLA haplotypes can have completely discordant growth patterns (18). This data implies that the DLA genotype of dogs can affect the growth rate of CTVT and how quickly the tumour enters a stationary phase or regresses. In addition, loss of heterozygosity (LOH) may have been positively selected during CTVT evolution, reducing the MHC mismatches between tumour and host dogs (1). CTVT tumours are diploid for the MHC class II genes DRA and DRB1 as well as the class I gene DLA-88, but some tumours are haploid for DQA and DQB. The diploid loci are homozygous with the exception of DRB1, which it is heterozygous, with the alleles differing by one non-synonymous substitution (1).

The Tasmanian devil has been confined to the island of Tasmania for 400 years and underwent a severe population decline in the early 20th century (38). A likely consequence is that the population has reduced genetic diversity at both MHC class I and class II genes (37, 39) as well as microsatellite markers (40). Tasmanian devils have three known classical MHC class I loci, *SahaUA*, *SahaUB* and *SahaUC*, with classical class I alleles from these loci sharing between 91-99% amino acid identity (41). Interestingly, 54% of devils carry a haplotype in which UA is a pseudogene, leaving these animals with two classical class I genes (42).

There have been a number of studies investigating the role of MHC diversity in the spread of DFT1 (37, 41, 43). Although there is no evidence that the MHC genotype of host devils impacts susceptibility or resistance to DFT1, the genetic background of the host devil may play a more subtle role in tumour growth rates that is difficult to isolate from other variables in a wild population. With the recent discovery of a small number of animals that have raised antibodies to DFT1 cells (22) the potential for genetic resistance to the contagious cancer needs to be further investigated.

*Conclusions*

Contagious cancers can only emerge and spread where certain conditions are met, allowing these cells to avoid the immune response usually targeting foreign cells. DFT1 and CTVT share common features that facilitate their transmission, perhaps the most important being the down regulation of MHC molecules. Although loss of MHC is important for transmission, both tumours upregulate MHC molecules in some situations, opening the door for an effective immune response against the tumour. This may have an evolutionary benefit to the tumour, allowing its host to survive for longer and transmit the tumour cells to a new individual. The expression of immunosuppressive cytokines is also important in CTVT growth, but their role seems less crucial in DFT1, perhaps indicating that overcoming MHC barriers is more important than general suppression of T cells and NK cells. Given that many single organism tumours also regulate MHC expression, this alone cannot explain transmissibility and characteristics of the host species must also be important. There is some evidence that the MHC genotype of host dogs affects CTVT growth and the emergence of CTVT in a wild dog or wolf may have been due to the genetic similarity that is characteristic of animals that live in family packs (1). Despite the limited genetic diversity in the Tasmanian devil population there is no evidence that MHC genotype affects transmission or growth, but this is an area that needs further research. In addition to these immunological and genetic factors, host characteristics such as physiology and behavior may also facilitate cell transmission. In dogs, features of coitus may play a role and in the Tasmanian devil biting behavior to establish dominance and hierarchy may be key to transmission (44). Thus, the emergence of a contagious cancer most likely requires features of both the tumour cells and the host and their success is due to a complex interaction between the host immune system and the tumour. The populations at risk of these tumours may have reduced genetic diversity, individuals that are regularly immunocompromised and develop tumours that have the ability to modulate MHC expression. By understanding the mechanisms that facilitate tumour transmission and immune escape we can shed light on how the histocompatibility system can break down, which has implications for cancer biology and transplantation.

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*Figure Legend*

**Figure 1.** A tabular comparison of the characteristics of CTVT and DFT1 cells and their respective hosts. The comparison is confined to CTVT and DFT1 as these tumours are the most well understood of the contagious cancers.