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The role of the Major Histocompatibility Complex in the spread of contagious cancers

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Abstract Major Histocompatibility Complex (MHC) genes play a key role in immune response to infectious diseases, immunosurveillance, and self/nonself recognition. Matching MHC alleles is critical for organ transplantation, while changes in the MHC profile of tumour cells allow effective evasion of the immune response. Two unique cancers have exploited these features to become transmissible. In this review I discuss the functional role of MHC molecules in the emergence and evolution of Devil Facial Tumour Disease (DFTD) and Canine Transmissible Venereal Tumour (CTVT). High levels of genetic diversity at MHC genes play a critical role in protecting populations of vertebrate species from contagious cancer. However, species that have undergone genetic bottlenecks and have lost diversity at MHC genes are at risk of transmissible tumours. Moreover, evolution and selection for tumour variants capable of evading the immune response allow contagious cancers to cross MHC barriers. Transmissible cancers are rare but they can provide unique insights into the genetics and immunology of tumours and organ transplants.

Introduction

The immune gene repertoire of an individual protects him/her from infectious diseases and parasites by generating a broad range of immune molecules. One key family of immune genes that plays a central role in defence against infectious disease is the Major Histocompatibility Complex (MHC). High levels of genetic diversity at MHC genes increase the immunological fitness of a population by increasing the likelihood that some individuals within a population are able to generate an immune response to every pathogen (Radwan et al. 2010). However, evidence is emerging that the role of the MHC extends beyond protecting individuals from infection by viruses, bacteria, and parasites to protecting them from infections by transmissible cancers (Kurbel et al. 2007; Murgia et al. 2006). Here I review the literature on two transmissible cancers, Devil Facial Tumour Disease (DFTD) and Canine Transmissible Venereal Tumour (CTVT), and the role that genetic bottlenecks and the loss of MHC diversity have played on the emergence and spread of these contagious cancers.

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The Major Histocompatibility Complex (MHC)

MHC genes are found in all jawed vertebrates. There are two main classes of MHC genes involved in antigen presentation, Class I and Class II. Both Class I and Class II genes are codominantly expressed, with Class I molecules expressed on all nucleated cells and platelets and Class II molecules on B lymphocytes, some macrophages and monocytes, Langerhans cells, and dendritic cells (reviewed in Kelley et al. 2005).

MHC Class I antigens are composed of an α chain, which is encoded within the MHC, and a β_2-microglobulin, whose gene is found outside the MHC. The number of MHC Class I loci varies greatly among species, as do their functional roles (reviewed in Kelley et al. 2005).

The MHC Class I genes can be divided broadly into classical and nonclassical molecules. Classical Class I molecules include the human HLA-A, HLA-B, and HLA-C. They are involved in presenting self and nonself peptides to T

cells. The peptide-binding region is found within the α1 and α2 domains of the Class I peptide. The amount of polymorphism within the peptide-binding region is extremely high, with 1001 HLA-A, 1605 HLA-B, and 690 HLA-C molecules characterised in human populations to date (IMGT/HLA database, http://www.ebi.ac.uk/imgt/hla/stats.html).

Nonclassical Class I genes are not involved in antigen presentation and tend to have limited expression in different tissues and are not necessarily polymorphic (Siddle et al. 2009). By modulating the expression of classical and nonclassical MHC Class I molecules, cells have evolved strategies to evade immune detection (Algarra et al. 2000, 2004; Bubenik 2004; Cabrera et al. 2003; Ferrone and Marincola 1995; Garcia-Lora et al. 2003; Ugurel et al. 2002; Zitvogel et al. 2006). A classic example of this occurs at the maternal-fetal interface. The conceptus is a semiallogeneic tissue with paternal MHC alleles that are foreign to the maternal immune system. The fetus is protected from immune-mediated rejection by the downregulation of classical MHC Class I molecules on fetal trophoblast cells that form the external layer of the placenta (Moffett and Loke 2006). Cells devoid of cell surface MHC should be destroyed by natural killer cells, but by displaying the structurally similar nonclassical HLA-G molecules, trophoblast cells avoid this (Moffett and Loke 2006).

The MHC Class II antigens consist of an α chain and a β chain. The genes for both are encoded within the MHC. The peptide-binding region is located within the α1 and β1 domains. Again, the number of MHC Class II genes varies between, and even within, species.

Importance of allelic variation in MHC

The MHC genes are the most polymorphic genes in vertebrates (Kelley et al. 2005). Variation in immune response occurs through allelic variation in the peptide-binding regions of the MHC molecules, resulting in differential peptide binding and presentation, as well as differential thymic selection of T cells. MHC diversity is also generated through gene copy number variation.

MHC diversity can be measured using mixed lymphocyte response assay (MLR) or molecular methods. MLR assays involve lymphocytes from one donor being cultured with lymphocytes from an unrelated donor. Measurable proliferative responses are primarily due to a disparity in MHC antigens of the two individuals. Various molecular typing methods are used to characterise MHC variants. The most common of these methods involves PCR amplification of the peptide-binding regions of the molecules followed by cloning and sequencing of the alleles. In many nonmodel species, a single PCR reaction amplifies multiple MHC loci due to high sequence similarity of recently duplicated genes (Siddle et al. 2009).

The role of the MHC in transplantation

The MHC was first discovered for its role in graft rejection (Dausset et al. 1965). Histocompatibility antigens were described as transplantation antigens because of their ability to induce graft rejection in a genetically nonidentical recipient (allograft rejection). We now know that cumulative mismatches at MHC are associated with increasingly poor graft survival (Bradley 1991). MHC-incompatible tissues can induce strong primary immune responses and lead in vivo to allograft rejection and graft-versus-host disease, and in vitro to MLR (Warrens et al. 1994). Alloreactive T cells are specific for peptide-MHC complexes, so the bound peptides can also contribute to alloreactivity. Foreign MHC molecules (from the donor) can also be processed and bound as peptides to the recipient's MHC, resulting in recognition by T cells, like any other foreign protein. This is called indirect alloreactivity. In addition, minor histocompatibility antigens can play an important role in graft rejection. Minor histocompatibility antigens are simply donor tissue proteins that contain polymorphisms compared to host proteins. These polymorphisms can be recognised by the recipient, resulting in an immune response. The effect of a number of minor histocompatibilities together may be as strong as incompatibility at the MHC (reviewed in Warrens et al. 1994).

The role of the MHC in cancer immunosurveillance

In 1957 Burnet and Thomas proposed the theory of cancer immunosurveillance (Burnet 1957; Thomas 1959). They suggested that lymphocytes patrol the body and eliminate continuously arising tumour cells. Although still a matter of debate, it appears that cancers may arise as the result of a two-hit process. The first hit involves the oncogenic mutation, which is followed by a second event that leads to a deficiency in the immune response against the tumour cells (Zitvogel et al. 2006). This occurs through the selection of cancer cell variants with an ability to avoid immunosurveillance.

The most common mechanism of tumour immune evasion is loss of MHC I molecules of tumour cells (Algarra et al. 2004; Cabrera et al. 2003; Garcia-Lora et al. 2003). This can occur through total Class I loss via β_2-microglobulin mutations or alterations in antigen-processing machinery, MHC haplotype loss, allelic loss, MHC downregulation, or compound phenotypes. Class I loss is

observed in 90% of cervical carcinomas, 73% of colorectal carcinomas, 88% of breast carcinomas, 51% of melanomas, and 66% of laryngeal carcinomas (reviewed in Cabrera et al. 2003). This tends to be accompanied by the aberrant expression of the nonclassical MHC Class I molecules HLA-G and HLA-E, e.g., melanoma (Ugurel et al. 2002), breast cancer (Lefebvre et al. 2002), and lung carcinoma (Pangault et al. 1999).

Our understanding of the impact that the immune system has on shaping the evolution of tumour variants came from tumour transplantation studies between MHC-incompatible mouse strains (Snell 1953). Tumour cells from a parental strain that were transplanted into an F1 hybrid came under strong selection pressure not to express the MHC-incompatible antigens. However, such variants did not emerge in MHC-compatible strains or when tumours were transplanted into immunocompromised mice (reviewed in Fassati and Mitchison 2010).

Devil Facial Tumour Disease

Tasmanian devils are the world's largest remaining marsupial carnivores. They became extinct on mainland Australia as recently as 400 years ago (Johnson 2006) and are now found only in Tasmania. Tasmanian animals have been isolated on the island since the last ice age, about 12,000 years ago, and are known to have been through at least three major population crashes in recent history (Guiler 1992), resulting in low levels of genetic diversity at microsatellite markers (Jones et al. 2004). Until the emergence of a new infectious disease in 1996, Tasmanian devils were common and widespread in Tasmania (McCallum 2008). Since then, Devil Facial Tumour Disease (DFTD) has led to an 80% decline in overall devil sighting and up to 95% in northeastern populations, where the disease emerged (http://www.tassiedevil.com.au/tasdevil.nsf/Mapping-the-disease/A140AACCA1B1F6B0CA2576CB0011BD2C). Current estimates predict extinction in the wild within 25 years (McCallum et al. 2007).

DFTD causes tumours primarily around the face and the jaw and in the oral cavity and metastasizes in 65% of cases (Loh et al. 2006a). Death occurs due to an inability to feed, secondary infection, and organ failure due to metastases (McCallum 2008; Pyecroft et al. 2007). DFTD is not caused by a traditional pathogen but by a rogue cell line—an allograft (Pearse and Swift 2006). Cytogenetic analyses have shown that the tumour karyotype is highly conserved between tumours yet is dramatically different from that of the normal devil karyotype (Pearse and Swift 2006). It involves complex chromosomal rearrangement and loss. Tumour karyotyping (Pearse and Swift 2006) and genotyping (Murchison et al. 2010; Siddle et al. 2007) refute de novo origin of the tumour in each individual and confirm that transmission is the only feasible alternative. Tumour cells are transmitted from animal to animal by biting (Obendorf and McGlashan 2008). Immunohistological and molecular studies suggest that the tumour has a neural crest origin (Loh et al. 2006b; Murchison et al. 2010), most likely Schwann cell origin (Murchison et al. 2010). There is no evidence of devils mounting an immune response to DFTD (Wood et al. 2007). In fact, infiltrating lymphocytes are seen in only 7% of DFTD tumours (Loh et al. 2006b). The disease kills animals within 6 months of the first appearance of lesions. To date, no animals have recovered after developing DFTD lesions.

From an immunological point of view, transmission of cells from one individual to another should lead to rapid immune response and rejection of the foreign tissue due to recognition of nonself antigens on the cell surface. We have shown that DFTD is able to spread due to a lack of MHC Class I diversity in Tasmanian devils (Siddle et al. 2007). Genetic diversity at MHC Class I was measured by both MLR and cloning and sequencing of the peptide-binding regions of the Class I molecules. Devils on the east coast of Tasmania are essentially identical at their MHC genes (Siddle et al. 2007). Moreover, they share the same MHC alleles as DFTD cells, which are, of course, of devil origin. Therefore, the devil's immune system fails to see the DFTD cells as nonself and does not mount an immune response against them.

To confirm that lack of MHC diversity alone allows DFTD to be so readily transmitted requires experimental transplantation of skin between unrelated devils. A classic study showed that lack of MHC diversity in inbred cheetahs resulted in successful transplantation of skin between unrelated individuals (O'Brien et al. 1985). Until this is done in devils, we cannot rule out that the tumour is actively suppressing the immune response in some way.

Prior studies have shown that northwestern devils differ from eastern devils at neutral microsatellite markers (Jones et al. 2004). This is also true for diversity at MHC (Siddle et al. 2010). Interestingly, these animals do not produce different allelic variants from their eastern counterparts. Instead of exhibiting variation in the peptide-binding regions of their MHC antigens, these animals differ in the number of copies of MHC loci they possess (Siddle et al. 2010). Strikingly, some animals have a restricted MHC repertoire, lacking Class I loci. To understand this more completely, BAC sequencing of MHC haplotypes is in progress. This is necessary because at present it is impossible to amplify individual MHC loci and a single PCR reaction results in the amplification of two to seven MHC variants. These variants are highly similar and their genomic organisation is unknown. We predict that two to five loci are found on a single haplotype if, in fact, the MHC

alleles are inherited as a single complex. This may not necessarily be the case as the Class I genes in the tammar wallaby, a distantly related marsupial species, are unlinked (Siddle et al. 2009).

The devil MHC alleles fall into two subgroups based on sequence similarity (Siddle et al. 2010). Some animals lack antigens belonging to one subgroup (Siddle et al. 2010). The tumour cells express cDNA transcripts of both of these groups of genes, which led us to hypothesize that the immune system of individuals that lack one of these subgroups may see that group of antigens as on the surface of the tumour as nonself. This theory remains to be proven.

It is interesting to note that initial reports suggest that the DFTD is behaving differently in populations that contain these genetically different hosts. Fewer animals than expected are contracting the disease (Rodrigo Hamede, University of Tasmania, personal communication). Research is currently in progress to determine whether MHC-disparate animals are able to mount an immune response to DFTD.

Canine Transmissible Venereal Tumour

Canine Transmissible Venereal Tumour (CTVT) was first described in 1876 by Novinski (1876), who demonstrated that CTVT could be transmitted between unrelated dogs by the direct transfer of cancer cells or tumour tissue. Further studies have shown that CTVT can be transmitted using only live cells, not cellular filtrates or killed cells, which demonstrates the transmissible nature of the cells themselves rather than infectious particles (Das and Das 2000; De Monbreun and Goodpasturem 1934; Murgia et al. 2006; Rust 1949). CTVT primarily causes lesions on the external genitalia of dogs and is spread during coitus, but can also be spread by licking, sniffing, or scratching of affected areas and develop on other areas of the body (Das and Das 2000). The disease has evolved to be an effective parasite as it spontaneously regresses in most healthy dogs and rarely metastasizes. Metastases tend to occur in immunocompromised animals, including dogs that have been irradiated experimentally to induce immunosuppression. Spontaneous regression usually starts within 3 months of implantation of the tumour and the chance of self-regression is remote in tumours older than 9 months (Das and Das 2000).

CTVT is widespread and has been described on six continents (Das and Das 2000). Recent studies have shown that CTVT is a clonal cell line. The CTVT genome has an insertion of a LINE-1 element near the c-myc oncogene that is not found in host genomes (Liao et al. 2003). Normal canine cells have 78 chromosomes. CTVT cells have a vastly rearranged karyotype containing 58–59 chromosomes (Adams et al. 1981; Wright et al. 1970). The tumour cells are aneuploid but remarkably stable. Recent studies have shown that tumours from distinct geographic regions feature unique chromosome patterns of gain and loss (cited in Murgia et al. 2006). Conclusive proof for the "allograft theory" came from a pivotal study by Murgia et al. (2006) and was reinforced by Rebbeck et al. (2009), who showed that the tumours are closely related genetically, with a monophyletic origin, and are genetically different from the host. Based on the microsatellite diversity, modern variants of CTVT emerged between 47 and 470 years ago (Rebbeck et al. 2009) or 250-2500 years ago (Murgia et al. 2006) and fall into two major subgroups (Murgia et al. 2006). These represent recent successful variants, but the tumour itself probably emerged in inbred wolves around the time that the dog was domesticated (Rebbeck et al. 2009).

Histological studies suggest that CTVT evolved from a myeloid cell, possibly from the macrophage lineage (reviewed in Murchison 2009). This is supported by the ability of the cells to express both MHC Class I and Class II antigens.

MHC diversity in dogs has been studied extensively by Lorna Kennedy and colleagues. A comprehensive account of canine MHC Class I and Class II alleles can be found at http://www.ebi.ac.uk/ipd/mhc/dla/index.html. One hundred DLA-DRB1, 26 DLA-DQA1, and 60 DLA-DQB1 alleles were identified in 937 dogs over 80 different breeds (Kennedy et al. 2007b). Eighty-eight haplotypes were identified in more than one dog, but no breed had all haplotypes. Jack Russell terriers had the most, with 21 different haplotypes. As expected, a large number of haplotypes were also found in mongrels. Dogs, wolves, and coyotes share MHC alleles. Twenty-eight haplotypes were found in 175 gray wolves, many of which are also seen in dogs (Kennedy et al. 2007a). Thirty-five wolves were homozygous for all three loci, and overall levels of genetic diversity in wolves were much lower than those seen in dogs.

While DFTD is spread without invoking an immune response in populations that are MHC-identical, CTVT can trigger both cellular and humoral immune responses and can be transplanted across MHC barriers. During progressive growth of CTVT, β_2-microglobulin (Cohen et al. 1984), MHC Class I gene (Murgia et al. 2006), and protein expression is low. However, normal levels of MHC Class I and β_2-microglobulin expression are seen during the regressive phase (Murgia et al. 2006; Yang et al. 1987).

Interestingly, some cell-surface MHC Class I expression remains during the progressive growth phase, presumably to prevent recognition and killing of CTVT cells by NK cells. Fassati and Mitchison (2010) have suggested that the evolutionary history of CTVT has been fine-tuned, with CTVT variants altogether lacking the ability to express

MHC Class I antigens, having been eliminated by NK cells, resulting in a scenario where CTVT variants have been selected through both positive and negative selection to evade most effectively both T cells and NK cells during the CTVT life cycle (Fassati and Mitchison 2010).

CTVT cells also downregulate MHC Class II expression during tumour progression (Murgia et al. 2006) and resume expression during regression. Expression of foreign Class II antigens on CTVT cells is likely to trigger the production of antibodies against CTVT and protect the host from future infection. Tumour regression is accompanied by the presence of circulating anti-tumour antibodies, which are associated with subsequent resistance to further successful implantation and growth of the tumour cells (reviewed in Das and Das 2000). Newborn puppies from immune dams (mothers with Ab to tumour) show longer latent periods for tumour development, and the neoplasms in these puppies are smaller and show more rapid spontaneous regression.

Modulation of MHC expression in CTVT appears to be controlled by the cytokines IL-6, IFNγ, and TGFβ (Hsiao et al. 2002, 2004, 2008). CTVT secretes substantial amounts of the downregulatory cytokine TGFβ, which exerts strong immunosuppressive effects by protecting tumour cells from infiltrating cytotoxic T lymphocytes and inhibiting NK cell activity. TGFβ also contributes to the tumour's MHC Class I and II downregulation by inhibiting IFNγ-induced MHC Class I and II gene expression.

The transition from progressive to regressive phase of CTVT is accompanied by an increase in immune cell infiltration. Regression appears to be triggered by cytokines produced by tumour-infiltrating lymphocytes. The production of high levels of IL-6 by infiltrating lymphocytes counteracts the immunosuppressive activity of TGFβ and acts synergistically with host-derived IFNγ to enhance MHC expression leading to the initiation of the regressive phase (Hsiao et al. 2002, 2004, 2008).

Threshold concentrations of TGFβ need to be reached within the tumour microenvironment to be protective and this is why CTVT tumours rarely metastasize (Hsiao et al. 2008). Tumour cells in circulation are simply unable to reach such levels, except in immunocompromised animals.

A dog can be cured of CTVT by surgical excision, radiotherapy, immunotherapy, and chemotherapy (reviewed in Das and Das 2000).

Transmission of other cancers

While DFTD and CTVT are the only known naturally occurring transmissible cancers, cancer transmission has also been recorded in the following cases.

Cancer can be transmitted through organ transplantation

Tumours can be transmitted to organ recipients but rarely are (Kauffman et al. 2002), with melanoma the most commonly transmitted (reviewed in Dingli and Nowak 2006). DFTD provides a good natural model for studying transmission of tumours through organ donation, with organ donors and recipients sharing MHC alleles. However, transplant recipients are given immunosuppressive drugs that dampen the immune surveillance which might otherwise recognise and react against donor-derived tumour cells. Whether DFTD is capable of immune suppression remains to be determined. O'Neill (2010) provides a good overview of the analogies between tumour transmission through transplantation and the two transmissible cancers (O'Neill 2010).

Cancer can be transmitted from mother to offspring during pregnancy

Seventeen cases of metastasis from mother to fetus mostly involving melanoma, leukaemia, or lymphoma have been reported and are summarized in a recent paper by Isoda et al. (2009). They also report the transmission of a leukemic cell clone from mother to child in utero through the loss of paternal MHC alleles on the tumour. Numerous reports describe the transmission of trophoblast-derived choriocarcinoma metastases to both the mother and the fetus (O'Neill 2010). Again, the MHC is involved, with trophoblast cells downregulating paternal cell surface MHC expression to evade rejection by the maternal immune system (Moffett and Loke 2006).

Cancer can be transplanted experimentally

As mentioned previously, the field of MHC genetics was pioneered by research involving tumour transplantation experiments between different mouse strains (Snell 1953). Deliberate tumour transplantation experiments have also been carried out in humans in the past. Scanlon et al. (1965) transplanted a small piece of melanoma from a cancer patient into her healthy mother. Mother and daughter had identical blood types and the daughter shared at least one of her mother's MHC haplotypes. The tumour grew in the mother and was cut out 24 days after transplantation. The mother died 451 days after transplantation from diffuse metastasis through the lungs, ribs, diaphragm, pericardium, skin, and lymph nodes. The melanoma metastases had a histological appearance identical to the daughter's tumour (Scanlon et al. 1965). More recently, a surgeon "caught" malignant fibrous histiocytoma after accidentally injuring his palm during surgery (cited in

Dingli and Nowak 2006). The MHC phenotypes of the surgeon and patient were not determined.

A cancer was transmitted by mosquitoes to inbred laboratory animal

Repeated passaging of a reticulum cell sarcoma through inbred laboratory hamsters led to the evolution of a transmissible cancer (Brindley and Banfield 1961). Cancer cells (but not cell filtrates) were transmitted via feeding (Brindley and Banfield 1961) and mosquitoes (Banfield et al. 1965) between animals that had no direct contact with each other. Clonality of the tumour was confirmed by karyotyping (Banfield et al. 1965).

Discussion

There are clear similarities between DFTD and CTVT, even though the two diseases emerged separately in two unrelated species. In both instances, the cancer cells themselves are the infectious agent. It appears that both diseases emerged in inbred populations of wolves and devils that lacked diversity at MHC genes. This lack of diversity allowed the cancer to spread without invoking immune responses.

The emergence of two contagious cancers raises the question: Why don't contagious cancers emerge more regularly? Some have speculated that the MHC evolved to protect vertebrates from transmissible cancers (Kurbel et al. 2007; Murgia et al. 2006). They argue that infection by bacteria and viruses is universal, affecting vertebrates and invertebrates alike. However, cancer affects only vertebrate species. Regardless of whether this is correct or not, the possibility of new contagious cancers emerging in the future in inbred vertebrate populations can not be discounted. The possibility of the emergence of another contagious cancer provides another incentive to maintain genetic diversity in our wildlife populations, particularly in isolated populations.

Traditionally, cancer cells evolve to be more aggressive and they achieve higher levels of fitness with time. The evolutionary history of cancer should be viewed as a Darwinian process, involving "descent with modification" and "natural selection" (Vincent 2010). With this in mind, over time, CTVT evolved the ability to downregulate cell surface MHC. This allowed it to cross the MHC barrier and then ultimately the species barrier from wolves to dogs and other species including jackals, coyotes, and foxes.

The immune system plays an integral role in the selection of tumour variants. Progressive tumour growth occurs not because the immune system is defective but because cancer cell variants develop a variety of strategies to escape immune recognition. Similarly, cancer cells acquire new biological properties to generate invasive capacity in order to migrate and colonize new tissues (Cabrera et al. 2003).

DFTD is now under strong selection pressure to evolve immune evasion strategies. The disease, for the first time, has encountered hosts that are genetically different at their MHC genes, and preliminary studies suggest that at least antibody responses can be generated to DFTD (Obendorf and McGlashan 2008). Selection for variants that can evade the immune response, through either MHC downregulation, production of suppressive cytokines, or any other mechanism, is going to be strong. Recent cytogenetic analyses show that DFTD is evolving (Pearse et al. unpublished). The phenotypic differences between DFTD strains, if they exist, are yet to be determined. Until now, DFTD has remained host-specific. Variants capable of immune evasion, if they evolve, should be "stamped out" as quickly as possible. Transmission to the closely related dasyurid quolls would be unthinkable.

To date, research has focused primarily on the role of the adaptive immune response and, specifically, on the role of the MHC in the spread of DFTD and CTVT. In the future, research should turn to the role of innate immunity in this process. Allorecognition dates back to colonial invertebrates and has been studied in Porifera (sponges), Cnidaria (corals and hyroids), Bryozoa (sea mats), and Urochordata (tunicates or sea squirts) (reviewed in LaRosa et al. 2007; McKitrick and De Tomaso 2010). These species do not have an adaptive immune response or MHC genes, yet they have a highly specific allorecognition system that restricts somatic fusion of individuals based on their genotype. This process is believed to have evolved to guard against stem cell or germline parasitism (Buss 1982). In Hydractinia, colonies fuse if they share at least one haplotype (at two loci, *alr1* and *alr2*), reject if they share no haplotypes, and display transitory fusion if they share only one allele in a haplotype (Lakkis et al. 2008; Nicotra et al. 2009; Rosa et al. 2010). A different locus governs fusion and rejection in the ascidian *Botryllus schlosseri*. When two colonies share one or both FuHC alleles, they fuse. If they have no alleles in common, an inflammatory-like rejection lesion is formed at the site of contact and the interacting ampullae are destroyed, preventing vascular fusion. This process is controlled by a single, highly polymorphic gene, at which hundreds of alleles have been characterised (De Tomaso et al. 2005; Stoner and Weissman 1996). Both systems are reminiscent of MHC in mammals but do not share common evolutionary origins.

Interestingly, invertebrate allorecognition is based on recognition of "missing self." When *Botryllus* colonies fuse, recognition of at least one common FuHC allele results in the inhibition of a default rejection reaction

(De Tomaso et al. 2005). This mechanism shares similarities to the interactions between activating and inhibitory NK cell receptors with MHC molecules in mammals (Ljunggren and Karre 1990). The impact of MHC copy number variation on NK cell activity in Tasmanian devils remains to be determined.

Conclusion

Remarkable similarities exist in the evolutionary history of the two known contagious cancers. Both transmissible cancers are likely to have emerged in inbred populations that lacked MHC diversity. CTVT variants then evolved immune evasion strategies that enabled them to cross the MHC barrier. DFTD has only recently encountered MHC-disparate hosts. Whether DFTD can affect these animals, or indeed will evolve to affect these animals, remains to be seen.

Both diseases provide a unique opportunity to study the role of immune response genes in transmission, growth, and evolution of contagious cancers. In addition, DFTD provides a new model for the study of allorecognition in mammals. We still have much to learn from these aggressive and highly effective parasites.

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