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Tasmanian Devil Facial Tumor Genomics and Transcriptomics used as a baseline to understand Transmissible Cancer in Humans

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ABSTRACT

Cancer is a challenge that still affect large number of populations today. Significant research is being carried out to try the curb this disease with some success. Etiologies of cancer of various organs are constantly being looked at molecular and genetic level. Most have spontaneous mutations leading to rapid uncontrolled growth. Almost all cancers are not contagious however, in some rare cases cancers are transmissible. Some examples include mother to fetus transmission namely melanoma/leukemia and Infectious transmission such as HPV. Transmittable cancer is also seen in animals. Conditions such as Canine Transmissible Venereal Tumor (CTVT) in dogs or Bivalve transmissible Neoplasia are just some examples. In this paper we will review the genetic mechanism of action of transmission of two independent cancers in Tasmanian Devil population to understand possible etiologies in other genetic modes of transmission.

Keywords: Tumor; Cancer; Humans

INTRODUCTION

The Tasmanian devil (*Sarcophilus harrisii*) is a large carnivorous marsupial that has been endemic to the island Tasmania for at least 400 years (Appendix-1).[1,2] The now endangered species has experienced many population declines attributable to anthropogenic factors like culling by European colonists in the 1800s and a series population bottlenecks of unknown cause in the nineteenth and twentieth centuries.[2]Currently, the entire species of devils has been experiencing its largest relative population decline recorded yet due to the spread of the devil facial tumor disease (DFTD) across the island of Tasmania.[1-6] DFTD is a transmissible cancer that initially presents as small nodules in facial subcutaneous tissue or oral submucosa, which rapidly develops into large masses that may obstruct vision or feeding. The tumors can quickly metastasize to abdominal or thoracic organs, making DFTD entirely lethal. DFTD cells from other devils can inoculate in bite wounds obtained during such interactions specifically as mating or feeding. DFTD is reported to have spread to across 95% of the geographical range of *S. harrisii* and to

have induced over an 80% population decline since 1996.[3,6] The pressure of DFTD has been shown to select for devils reaching sexual maturity at a younger age, because the transmissible tumors have forced devils to switch from a iteroparous mode of reproduction (multiple reproductive episodes) to semelparity (single episode) where devils are lucky to mate even once.[3,7] Interestingly, DFTD has been observed not to affect juvenile devils, who presumably have a weaker immune system than those of adult devils.

Devil facial tumor stain 1 (DFT1), the primary DFTD cell line known to have affected the overall devil population, is currently understood to have arisen from a Schwann cell in a female devil over 20 years ago.[1,2,8,9] DFT1 presents with a karyotype distinct from that of the host devil, containing four or five distinct marker chromosomes containing translocated regions primarily from both lost chromosome 1 copies, both missing X chromosomes, and a missing chromosome 5.[6] It should be noted that the M1 chromosome almost entirely consists of reordered chromosome 1 elements. It is largely suspected that the extensive translocations, inversions, and other chromosomal mutations of the marker chromosome in the DFT1 genome may have contributed to its potency. By contrast, devil facial tumor strain 2 (DFT2) is a much newer strain of transmissible tumors that was first documented in 2016. A single Y chromosome in DFT2 strongly suggests it originated in a male devil. DFT2 is characterized by a large copy of chromosome 1 with the entirety of a copy of chromosome 6 inserted.[1,2,6]

Major histocompatibility complex (MHC) class-I is a protein expressed on the outer surface of all of a mammal's nucleated cells, allowing its immune system to distinguish host cells from pathogenic or other foreign cells.[8,9] Past hypotheses suggested that DFTD is so easily transmissible due to the low genetic diversity in the *S. harrisii* gene pool for the MHC class-I protein.10 It is now understood that DFTD allografts evade immune detection, because MHC class-I molecules are not detectable on the surface of DFTD cells.[1,3,4] The β2 microglobulin and transporter-activator proteins (TAP) 1 and 2 essential to presentation of the MHC class-I protein experience diminished or not expressed.[8] Similar to canine transmissible venereal tumor (CTVT), a sexually transmissible tumor in dogs, and also non-transmissible tumors derived from host cells, DFTD can employ down regulation of MHC regulation via genetic or epigenetic modification of the MHC genes.

DISCUSSION

Transmission of disease to humans happens in many forms including bacteria, viruses, fungi, prions and parasites. The idea of transmission of cancer in humans is something new that has emerged recently such as Human T-lymphocyte type 1(HTLV 1). These cancers start as an infectious transmission that predisposes the host to development of cancer from their own cells. There are few transmissible cancers known in humans. Transplant recipients on chemotherapy and fetus to mother transmission are some examples. Tasmanian devil DFT1 and DFT2 are example of cancers that are passed in infection mode transmission and are being studied for the mechanism involved. Understanding these mechanisms are essential in understanding of possible cancer mechanisms in humans that are still not well understood.

The exact methods of how DFT1 or DFT2 are passed and transmitted are still being investigated. It is known that chromosomal changes are common denominator in these cancers. These changes have been shown in chromosome 1,3,4,5 and 6. X chromosomal changes either missing or changed are also shown in DFT1. In case of DFT2, Y chromosome has been noticed in tumor cells pointing to a male origin in this tumor. It is also shown that telomere abnormalities could be contributing to these chromosomal changes and secondarily leading to tumor development.
It is also important to mention that immune system is essential in elimination of transmittable cancer. The cells being inoculated by bite or other means would be expected to have a different MHC1 receptor present and therefore eliminated by host immune system. However, it has been noted that there is a down regulation of MHC expression in DFT1 cell and a method where host cell's MHC is also down regulated avoiding the recognition by immune system.

Observation has also shown that in few generations of the devils, spontaneous regression of tumor has happened. In one study,[11] the spontaneous mutation of genes involved in cell adhesion and p53 pathway has led to tumor regression. Other studies have shown that possible environment may contribute to selection of and resistance by devils that have biotic factors contributing to resistance to this disease.[12] Other have looked at spontaneous regression secondary to contributing genes such as PAX3, NBAS1 and TLL1. These genes have been showing to increase angiogenesis in the tumor therefore increasing the lymphocyte infiltration in the tumor[13] leading to regression and resistance to tumor development.

CONCLUSION

Non host tumor transmission, is a new phenomenon that has been observed in cancer literature. The condition of insertion of tapeworm DNA in immunocompromised host humans are just few examples discovered today. Better understanding of these mechanisms helps health providers provide therapeutic methods that target these transmissions early and hopefully stop the cancer from spreading. More studies at molecular level are needed to understand the DNA changes and immune responses to these changes can also help understand the molecular basis of cancer and treatment.

Appendix A.

Map of Tasmania (Retrieved from http://www.aspiredownunder.com/tasmania_map.html)


TASMANIA
BASS STRAIT
SOUTHERN OCEAN
BURNIE
DEVONPORT
LAUNCESTON
HOBART
QUEENSTOWN
STRAHAN
KING ISLAND
FLINDERS ISLAND
CAPE BARREN ISLAND
FURNEAUX GROUP
AUSTRALIA
Tasmania
TRAVELLING DISTANCES (km) AND TIMES
Launceston-St Helens (via Scottsdale) 163 2hrs20
Launceston-Bicheno (via Scottsdale) 236 3hrs30
Launceston-Hobart (via Midlands Hwy) 198 2hrs20
Bicheno-Hobart (via Sorell) 178 2hrs25
Hobart-Port Arthur 93 1hr30
Hobart-Queenstown 260 3hrs40
Queenstown-Burnie 176 2hrs25
Burnie-Devonport 49 40min
Burnie-Smithton 85 1hr
Devonport-Launceston 99 1hr15
Devonport-Hobart (via Midlands Hwy) 277 3hrs
Hobart-St Helens 265 3hrs40
Queenstown-Launceston (via Sheffield) 251 3hrs30

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