Universitat Autònoma de Barcelona
Patricia Prat Torres June 2017

Pathogenesis and Molecular Biology of a Transmissible Tumor in the Tasmanian Devil

1 Introduction

The Tasmanian devil is threatened with extinction by a fatal transmissible cancer, Devil Facial Tumor Disease (DFTD). Since its emergence in 1996, DFTD has spread rapidly throughout the country, having incidences over than 80% in some populations with a 100% mortality rate; i.e. the effects are devastating.
This neoplasm is unusual in that, contrary to widely held knowledge that cancer dies with its host, it has outlived its original host.

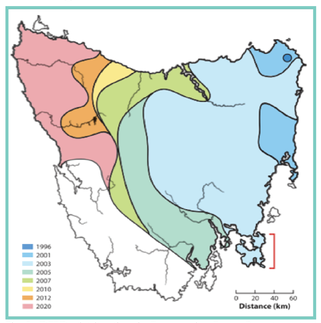


Fig.1. DFTD distribution in Tasmania. From Bender et al. (2014)

This **bibliographic review aims** to describe the molecular biology of this transmissible tumor especially focusing on transmission and the escape of the immune system response.

2 Pathology

- Tumors on facial area develop into large multifocal masses resulting in a locally invasive neoplasm.
- Tumor size obstructs feeding resulting in starvation.
- Cytology and Histology studies result non-especific. However, IHQ techniques show that all tumor cells stain positive for Periaxin, a Schwann cells specific marker.

DFTD originated from a peripheral nerve sheath tumor

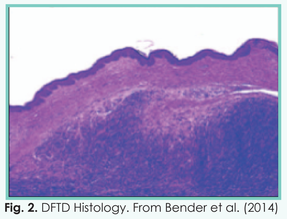


Fig. 2. DFTD Histology. From Bender et al. (2014)

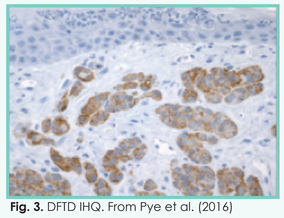
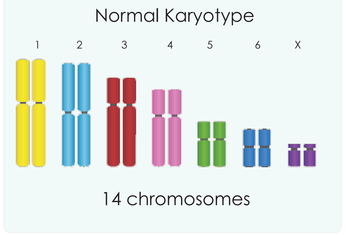


Fig. 3. DFTD IHQ. From Pye et al. (2016)

3 Transmission

3.1. Allograft Theory

- Cytogenetic shows that tumor karyotype is different from constitutional karyotype.
- In all cases tumor karyotype is identical, so it confirms that DFTD is a transmissible cancer.



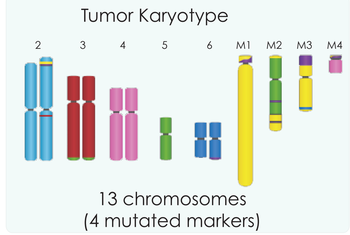


Fig. 4. Fighting habits. From Ostrander et al. (2016)

3.2. Tumor Implantation

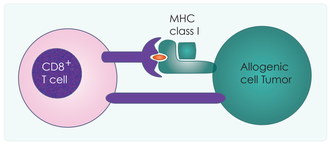
- Common anatomical location and the fighting behaviour suggest the possibility of bite transmission.
- Cytology studies confirm exfoliated tumor cells on canine teeth.

Clonal transmission occurs by biting during social interaction

4 Immune escape mechanisms

4.1. Reduced genetic diversity

- Initially, reduced genetic diversity was proposed to explain lack of allorecognition.
- Self/non-self recognition depends on Lymphocyte T / MHC-I interaction.



- Genome sequencing confirms low genetic diversity at MHC loci.
- However, skin allograft rejection is observed.

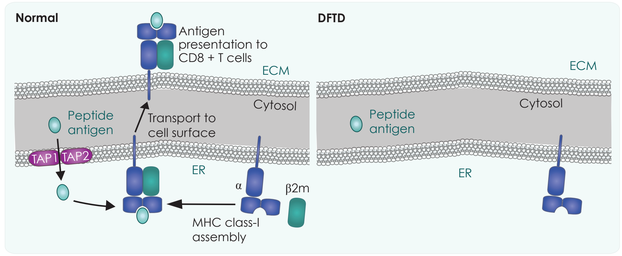
Fig. 5. Skin graft betwen unrelated Tasmanian devils . Kreiss et al. (2011)

Depleted MHC diversity doesn´t explain lack of allorecognition

4.2. Downregulation MHC-I expression

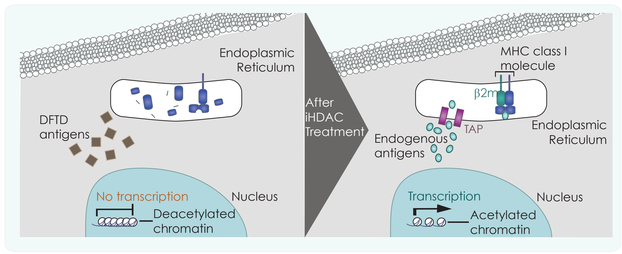
- Gene expression analysis RT-PCR reveals low levels of β2m, TAP1, TAP2 that results in disruption to the assembly of MHC-I and impariment of peptide transport.

Absence of MHC-I on cell surface allows DFTD to elude immune surveillance



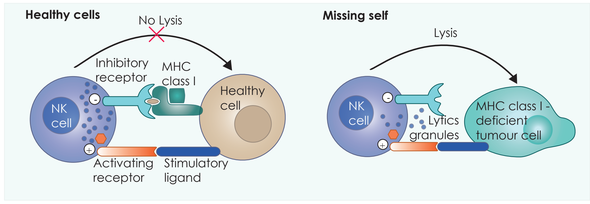
- Treatment with Histone Deacetylase inhibitors (iHDAC) upregulates expression of β2m, TAP1, TAP2.

Low expression of MHC-I is due to epigenetic regulation



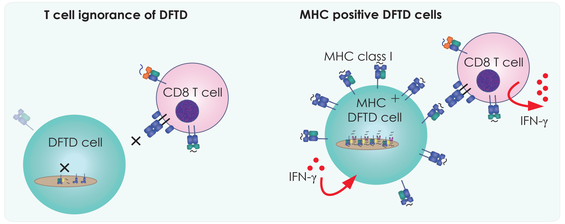
4.3. Natural Killer (NK)

- Absense of MHC-I should make tumor cells targets for NK because MHC-I is a ligand for the NK cell inhibitory receptor. But it doesn´t occur and it is still unknown why.



5 Disease Management

- Keep insurance population for release in the event of wild extinction.
- Research to identify resistant genotypes in the MHC gene complex.
- Vaccine development as a long term solution.



- IFN-γ treatment restores MHC-I on cell surface.
- Immunization is based on MHC-I + inoculation.

6 Conclusions

- **A singular infectious devil was the source of DFTD**
- **Transmission occurs due to intraspecific facial biting**
- **DFTD is a peripheral nerve sheath neoplasm of Shawnn cell origin**
- **Immune Response Escape Mechanisms are still unknown. Further research is necessary to identify new therapeutic targets**
- **Transmission is an interindividual metastasis process**
- **DFTD has illustrated the vulnerability of a population with limited genetic diversity**

Bibliography
• Bender HS, Marshall Graves JA, Deakin JE. 2014. Pathogenesis and Molecular Biology of a Transmissible Tumor in the Tasmanian Devil. Annu. Rev. Anim. Biosci. 2:165–187.• Kreiss A, Cheng Y, Kimble F, Wells B, Donovan S, Belov K, Woods GM. 2011. Ilorecognition in the tasmanian devil (sarcophilus harrisii), an endangered marsupial species with limited genetic diversity. PLoS One 6. • Pye RJ, Woods GM, Kreiss A. 2016. Devil Facial Tumor Disease. Vet. Pathol. 53:726–736. • Siddle H, Kauffman J. 2013, How the devil facial tumor disease escapes host immune response. Oncoinmunology 2:e25235.