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Review

The evolutionary ecology of transmissible cancers

Beata Ujvari [a,*,1], Robert A. Gatenby [b,1], Frédéric Thomas [c,1]

[a] Deakin University, Geelong, School of Life and Environmental Sciences, Centre for Integrative Ecology, Waurn Ponds, Vic 3216, Australia
[b] Department of Radiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA
[c] CREEC/MIVEGEC, UMR IRD/CNRS/UM 5290, Montpellier, France

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ABSTRACT

Transmissible tumours, while rare, present a fascinating opportunity to examine the evolutionary dynamics of cancer as both an infectious agent and an exotic, invasive species. Only three naturally-occurring transmissible cancers have been observed so far in the wild: Tasmanian devil facial tumour diseases, canine transmissible venereal tumour, and clam leukaemia. Here, we define four conditions that are necessary and sufficient for direct passage of cancer cells between either vertebrate or invertebrate hosts. Successful transmission requires environment and behaviours that facilitate transfer of tumour cells between hosts including: tumour tissue properties that promote shedding of large numbers of malignant cells, tumour cell plasticity that permits their survival during transmission and growth in a new host, and a 'permissible' host or host tissue. This rare confluence of multiple host- and tumour cell-traits both explains the rarity of tumour cell transmission and provides novel insights into the dynamics that both promote and constrain their growth.

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* Corresponding author at: Deakin University, Geelong, School of Life and Environmental Sciences, Centre for Integrative Ecology, Waurn Ponds, Vic 3216, Australia.
E-mail address: beata.ujvari@deakin.edu.au (B. Ujvari).

[1] BU, RAG and FT designed and wrote the manuscript, the authors contributed equally to the article.

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1. Introduction

Cancer development and progression represent an evolutionary and ecological process in which cells that acquire selective advantages via genetic and/or epigenetic modifications are able to proliferate autonomously, avoid immune recognition and undergo clonal expansion.

By infecting and colonizing another host (rather than dying with the host) and hence persisting in the population, transmissible cancers can occupy an empty niche not available to non-transmissible cancers. Here we investigate and discuss the key factors necessary for cancer cell transmission. We propose that similar to host–parasite interactions, successful transmission of cancer requires a 'perfect storm' with the confluence of multiple host (micro- and macro-environmental factors) and tumour cell traits.

2. Transmissible cancers in nature

Although many cancers are induced by infectious agents (Aktipis et al., 2015; de Martel et al., 2012; Ewald and Swain Ewald, 2015; Vittecoq et al., 2015, 2013), for a cancer to be truly transmissible, the cancer cell itself must move between hosts. So far only three transmissible cancers have been identified in the wild, but many more have been documented under experimental circumstances and in laboratory animals (Table 1, Box 1). In the current article we focus on transmissible cancers naturally occurring in the wild.

2.1. Canine transmissible venereal tumour (CTVT)

CTVT, is a globally distributed sexually transmitted tumour of canines (naturally occurring in dogs, experimentally transmitted to jackals and coyotes), that arose about 11,000 years ago in inbred dogs (Murchison et al., 2014; Murgia et al., 2006). CTVT has been proposed to have originated from a myeloid cell (reviewed in (Das and Das, 2000; Mukaratirwa and Gruys, 2003)) and is considered to be the oldest known somatic cell line (Murchison et al., 2014; Murgia et al., 2006; Strakova and Murchison, 2015). The neoplasms are located mainly on the external genitalia of dogs (Das and Das, 2000; Mukaratirwa and Gruys, 2003). The cancer cells are transmitted across the histocompatibility barriers during coitus (Belov, 2011). The extensive abrasions and bleeding of penile mucosa and vagina potentially facilitate the transmission of the malignant cells.

Experimental transplantation studies revealed three distinct life history phases of CTVT, described as progressive, stable and regressive stages (reviewed in Murchison (2008)).

The progressive phase generally lasts for a few weeks, followed by a stable phase lasting from weeks to months, resulting in an approximately 80–90% cell loss (Murchison, 2008). In experimental set ups, following the stable phase, CTVT cells either (i) enter a regressive phase lasting between 2 and 12 weeks and resulting in the disappearance of the tumours, or (ii) re-enter a progressive growth phase leading to metastasis (Murchison, 2008). In naturally occurring CTVT the progressive and stable phases have been documented in details, but only limited information describing spontaneous regression is available (reviewed in Murchison, 2008). Due to the various latencies of the different CTVT growth phases (lasting for weeks and months), and not all CTVT cells entering the different stages at the same time (e.g. 80–90% of CTVT cells enter the stable phase, the remaining 10–20% have the potential for transmission), there is a possibility for the tumour cells to be transmitted throughout the life of CTVTs.

2.2. Devil facial tumour diseases (DFTD)

DFTD was first observed in Tasmanian devils (*Sarcophilus harrisii*) in north-eastern Tasmania, Australia, in 1996 (Hawkins et al., 2006). The disease presents as large ulcerating tumours around the face and jaws of the devils. Since 1996 DFTD has spread across Tasmania and massively depleted devil numbers (McCallum et al., 2009). Similar to CTVT, transmission requires direct contact and DFTD is passed between devils by biting during social interactions (McCallum et al., 2009). DFTD frequently (70%) metastasizes to distant organs, and in most cases results in death within 6 to 9 months after the emergence of the first lesions (Pyecroft et al., 2007). In contrast to CTVT, DFTD does not enter a stable or regressive phase, and hence the host and the cancer have not reached a homeostatic stage, which would slow down the spread of DFTD.

Recently a second variant of DFTD (now described as DFTD2, and the previous lineage renamed as DFTD1) has been described in Tasmanian devils by Pye et al. (2015). The two devil cancers, DFT1 and DFT2 both cause phenotypically similar facial tumours, but with different underlying histological, karyotypic and genetic characteristics (Pye et al., 2015). The presence of remnants of X chromosomes in DFTD1, and a Y chromosomes in DFT2 further distinguishes the two aneuploid cancer lineages, and indicates that the former one has most likely arisen in a female, while the second one in a male devil (Murchison et al., 2012; Pye et al., 2015).

The emergence of DFTDs has been attributed to the extremely low level of genetic diversity of devils, with particularly reduced polymorphism at the non-self-recognising immune genes, the Major Histocompatibility Complex molecules (reviewed in Belov, 2012). Although the two lineages are carrying different MHC genotypes, they are both capable of colonizing MHC disparate hosts. Siddle et al. (2013b) proposed that DFT1 escapes T cells destruction by epigenetically downregulating MHC expression on the tumour cell surface. It is highly predictable that DFTD2 avoids immune recognition by following similar pathways, especially since the same mechanism is frequently employed by tumour cells in human malignancies (Fassati and Mitchison, 2010).

Whether epigenetic regulation facilitates the spread of DFTD2 remains to be answered. Nevertheless, the low genetic diversity of devils has most likely predisposed them to become ideal microenvironment for tumour development and evolution (as supported by the relatively high incidence of neoplasia in devils (Griner, 1979)).

2.3. Clam leukaemia (CL)

Although disseminated, haematopoietic or hemic neoplasia, have been described in many bivalves, it has only recently been shown that this malignant clonal cell line is horizontally transmitted in soft-shell clams (*Mya arenaria*) (Metzger et al., 2015). CL is characterized by abnormal amplification of cells in the haemolymph, diseased cells lose their phagocytic abilities, express a novel surface antigen, and display cytoplasmic sequestration of the *TP53* tumour suppressor protein (Walker et al., 2011). CL was first described in the 1970s, and is now distributed along the east coast of North America, causing the decimation of soft-shell clam populations (Metzger et al., 2015).

3. Transmissible cancers in evolutionary context

Cancer development and progression represent an evolutionary process as Darwinian selection drives cancer cells along evolutionary landscapes within a single host (Greaves and Maley, 2012). However, ultimately the malignant cells perish with the host so that every cancer must 're-invent' a successful strategy to overcome host defences.

Occasionally, rare events allow cancer cells to be transmitted from one host to another, leading to a special case of inter-individual metastasis. In the classical metastatic process, tumour cells adapted to the primary tissue site must evolve strategies to survive and proliferate in the 'foreign' environment of a distant and often quite different tissue (Box 1, 2) (Gatenby and Gillies, 2008). In contrast, in transmissible cancers, cancer cells typically grow in different hosts but in similar tissue. Here we examine the properties of both tumour cells and host organisms that permit transmission.

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