Opinion Paper

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Possible mechanisms of transmissible cancers in Tasmanian devils

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Abstract: Physical transfer of viable tumor cells from one organism to another is known as transmissible cancer, which is observed in dogs, Tasmanian devils, Syrian hamsters, and some soft-shell clams. Tasmanian devil facial tumor disease is transmitted like an infectious disease between individuals through biting and other close contact. This extinction type is quite different from the other extinction types such as ecological factors. Transmissible cancers’ cellular metabolism is also different from the both normal cellular metabolism and other types of cancers’ metabolism. The lack of an immune response against the Tasmanian devil facial tumor cells is the one of the key points in the transmission of the cancerous cells. The differentiated cellular metabolism and absence of immune reaction may be due to the organisms’ enzymes. Cells may have altered surface proteins by altering enzymatic activities that cannot be recognized by both the innate and adaptive responses. The promiscuity of the key enzymes may be associated with unwanted side effects, such as cannot recognize molecular patterns on the transmitted cell or hypomethylation of DNA by altering catalytic properties enzymes or altered matrix metalloproteinases or cathelicidins.

Keywords: Transmissible cancers; Promiscuity of enzymes; Tasmanian devil facial tumor disease; Cathelicidins; Hypomethylation of DNA.

Introduction

The Tasmanian devil (Sarcophilus harrisii) is a medium-sized carnivore and endemic to the Australian island state of Tasmania. These animals have transmissible tumors known as infectious cancers named as Devil Facial Tumor Disease (DFTD). Physical transfer of viable tumor cells or transmissible cancer was first reported in 1996 [1, 2]. Cancer rarely acts as an infectious disease, however DFTD is virtually 100% fatal and an overall species decline of more than 80% in less than 20 years [3]. Naturally occurring transmissible cancer cells, such as DFTD, canine transmissible venereal tumor, soft-shell clams leukemia and hamsters reticulum cell sarcoma are transmitted to the donors by in interesting ways. This disease is fatal and believed that started from a mutation. DFTD gives us a different perspective to dynamic cancer paradox [4, 5].

The origin of DFTD was a Schwann cell from a female devil and this disease is transmitted when devils bite each other from the facial areas. Once the devil that is ‘infected’ with DFTD dies from the cancer. Transmissible tumors have a very complex property, which allow them to escape immune detection both in Tasmanian devil and/or domestic dog (Canis lupus familiaris) [6, 7]. DFTD caused the majority of diseased populations died and if this decline continues, species could face extinction because DFTD acts as an infectious disease [3].

Pathology have been well reported for DFTD however, the literature reporting clinical signs of disease such as plasma or serum biochemical variables in Tasmanian devil is very limited. There is a lack of information on hematologic and biochemical alterations associated with DFTD [8]. Recent whole-metabolism of DFTD was studied by a group of researcher and they have shown in their research that peptide segments of fibrinogen that were radically elevated in this disease [9]. However, in a previous study, researchers determined the sex and age differences hematologic and biochemistry variables for healthy Tasmanian devils and found out that higher relative neutrophil counts, hemoglobin, mean corpuscular hemoglobin (MCH), creatinine, creatine phosphokinase, and cholesterol were seen in males compared to females, while higher white cell counts (WBC) and lymphocyte counts (absolute and relative) were seen in females. Subadults have higher red blood cell counts, WBC, lymphocytes (absolute and relative), calcium and phosphorus, alkaline phosphatase, glutamate dehydrogenase, glucose, and albumin than adults;
whereas, adults have higher relative neutrophils, relative eosinophils, mean corpuscular volume, MCH, platelets, total solids, total plasma proteins, globulins, and chloride than subjects. Many of the differences observed between in males compared to females, and on the other side of the medallion, transmissible cancer progression requires many changes; increased enzyme concentration, immune depleted or blocked activity of an enzyme may trigger cancer in various pathways [10]. Once the DFTD cells have been transmitted, they appear to develop into a cancer without inducing an immune response [7]. So that, species extinctions are much more complicated and we have to make our assessments on cellular and macromolecular level and enzymes have a vital role in the extinction of species. Promiscuity of enzymes is one of the key factors in extinction, which is defined as adaptation to changing environmental conditions. Inhibition of an enzyme may turn off numerous fundamental cellular reactions can be lethal and may have a greater role in evolutionary steps and species extinctions [11, 12]. Tasmanian devils' transmissible cancers spread among individuals of transmission of somatic living cancer cells at least two different transmissible cancer types DFT1 and DFT2. These two types of tumors are cytogenetically distinct from each other [13].

### Possible mechanisms on devil extinction

Less is known about possible underlying extinction event mechanisms of the Tasmanian devil. The first killer possible mechanism may be hypomethylation of DNA [14, 15]. Methylation differentiations in DNA play pivotal roles which are very similar to genetic mutations in cancer. Hypomethylation of DNA accepted as an epigenetic abnormality and often increase with tumor progression and seen almost all types of cancer [14, 16]. It has been known that cancer-associated DNA hypomethylation is as important as cancer-linked hypermethylation and both of these alterations occurs in the nucleus. However, saving endangered Tasmanian devil from becoming extinct and protecting their wild places, extremely hard if these two types of epigenetic abnormalities are responsible for the transfer of living cancer cells.

A second possible proposed mechanism may involve matrix metalloproteinase enzymes and plasminogen activators which are important factors in cancer invasion and metastasis [17]. Another important finding is that the DFTD cancer cells avoid allogeneic recognition since they do not express MHC class I molecules on the cell surface and these MHC-I proteins load short peptides derived from proteolytic cleavage of endogenous proteins [2, 18]. Matrix-degrading proteases may have a greater role in cancer cell transmission [19]. Saliva of these organisms needs to be investigated if the activity of these proteases is too high, potential use of protease inhibitors to their drinking water to their natural living environment for effective control of the tragic decline of Tasmanian devil extinction from the ecosystem.

A third possible proposed mechanism may involve defective cathelicidins. Cathelicidins are antimicrobial peptides, exhibit direct antimicrobial activities against a broad spectrum of bacteria, enveloped viruses, and fungi. In addition to their antimicrobial effects cathelicidins can also trigger specific defense responses [20, 21]. It has been investigated that these peptides have key roles in immune response; chemotaxis properties for neutrophils, monocytes, mast cells, and T cells; induces degradation of mast cells; alters transcriptional responses in macrophages; stimulates wound vascularization and re-epithelialization of healing skin [22]. Cathelicidins proteolytically activated peptides [20]. Since the Tasmanian devil has a broad repertoire of cathelicidins [23]. The Tasmanian devil is now on the brink of extinction and so that, every detail such as cathelicidins and their activators, proteolytic enzymes should not be forgotten in the therapy of their transmissible cancers. If there is a disorder the proteolytic enzymes or any deficiency in cathelicidins devil body cannot generate efficacious an immune response against on various responses such as oncoviruses, bacteria, viruses, other microorganisms, or cancer cells.

A fourth possible proposed mechanism may involve overexpression of the some chemotherapy resistance enzymes in transmissible tumors [24, 25]. It has been reported that P-glycoprotein (P-gp) the efflux pump, and glutathione-S-transferase (GSTpi) which is associated with multidrug resistance of tumor cells and are involved in drug detoxification and control of apoptosis were significantly overexpressed in canine transmissible venereal tumor mainly at cytoplasm and nuclei and both of these proteins are associated with multidrug resistance to chemotherapy in neoplasms [25–27]. Telomerase is up-regulated in Tasmanian devil cancer cells but not in normal tissues. These data show that inhibiting P-gp, telomerase and GST pi can be used as an effective way for saving devils from extinction our world. It seems that chemotherapy is an important strategy for the treatment transmissible cancers therefore the use of more potent and safe anticancer drugs that are substrates of these proteins should be carefully evaluated for DFTD. Therefore,
combined treatment with chemotherapy and GST inhibitors might be an interesting option for Tasmanian devil facial tumor disease for saving devils from extinction.

After these all possible mechanisms which may have key roles in the potential mechanisms of transmissible cancers in Tasmanian devils I have read with great interest the recent published article by Peck et al. [8]. It was aimed to determine whether an association exists between serum hematologic and serum biochemical variation in devils with 41 samples with DFTD compared with 325 healthy devils in pre and post tumor development and the researchers concluded that hematologic and clinical chemistry changes most likely reflect ongoing inflammation and tissue damage associated with DFTD rather than specific DFTD changes or paraneoplastic syndromes. They have found that significant hematologic changes included increased WBC and neutrophil counts, and fibrinogen concentration, and decreased lymphocyte counts and albumin concentration when comparing DFTD-affected with healthy devils which is not a surprising, it is an expected conclusion. It has been also investigated that there were no significant differences between clinically healthy devils and wounded devils. It is known that cancer can weaken the immune system, however, cancer rarely acts as an infectious disease [28]. DFTD is extremely unusual that the allograft tumors are not rejected by the host immune system [29].

If the Tasmanian devils’ enzymatic defense system have a defect or failure, which is responsible for triggering an immune system response may allow physical transfer of viable tumor cells from one organism to another. An abnormal immune response consists of unrecognizing viable tumor cells needs more researches for clarifying mechanisms of transmissible cancers.

### Conclusion

Cancer is not often acts as an infectious disease, however transmissible cancer in Tasmanian devils is virtually fatal. Unlike previous thoughts mass extinctions, caused by events like diverse ecological factors, extinction via transmissible cancer. Understanding how this transmissible cancer works could help us a new perspective to stop cancer. Many animals get cancer just like humans do some get cancer extremely different way and some get lower cancer rates but some does not get cancer. So far we do not know exactly differences which factors, genes, mutations, enzymes and other cellular mechanism are involved. Organisms or else cells have plenty of reasons, become cancerous, and understanding cancer from an enzymes’ activity perspective which are responsible for immune response can allow us to appreciate better why cancers predominantly occur.

DFTD is an excellent model to investigate properties of transmissible cancer type and related cellular processes. Cellular macro and micro-environment and host immune system on tumorigenesis, which may give a novel ideas in combination of targeted therapy, new explanations for the success individualized tumor response and designing more efficient patient specific chemotherapy. Finally, DFTD maybe give us novel perspectives to test us the effectiveness of novel antitumor compounds on novel enzyme targets and test the sensitivity and/or drug resistance of cancer cells to varying antitumor drugs in various tumor types.

**Conflict of interest statement:** The author declares that no conflict of interest.

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