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Commentary

Contagious Cancer

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ABSTRACT

Although cancer can on occasion be caused by infectious agents such as specific bacteria, parasites, and viruses, it is not generally considered a transmissible disease. In rare circumstances, however, direct communication from one host to another has been documented. The Tasmanian devil is now threatened with extinction in the wild because of a fatal transmissible cancer, devil facial tumor disease (DFTD). Another example is canine transmissible venereal tumor (CTVT or Sticker's sarcoma) in dogs. There is a vast difference in prognosis between these two conditions. DFTD is often fatal within 6 months, whereas most cases of CTVT are eventually rejected by the host dog, who then is conferred lifelong immunity. In man, only scattered case reports exist about such communicable cancers, most often in the setting of organ or hematopoietic stem cell transplants and cancers arising during pregnancy that are transmitted to the fetus. In about one third of cases, transplant recipients develop cancers from donor organs from individuals who were found to harbor malignancies after the transplantation. The fact that two thirds of the time cancer does not develop, along with the fact that cancer very rarely is transmitted from person to person, supports the notion that natural immunity prevents such cancers from taking hold in man. These observations might hold invaluable clues to the immunobiology and possible immunotherapy of cancer. ***The Oncologist*** 2011; 16:1–4

INTRODUCTION

In the cancer clinic, physicians and other oncology caregivers are occasionally asked whether cancer can ever be passed along from one individual to another. One example is the wife who asks whether she could ever "catch" cancer from her husband with prostate cancer. Although the answer to that one is no, the question of a man "catching" cancer from a partner with cervical cancer is not unrealistic since various strains of human papilloma virus are known causes of cervical cancer as well as penile cancer. Pathogens including certain viruses, bacteria, and parasites represent major causes of cancer in developing parts of the world. In fact, an estimated 1.5 million cases per year or 15% of all cancers worldwide can be attributed to infectious etiologies, mostly (~11%) due to viral infections. Some specific examples among DNA viruses include the follow-

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ing: hepadnaviruses such as hepatitis B virus (hepatocellular carcinoma); herpesviruses such as Kaposi sarcoma–associated herpesvirus, also known as human herpesvirus-8 (Kaposi sarcoma and primary effusion lymphoma), and Epstein-Barr virus (nasopharyngeal carcinoma and non-Hodgkin and Hodgkin lymphomas); polyomaviruses such as Merkel cell virus (Merkel cell carcinoma) [1]; and specific human papilloma virus strains (anogenital cancers in men and women and some head and neck cancers). Interestingly, the specific human papilloma virus (HPV) strains achieve their carcinogenicity through degradation or inactivation of p53 and Rb via the products of their "early genes" E6 and E7, respectively. This mechanism targeting of the key proteins, p53 and Rb, is a common theme uncovered during the early investigations of oncogenic DNA viruses such as the SV40 polyoma virus and certain adenoviruses that caused cancers in animals. Thus, early investigations of these DNA viral mechanisms were instrumental in the discovery of p53 [2, 3] and Rb [4, 5]

RNA viruses implicated in human cancers include flaviviruses such as hepatitis C virus, another known cause of hepatocellular carcinoma and retroviruses such as human T-lymphotropic virus 1 (HTLV-1), which causes adult T-cell leukemia/lymphoma. Another retrovirus putatively associated with human cancers at the time of this writing is HTLV-2, which may be linked to hairy cell leukemia [6]. A retrovirus named HTLV-5 was reported to be associated with cutaneous T-cell lymphoma (mycosis fungoides) over 2 decades ago but no further confirmatory data has arisen [7]. Human immunodeficiency virus (HIV), as a cofactor, has been associated with increased incidence of several non-AIDS defining cancers, including Hodgkin lymphoma, lung cancer, renal cell carcinoma, and hepatocellular carcinoma among others [8].

Bacterial infections such as CagA-positive strains of *Helicobacter pylori* are associated with gastric carcinomas and MALT lymphomas. *Chlamydia psittaci*, the cause of psittacosis, has been linked to ocular adnexal lymphomas [9]. *Borellia burgdorferi*, the cause of Lyme disease, has also been linked to primary cutaneous B-cell lymphomas [10] and *Campylobacter jejuni* appears associated with immunoproliferative disease of the small intestine [11]. As far as parasites go, practically all medical students are aware of the link between squamous cell carcinoma of the bladder and *Schistosoma hematobium*. *Opisthorchis viverrini* is classified by the International Agency for Research on Cancer as a Group I Carcinogen for cholangiocarcinoma, whereas *Clonorchis sinensis* was categorized as a probable cause (Group 2A) [12].

These infectious causes of cancer are well studied and investigations of virally caused cancers in animals have contributed immensely to the understanding about the molecular biology of cancer. However, a very different and less well-studied form of "contagious cancer" is currently wreaking havoc in the natural world—and one wonders whether a deeper understanding of these transmissible cancers might similarly prove fruitful in furthering the understanding of cancer biology and treatment.

The largest extant carnivorous marsupial, the Tasmanian devil, *Sarcophilius harrisii*, could possibly become extinct in the wild because of a communicable cancer known as devil facial tumor disease (DFTD). Since first being recognized in 1996, it is estimated that the wild population has declined by about 50% and the Tasmanian devil has been listed as endangered by the International Union for Conservation of Nature. The cancer is spreading so rapidly that some researchers fear there may be no disease-free Tasmanian devils left in the wild within 5 years and that the species could become extinct within 20 years. The locally aggressive malignancy often causes death within 6 months because of consequences of airway obstruction and inability to feed. DFTD is directly transmitted during fighting and courtship battles in which facial tumor cells of one animal are transferred to another as an allograft. Confirmation that this same tumor has been passed along in this fashion for over a decade now is provided by elegant cytogenetic studies that have documented identical aneuploidy in all tumor samples (13 total chromosomes) in contrast to the 14 chromosomes in normal host cells [13, 14]. A recent analysis has indicated that DFTD is of Schwann cell origin [15].

In stark contrast to the fatal DFTD, another contagious cancer, canine transmissible venereal tumor (CTVT), is normally not lethal to its dog hosts. Also known as Sticker's sarcoma, CTVT was initially described in 1876 and may have originated in a wolf as long as 2,500 years ago. It has been passed along among canines ever since, making it the oldest recognized malignant cell line [16, 17]. There is solid evidence that this tumor is passed on as an allograft, including the fact that CTVT cells have a strikingly different karyotype from the host's cells, yet are similar to each other even when the hosts are from different continents. The cancer is typically transmitted during mating when the malignant tumor cells from one dog are directly transferred to another dog via coitus, licking, biting, and sniffing tumor-affected areas (the genitals, nose, or mouth). Although capable of metastasizing, CTVT often does not require treatment, as spontaneous regression is the general rule.

Although customarily CTVT is ultimately rejected, it has some fascinating properties that have allowed it to persist and be transmitted for so many generations. First, it downregulates its MHC I expression, thereby reducing its initial visibility to the host's immune system [17]. This

clever downregulation (rather than complete absence) allows it to not only escape T-cell–mediated immunity (which would occur if MHC I were fully expressed) but also natural killer cells (which would eradicate the cells were they completely devoid of MHC I). In most cases, the dog's immune system eventually reacts to the allograft and clears it, rendering the dog immune to future challenges. The fact that immunosuppressed dogs can develop metastatic CTVT supports the concept of immune-mediated rejection in healthy animals.

Thus, there is an interesting contrast between the lethal DFTD of Tasmanian devils and the normally nonfatal CTVT of dogs. It appears that Tasmanian devil populations are lacking in genetic diversity and the transplanted tumors cells are not rejected as they are in dogs, allowing disease progression and a fatal outcome. In both cases the transmitted cancer is essentially a somatic cell line that has become a transmissible parasite. Such observations have led Murgia et al. [17] to speculate that one reason for MHC diversity in vertebrates is precisely to ensure that cancer is *not* communicable.

Direct transmissions of cancers are not entirely restricted to animals. There are approximately 3,500 women per year in the United States who develop a malignancy during pregnancy, and in rare cases, mother-to-fetus transmission of melanoma, lymphoma, leukemias, and carcinomas have been reported as well as fetus-to-fetus transmission in twins. Although exceedingly rare, 0.04% of organ transplant recipients contract cancer from the donor organ (mostly melanomas) and hematologic malignancies have been observed in about 0.06% of hematopoietic stem cell transplants. Penn [18] observed that about one third of recipients of organs from donors with some form of cancer at the time of donation eventually developed the same malignancy as in the donor. Curiously, the remaining two thirds did not show evidence of a transmitted cancer. Naturally, this could be due to an absence of neoplastic cells in the donated organ but alternatively it could be due to the host's rejection of foreign malignant clones. The latter concept is bolstered by the fact that in cases in which cancer does develop following transplantation of an organ from a donor with cancer, the malignant process may regress after the graft has been removed and immunosuppression discontinued [19–22]. Another report described a situation in which a kidney and liver were transplanted from a donor who was found to harbor pancreatic adenocarcinoma. The liver recipient was re-transplanted shortly after the discovery of the donor's cancer whereas the kidney recipient opted not to undergo removal of the transplanted organ; the kidney recipient died with metastatic pancreatic adenocarcinoma 15 months after transplantation [23]. A slight variation of this scenario might be presented by the fact that solid organ transplantation carries a 1 out of 200 risk of Kaposi sarcoma in the United States [24, 25]. In principle the disease could originate directly from donated neoplastic cells or as a result of reactivation of the Kaposi sarcoma–associated herpesvirus (KSHV) carried along in the transplanted cells or as a result of immunosuppression that allows KSHV to induce a de novo malignancy. Barrozi et al. [25] showed that the KSHV-infected neoplastic cells from transplant recipients with Kaposi sarcoma in 5 of 8 renal transplant patients harbored genetic or antigenic markers of their matched donors, suggesting that they were transplanted malignancies rather than KSHV-caused Kaposi sarcomas that might have arisen due to immunosuppression. The authors even suggested the use of donor-derived KSHV-specific T cells for the control of post-transplant Kaposi sarcoma.

Other unusual reports of human-to-human transmissions include colon cancer transmission via needle stick [26], a volunteer with impaired health who developed metastases from transferred allogeneic tumor cells [27], a case of transplanted melanoma from a daughter to her elderly mother [28], and a well-documented genetic analysis of a case in which a surgeon contracted a malignant fibrous histiocytoma from a patient following an intraoperative cut to his left palm [29]. The surgeon had neither immunodeficiency nor genetic relationship to the patient. The tumor, which was successfully excised, proved to be a chimeric constellation of alleles with some contributed by the tumor and others from the surgeon host. Fortunately, survival of transplanted cancers in healthy humans is exceedingly rare and documented by only a small handful of cases. Thus, friends and family members of cancer patients and we, as caregivers of cancer patients, need not be unduly concerned with the remote possibility of "catching cancer."

As for the Tasmanian devils, researchers thought they might have found an individual named Cedric who possessed immunity to DFTD and could be a savior for the dwindling population. After initially inoculating Cedric and his half-brother Clinky with irradiated tumor cells, followed by injections with live tumor cells, Clinky rapidly succumbed to the cancer. However, Cedric produced antibodies and developed no tumors, prompting speculation about the existence of resistant animals. Unfortunately, in a follow-up study, Cedric was injected with a slightly different strain of DFTD and wound up developing tumors—dashing hopes of finding a resistant population. This was naturally demoralizing news for conservationists but confirmed that there are different strains of the tumor and it may be possible for an animal to be immune to one strain but not others.

Such subtleties of DFTD immunity along with the gross immunity to CTVT in dogs are important for their pure scientific interest. Similarly, the natural resistance humans possess against transmitted malignancies (except under unusual circumstances such as organ transplantation followed by chronic immunosuppression or immunosuppression from other reasons) is of scientific interest. Together, the observations might provide some critical clues that could someday be of real practical value in advancing our battle against cancer in the clinic.

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REFERENCES

1 Feng H, Shuda M, Chang Y et al. Clonal integration of a polyomavirus in human merkel cell carcinoma. Science 2008;319(5866):1096–1100.

2 Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. Nature 1979;278:261–263.

3 Linzer DIH, Levine AJ. Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. Cell 1979;17(1):43–52.

4 DeCaprio JA, Ludlow JW, Figge J et al. SV40 large tumor antigen forms a specific complex with the product of the retinoblastoma susceptibility gene. Cell 1988;54(2):275–283.

5 Whyte P et al. Association between an oncogene and an anti-oncogene: The adenovirus E1A proteins bind to the retinoblastoma gene product. Nature 1988;334:124–129.

6 Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M et al. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 1982;218(4572):571–573.

7 Manzari V, Gismondi A, Barillari G et al. HTLV-V: a new human retrovirus isolated in a Tac-negative T cell lymphoma/leukemia. Science 1987; 238(4833):1581–1583.

8 Pantanowitz L, Dezube BJ. Evolving spectrum and incidence of non-AIDS-defining malignancies. Curr Opin HIV AIDS 2009;4(1):27–34.

9 Ferreri AJ, Guidoboni M, Ponzoni M et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004;96:586–594.

10 Garbe C, Stein H, Dienemann D et al. Borrelia burgdorferi-associated cutaneous B cell lymphoma: clinical and immunohistologic characterization of four cases. J Am Acad Dermatol 1991;24(4):584–590.

11 Lecuit M, Abachin E, Martin A et al. Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med 2004;350: 239–248.

12 International Agency for Research on Cancer (IARC). Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 61: Schistosomes, Liver Flukes and Helicobacter pylori. Lyon, France: International Agency for Research on Cancer (IARC) Press, 1993.

13 Pearse AM, Swift K. Allograft theory: transmission of devil facial-tumour disease. Nature 2006;439(7076):549.

14 Dingli D, Nowak MA. Cancer biology: infectious tumour cells. Nature 2006;443(7107):35–36.

15 Murchison EP, Tovar C, Hsu A et al. The Tasmanian devil transcriptome reveals schwann cell origins of a clonally transmissible cancer. Science 2010;327:84–87.

16 Mukaratirwa S, Gruys E. Canine transmissible venereal tumour: cytogenetic origin, immunophenotype, and immunobiology. A review. Vet Q 2003;25(3):101–111.

17 Murgia C, Pritchard JK, Kim SY et al. Clonal origin and evolution of a transmissible cancer. Cell 2006;126(3):477–487.

18 Penn I. Tumors arising in organ transplant recipients. Adv Cancer Res 1978;28:31–61.

19 Wilson RE, Hager EB, Hampers CL et al. Immunologic rejection of human cancer transplanted with a renal allograph. N Engl J Med 1968;278(9):479–483.

20 Matter B, Zukoski CF, Killen DA et al. Transplanted carcinoma in an immunosuppressed patient. Transplantation 1970;9(1):71–74.

21 Gokel JM, Rjosk HK, Meister P et al. Metastatic choriocarcinoma transplanted with cadaver kidney. Cancer 1977;39(3):1317–1321.

22 Forbes GB, Goggin MJ, Dische FE et al. Accidental transplantion of bronchial carcinoma from a cadaver donor to two recipients of renal allografts. J Clin Pathol 1981;34:109–115.

23 Gerstenkorn C, Thomusch O. Transmission of a pancreatic adenocarcinoma to a renal transplant recipient. Clin Transplant 2003;17:473–476.

24 Moore PS. Transplanting cancer: donor-cell transmission of Kaposi sarcoma. Nat Med 2003;9(5):506–508.

25 Barozzi P, Luppi M, Facchetti F et al. Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. Nat Med 2003;9(5): 554–561.

26 Gugel EA, Sanders ME. Needle-stick transmission of human colonic adenocarcinoma. N Engl J Med 1986;315(23):1487.

27 Southam CM, Moore AE. Induced immunity to cancer cell homografts in man. Ann N Y Acad Sci 1958;73(3):635–653.

28 Scanlon EF, Hawkins RA, Fox WW et al. Fatal homotransplanted melanoma: a case report. Cancer 1965;18:782–789.

29 Gärtner HV, Seidl C, Luckenbach C et al. Genetic analysis of a sarcoma accidentally transplanted from a patient to a surgeon. N Engl J Med 1996; 335(20):1494–1496.