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Citation	Dingli, David, and Martin A. Nowak. 2006. Cancer biology: Infectious tumour cells. Nature 443(7107): 35-36.
Published Version	doi:10.1038/443035a
Accessed	February 18, 2015 6:36:39 PM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:4318027
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Infectious Cancer Cells

David Dingli^{1,2} and Martin A. Nowak¹

New evidence is mounting that cancer cells can evolve to become infectious agents and be transmitted between individuals.

The current view of carcinogenesis is that normal cells are transformed into tumour cells by mutations that activate oncogenes, silence tumour suppressor genes or trigger genetic instabilities. As a consequence, every tumour is the result of a unique evolutionary process that begins in its individual host and ends with the elimination of the tumour or the death of the host. Two recent studies, however, suggest that tumour cells can behave like infectious agents and move from one host to another^{1,2}.

It has long been suspected that canine transmissible venereal tumour (CTVT) is transferred between dogs by implantation of tumour cells from donor to the recipient, where the tumour grows as an allograft³. Several lines of evidence provided indirect support for this hypothesis. The tumour can only be induced by the implantation of whole tumour cells but not by cell extracts or dead cells. Normal canine cells have 78 chromosomes but karyotypes of tumour cells isolated from different animals have shown a characteristic and persistent pattern of aneuploidy with 58 to 59 chromosomes⁴. In addition, a LINE-1 insertion close to *c-myc* has been found in all tumour samples⁵. If the allograft transfer hypothesis is correct, tumour cells from different animals should be genetically clustered *and* different from normal cells of the host animal. Formal proof of

the allograft hypothesis for CTVT was recently provided by Claudio Murgia, Robin Weiss and colleagues ¹.

They studied tumour and normal cells isolated from dogs harboring CTVT from three continents. Using a combination of dog leukocyte antigen (DLA) haplotyping, microsatellite DNA and mitochondrial DNA sequencing, they proved that all the tumours are closely related genetically and different from normal cells of the host dog ¹.

Sequencing of microsatellite DNA regions showed that tumours from different animals had less variability than what is observed within the most inbred breed of dogs. Therefore, the tumours could not arise from the separate transformations of cells within individual animals but were transmitted from one dog to another confirming the spread of this tumour from an ancestral clone. Moreover, by comparing tumour and various canine microsatellite markers, it was estimated that the clone had arisen between 250 and 2500 years ago making it the oldest known continuously replicating somatic cell line ¹.

In an independent study, Pearse and Swift ² have reported that devil facial tumour disease is caused by horizontal tumour cell transmission between Tasmanian devils. Cancer cells isolated from different animals that harbored tumours of different age and size share the same aneuploid karyotype. Furthermore, one animal had a constitutional pericentric inversion of chromosome 5 but this abnormality was not found in any of the cells isolated from the tumour, providing further support that the tumour did not arise from host cells.

Given that tumour cells can behave like infectious agents in some mammals, the question arises if infectious transmission of cancer can also occur in humans. There is no evidence (yet) for direct horizontal transmission of tumour cells between humans with

normal social contact. The only known physiological route for tumour cell transmission in humans is during pregnancy. Every year about 3,500 pregnant women in the United States have a concomitant malignancy. Transplacental transmission of lymphoma, acute leukaemia, melanoma and carcinoma from mother to fetus have been observed ⁶. Acute leukaemia cells have also been transferred between fetuses (in mothers with a multiple pregnancy) followed by the development of disease in both fetuses ⁶.

Organ transplantation represents another possible route of tumour cell transmission between humans. The immunosuppressive therapy required for survival of the transplanted organ blunts immune surveillance and may facilitate engraftment and growth of donor derived tumour cells. Fortunately, the development of donor derived tumours in solid organ transplant recipients is rare (0.04%) ⁷. The main culprit seems to be malignant melanoma that is undetected in the donor at the time of organ harvest: in one report, metastatic melanoma developed in both kidney and liver recipients from a donor with occult disease ⁸. Another example is the transfer of haematological malignancy by haematopoietic stem cell transplantation ⁹. Again the frequency is low (0.06%). Finally, we came across one case report where a surgeon developed malignant fibrous histiocytoma after accidentally injuring his palm during surgical removal of the tumour from a patient ¹⁰.

The transfer of tumour cells between individuals seems to be a rare event in humans. Differences in the human lymphocyte antigens may protect against successful tumour cell engraftment by inducing an immune response that eliminates the implanted cells. CTVT cells avoid immune mediated destruction by down-regulating DLA expression ¹. This is an important adaptation since complete absence of DLA antigens

would allow natural killer cells to destroy the tumour, while normal expression of DLA antigens activates cytotoxic T-cells with a similar outcome. In many dogs, an immune attack against CTVT ultimately develops and leads to tumour eradication and immunity to re-challenge³. This evidence also strengthens the hope that the immune system can be coached to eradicate established tumours in humans.

The emergence of multi-cellular life forms required cooperation between cells of a given organism. Cancer entails loss of this cooperation, and from the perspective of evolutionary game theory cancer is a ‘defector’¹¹. Breakdown of cooperation can lead to the death of the host, but then the tumour also meets its own demise. Therefore, a tumour, which can be transmitted from one host to the next, maneuvers around the specific evolutionary mechanism that is meant to control it.

Why is cancer in general not transmissible between people? A main reason is tissue graft rejection caused by MHC incompatibility. The cancer cells of the donor should induce a vigorous immune response in a healthy recipient. Tumour transfer in mice is only possible between syngeneic animals (that share the same MHC) or if the recipient is severely immunosuppressed. This leads to the interesting speculation, suggested by Murgia et al¹, that a main reason for MHC diversity in humans and other vertebrates is to ensure that cancer is not an infectious disease.

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