

CANCER BIOLOGY

Infectious tumour cells

David Dingli and Martin A. Nowak

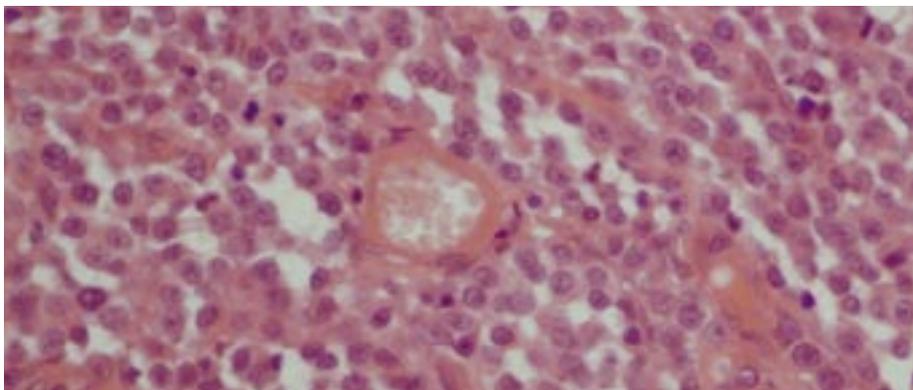
Cancer cells are generally viewed as a problem innate to their host, but evidence is mounting that they can evolve to become infectious agents and be transmitted between individuals.

The current view of cancer development is that normal cells are transformed into tumour cells by sequential mutations that activate cancer-promoting 'oncogenes', or inhibit genes that would otherwise suppress tumours, or trigger genetic instabilities. As a consequence, every tumour is the result of a unique evolutionary process as the cancer cells adapt to out-compete their neighbours. This process begins in its individual host and ends with the elimination of the tumour or the death of the host. Two studies^{1,2}, however, suggest that some tumour cells can behave like infectious agents and move from one host to another.

It has long been suspected that canine transmissible venereal tumour (CTVT) is transferred between dogs by implantation of tumour cells from the donor to the recipient, where the tumour grows as a graft (Fig. 1)³. Several lines of evidence provided indirect support for this hypothesis. A tumour can only be induced by the implantation of whole CTVT cells, and not by cell extracts or dead cells. Normal canine cells have 78 chromosomes, but the tumour cells isolated from different animals characteristically have 58 to 59 chromosomes⁴. In addition, a particular insertion near the *c-myc* oncogene is present in all tumour samples⁵. If the graft transfer hypothesis is correct, tumour cells from different animals should all be similar genetically, and should be different from the normal cells of the host animal.

Writing in *Cell*, Murgia *et al.*¹ now provide a formal proof of the graft hypothesis for CTVT. They studied CTVT cells and normal cells isolated from dogs from five continents. They show that all the tumours are closely related genetically, and different from normal cells of the host dog, by using a combination of genetic techniques (dog leukocyte antigen (DLA) haplotyping, microsatellite DNA and mitochondrial DNA sequencing).

The tumours from different animals had less genetic variability than that observed within even the most inbred breed of dog. Therefore, the tumours could not have arisen from the separate cancerous transformations of cells within individual animals, but have been transmitted from one dog to another, spreading from an ancestral clone. Murgia *et al.*¹ estimate that



C. MURGIA

Figure 1 | A canine transmissible venereal tumour in the progressive stage.

this clone arose between 250 and 2,500 years ago, making it the oldest known continuously replicating cancer cell line in animals¹.

In an independent study, Pearse and Swift² reported that devil facial tumour disease is caused by tumour cell transmission between Tasmanian devils. Cancer cells isolated from different animals with tumours of different age and size have the same pattern of chromosomal abnormalities. Furthermore, all the normal cells from one animal had part of one chromosome inverted, but this inversion was not found in any of the tumour cells from that animal, suggesting that the tumour did not arise from host cells.

So, can infectious transmission of cancer also occur between people? There is no evidence (yet) for direct person-to-person transmission of tumour cells during normal social contact. The only known physiological route for tumour cell transmission in humans is during pregnancy. In the United States every year, about 3,500 pregnant women also have a malignancy, and transplacental transmission of acute leukaemia, lymphoma, melanoma and carcinoma from mother to fetus has been observed⁶. Acute leukaemia cells have also been transferred between fetuses in mothers with a multiple pregnancy, followed by the development of disease in both fetuses⁶.

Organ transplantation is another possible route of tumour cell transmission between people. The immunosuppressive therapy required for survival of the transplanted organ blunts

the immune surveillance that might otherwise recognize and react against donor-derived tumour cells. Fortunately, the development of donor-derived tumours is rare: 0.04% of solid organ transplant recipients develop a cancer that was transferred from their donor⁷, and 0.06% of recipients of haematopoietic stem-cell transplants develop blood cancers from the transferred cells⁸. The main culprit seems to be malignant melanoma that is undetected in the donor at the time of organ harvest⁷. Finally, we came across a case report where a surgeon developed malignant fibrous histiocytoma after accidentally injuring his palm during surgical removal of the tumour from a patient⁹.

Why is cancer in general not transmissible between people? A main reason is tissue graft rejection caused by so-called MHC incompatibility. In humans and other vertebrates, the immune system uses cell-surface proteins called MHC antigens to differentiate 'self' from 'non-self' cells because these proteins vary between individuals. The immune system then reacts against those cells that display non-self MHC antigens. Such reactions may protect against tumour cell engraftment by eliminating implanted cells.

In support of this idea, CTVT cells avoid immune-mediated destruction by down-regulating the expression of the canine MHC antigens (the DLAs)¹. This adaptation of the cancer cells is crucial because complete absence of DLAs would allow an immune response in which natural killer cells destroy the tumour,

whereas normal expression of DLAs activates a different immune reaction involving killer T cells with a similar outcome. In many dogs, an immune attack against CTVT ultimately develops, leading to eradication of the tumour and immunity to reinfection³. This evidence also strengthens the hope that the immune system might be coaxed into eradicating established tumours in humans.

The emergence of multicellular life forms required cooperation between the cells of an individual organism. Cancer entails loss of this cooperation, and from the perspective of evolutionary game theory, cancer is a 'defector'¹⁰. Breakdown of cooperation can lead to the death of the host, but the tumour also meets its own demise. Therefore, a tumour that can be transmitted from one host to the next manoeuvres around the specific evolutionary mechanism that is meant to control it.

MHC incompatibility means that the cancer cells of a donor should induce a vigorous immune response in a healthy recipient. Indeed, tumour transfer in mice is only possible between animals that share the same MHC, or if the recipient is severely immunosuppressed. This leads to the interesting speculation, suggested by Murgia *et al.*¹, that a main

reason for MHC diversity in humans and other vertebrates is to ensure that cancer is not normally an infectious disease. If so, it seems that certain cancers have evolved mechanisms to get around these safeguards. ■

David Dingli and Martin A. Nowak are in the Program for Evolutionary Dynamics, Department of Organismic and Evolutionary Biology, Department of Mathematics, Harvard University, Cambridge, Massachusetts 02138, USA. David Dingli is also at the Mayo Clinic College of Medicine, Rochester, Minnesota 55905, USA. e-mails: dingli.david@mayo.edu; martin_nowak@harvard.edu

1. Murgia, C., Pritchard, J. K., Kim, S. Y., Fassati, A. & Weiss, R. A. *Cell* **126**, 477–487 (2006).
2. Pearce, A. M. & Swift, K. *Nature* **439**, 549 (2006).
3. Das, U. & Das, A. K. *Vet. Res. Commun.* **24**, 545–556 (2000).
4. Wright, D. H., Peel, S., Cooper, E. H. & Hughes, D. T. *Rev. Eur. Stud. Clin. Biol.* **15**, 155–160 (1970).
5. Katzir, N., Arman, E., Cohen, D., Givol, D. & Rechavi, G. *Oncogene* **1**, 445–448 (1987).
6. Tolar, J. & Neglia, J. P. *J. Pediatr. Hematol. Oncol.* **25**, 430–434 (2003).
7. Kauffman, H. M. *et al. Transplantation* **74**, 358–362 (2002).
8. Sala-Torra, O. *et al. Biol. Blood Marrow Transplant.* **12**, 511–517 (2006).
9. Gartner, H. V. *et al. New Engl. J. Med.* **335**, 1494–1496 (1996).
10. Nowak, M. A. in *Evolutionary Dynamics: Exploring the Equations of Life* (Belknap/Harvard Univ. Press, Cambridge, MA, 2006).