Looking Farther Afield

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Transmittable Tumors: NOT the Devil's (nor the Dog's) Advocate

Tasmanian devils in Australia, through their very nature, fight and bite each other frequently, often in the facial area. It has been noted that more than 50% of the devil population is affected by facial tumors. Unfortunately, this is devastating the population because the animals affected can ultimately starve due to tumor burden. There is intense interest in determining the mode of transmission of the tumor from one devil to the next. In this report (1), the authors evaluate the transmission of facial tumor disease in devils. They evaluated tumors from 11 affected devils. Notably, devils have 14 chromosomes, including the sex chromosomes. All the tumors studied (from 11 different devils) had an identical complex karyotype with only 13 chromosomes, including deletion of both sex chromosomes and chromosomes 2, and one chromosome 6. Further, a deletion of the long arm of chromosome 1 and four unidentified marker chromosomes were present. No intermediate stages were found between normal and tumor chromosomes, even in small primary cancers. Further, in one devil, there was a constitutional pericentric inversion of chromosome 5, but this inversion was not found in the facial tumor cells, indicating that the tumor did not arise from his own tissue. Thus, it is likely that these tumors are being passed by allograft. The authors did not speculate about how the tumor cells are transmitted, but one would have to assume that these cells are transmitted through saliva.

Canine transmissible venereal tumor (CTVT), also called Stickler's tumor, can be transmitted among dogs through intercourse, or through licking, biting, or sniffing tumor-affected areas. It has been speculated that the tumor is transmitted through allograft by three lines of evidence: (*a*) CTVT can only be transmitted through live whole cells, not by cell parts or dead cells (2); (*b*) there is a characteristic chromosome number in the tumor regardless of geographic region (3); and (*c*) a transposon gene is inserted near the c-*myc* locus in all tumors examined (4). However, the evidence was still not conclusive. In their report, Murgia et al. (5) verified that CTVT is indeed transmitted as a contagion. In a series of elegant experiments, they examined CTVT tumors isolated from dogs across five continents. They first identified the LINE-1 element inserted near the c-*myc* site only in the tumors and not in any of the matched normal samples. Second, they used polymorphic markers in the canine MHC and found varying haplotypes in normal tissue from the hosts but an identical haplotype among tumors. Using microsatellite analysis, they were also able to show that none of the host dogs were closely related to each other across different continents, but that the tumors arose from two clusters. Thus, the authors identified two subclades of the CTVT tumor that were then broadly distributed across different countries. Further experiments suggest that the CTVT tumor clone may have originated in wolves between 200 and 2,500 years ago.

Comment: These are fascinating studies that implicate transmission of tumors through infection, perpetuated by allografting. An engaging *Nature* editorial by Dingli and Nowak (6) discussed these two reports and offered further insight into why there is not (yet) evidence of this type of cancer transmission through social contact in humans. [Although rare, there are examples where transmission of human malignancy occurs through organ transplantation or through transplacental transfer]. They speculate that the MHC works to identify ''self'' from ''nonself'' and thus protects the host organism from tumor cell engraftment. In the case of dogs, it has been found that the CTVT tumor cells down-regulate host expression of MHC antigens (5). Whereas CTVT tumors can result in the destruction of the host, transmission of the tumor occurs easily. However, some dogs can mound an immune attack against CTVT tumor that makes them immune to reinfection. Unfortunately, devils are a genetically fairly closed population with limited genetic diversity and may be unable to mount an immune response to reject allogeneic tumors. Because facial tumors could result in the devastation of the devil population, it is especially important to determine the natural history of disease in the population and determine whether a vaccine can be developed.—Julie Ross

References

1. Pearse AM, Swift K. Allograft theory: transmission of devil facial-tumour disease. Nature 2006;439:549.
2. Cohen D. The canine transmissible venereal tumor: a unique result of tumor progression. Adv Cancer Res 1985;43:75–112.
3. Murray M, James ZH, Martin WB. A study of the cytology and karyotype of the canine transmissible venereal tumour. Res Vet Sci 1969;10:565–8.
4. Katzir N, Arman E, Cohen D, Givol D, Rechavi G. Common origin of transmissible venereal tumors (TVT) in dogs. Oncogene 1987;1:445–8.
5. Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA. Clonal origin and evolution of a transmissible cancer. Cell 2006;126:477–87.
6. Dingli D, Nowak MA. Cancer biology: infectious tumour cells. Nature 2006; 443:35–6.

On Being and Be(ak)coming a Galapagos Finch

When Darwin visited the Galapagos, he collected a number of birds; today these are known as Darwin's finches and there are about a dozen species. At the time he collected them, he did not recognize them as all of the same genus. They did not contribute significantly, if at all, to Darwin's formulation of the mechanisms of evolution, but today, they are recognized as being very closely related and as having evolved over a short time—just a few million years. The Grants (1, 2) have shown that changes in the environment can alter the distribution of beak sizes (length, depth, and width) within species and have argued cogently that the beak differences between species have almost certainly been selected for by cumulative pressures associated with the food supply and these, in turn, have been determined by physical conditions (temperature, rainfall, etc.) on the islands. Reference 3 is a well-written, nontechnical, book on both the Grants' field work and the process of selection in the finches.

Two years ago, Abzhanov et al. (4) pursued a candidate-gene approach to the identification of the genetic sources of variation among the finches and showed that BMP4 (known to be involved in skeletal morphogenesis) was more extensively expressed during the embryogenesis of finches with deep and

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wide beaks than in the development of those with narrow beaks. Experimental overexpression of BMP4 in chick embryos produced an exactly parallel phenotype.

Abzhanov et al. (5) have now pursued a broader approach to expression patterns with cDNA microarrays, asking what distinguishes species with long, pointed beaks (cactus finches) from those with short beaks (ground finches)—a difference not explained in the earlier candidate-gene studies. What they found was that much of the difference in beak length can be explained by higher levels of expression of calmodulin (CaM) in the cactus finch embryos than in the embryos of other finches. They further showed that experimentally manipulating levels of a downstream effector of CaM [CaM kinase kinase (CaMKII)] in chick embryos produced similar modifications: higher CaMKII results in longer beaks.

This work establishes that at least two signaling systems are involved in beak morphology: BMP4 in depth and width and CaM in length. It further provides an additional data point for the question of what drives evolutionary change: multiple changes with small effects or a single change with large effects? It leaves unanswered, at present, what the cause of the differential expression patterns in embryogenesis is. Further questions arise in relation to speciation. If species are defined by the inability to breed and produce fertile offspring, at what point do other genetic differences emerge that prohibit successful reproduction: before or after the mutation(?) that leads to differences in beak size? Do beak size and shape act as a source of sexual selection? Does diet, which acts to select beak size and shape, subsequently act as an agent of speciation by altering DNA methylation or histone acetylation? Is speciation about food as well as isolation and sex?—John Potter

References

1. Grant PR, Grant BR. Evolution of character displacement in Darwin's finches. Science 2006;313:224–6.
2. Grant PR. The Ecology and evolution of Darwin's finches. Princeton (NJ): Princeton Univ. Press; 1999.
3. Weiner J. The beak of the finch. A story of evolution in our time. New York: Alfred A. Knopf; 1994.
4. Abzhanov A, Protas M, Grant BR, Grant PR, Tabin CJ. Bmp4 and morphological variation of beaks in Darwin's finches. Science 2004;305:1462–5.
5. Abzhanov A, Kuo WP, Hartmann C, Grant BR, Grant PR, Tabin CJ. The calmodulin pathway and evolution of elongated beak morphology in Darwin's finches. Nature 2006;442:563–7.