Aurora and the hunt for cancer-modifying genes

William Dove

Quantitative modifiers of neoplastic pathways are greatly treasured but difficult to identify at the molecular level. An apparent success has now identified a centrosomal protein kinase that affects many cancer histotypes.

The simple paradigm for discovering genes and their cognate molecules that can affect a neoplastic pathway is to search for mutated alleles that predispose to cancer with high probability ('penetrance'). This strategy has led to a long list of genes that are somatically activated in human or murine cancers. Given an appropriate recipient cell type, such activated oncogenes can engender a surrogate transformed phenotype in culture.

This paradigm has also led to a steadily growing list of tumor suppressor genes; for these, an inactivating mutated allele predisposes carriers to a particular neoplasm with high probability. The implementation of this simple idea has identified, from the tumor suppressors, main 'gatekeeper' functions[1] that must be inactivated to open a particular neoplastic pathway and, from the oncogenes, main signaling pathways that are activated in that neoplastic pathway. The power of the simple pathway metaphor in the analysis of the biology of cancer is undoubted, but (as Adlai Stevenson said of flattery) it must not be inhaled. Do any two different types of cancer develop along the same pathway? Does any one cancer type arise along a unique linear pathway?

A pathway for cancer can be quantitatively modulated in its flux or in the stability of particular neoplastic states along the pathway. The search for the salient genes and their cognate molecules is vastly more difficult when the impact of variation on the cancer phenotype is only quantitative, not all-or-none. But the potential fruits of this labor appeal greatly to cancer biologists. The discovered molecules may serve as reagents for stage-specific diagnostics of the tumor. If expressed from cells surrounding the tumor, quantitative modifiers may act as lead compounds for therapeutics more efficient than strategies requiring delivery into the entire tumor cell population[2].

On page 403, Amanda Ewart-Toland, Paraskevi Briassouli and their colleagues[3] address these issues. Further consideration of their report highlights the contrast between the issues of risk estimation for cancer and those involving early detection and therapeutics. The report by the San Francisco/London/Sutton/Cambridge/Newcastle ensemble of scientists also illustrates the magnitude of the labor involved in the discovery of a quantitative modifier of cancer susceptibility. As Herculean computing tasks are tackled by ensembles of PCs, this report shows how an

© Geoffrey Clements/CORBIS

Hail, Bright Aurora. In Roman mythology, Aurora abandons the hunter Orion each morning to bring light to the world.

William Dove is in the University of Wisconsin, McArdle Laboratory for Cancer Research and Laboratory of Genetics, 1400 University Ave, Madison, Wisconsin 53706, USA.
e-mail: dove@oncology.wisc.edu

international 'collaboratory' was assembled for the task at hand.

Location, location, location

Identifying and mapping quantitative modifiers of a cancer phenotype in the laboratory mouse has involved a range of initial conditions provoking the cancer: chemical carcinogenesis[4], germline mutation in a tumor suppressor gene[5] or transgenesis involving an activated oncogene[6]. In the first case, there is sometimes a preferred tissue and oncogenic pathway involved in the carcinogenesis protocol; in the second and third cases, specificity is pre-established. In this study, Allan Balmain and his colleagues[3] have explored dominant resistance/susceptibility modifiers of skin papilloma and carcinoma formation by crossing *Mus musculus* mice transgenic for the activated oncogene *Kras2* to mice derived from the *Mus spretus* subspecies. One region of the mouse genome found to be polymorphic in this search lies around 95–100 cM on mouse chromosome 2. Because the modification of papilloma multiplicity is only quantitative, the resolution for mapping the modifier(s) in this region by backcross analysis is limited to 10–20 cM. The investigators improved their resolution to 1 cM by capitalizing on a set of recombinant haplotypes that vary among different inbred and outbred isolates of *Mus spretus*.

Further resolution of the location of the modifier at this locus involved a leap to the somatic genetics of human cancer and consideration of cancer histotypes other than skin. The region of the human genome orthologous to the salient region of the mouse genome is human chromosome region 20q13.2, where a 3-Mb amplicon and subamplicons as small as 300 kb have been found in advanced tumors of the breast, colon and ovary.

Study structure, then function

The resolution from mapping, haplotype analysis and somatic genetics retained more than a single gene. Thus, the final stages of the search for the presumed broadly acting cancer modifier led these investigators to a cluster of functional studies depending on regulatory and structural allelic differences in the mouse (*Stk6*) and human (*STK15*) orthologs encoding the serine-threonine protein kinase that has been variously dubbed Aurora[7,8], BTAK[9] and STK15 (ref. 10). A frequent sequence polymorphism in codon 31 of the human gene results in the amino acid substitution F31I. In a set of individuals with colon cancer studied by John Burns and his colleagues in Newcastle, heterozygotes with respect to the codon 31 polymorphism more commonly amplified the allele encoding the Ile31 variant. Genomic instability in progressed colon tumors was assessed by comparative genome hybridization; again the genomes of cancers from individuals heterozygous with respect to the codon 31 polymorphism were often more unstable than those from homozygotes with respect to the allele encoding the Phe31 variant.

Spiros Linardopoulos and his colleagues in London carried out cell biological studies of this kinase, including its association with the centrosome. Here too, the two alleles show differences; the tumor-enhancing allele encoding the Ile31 variant associated less strongly with the UBE2N ubiquitin ligase and the centrosome than the allele encoding the Phe31 variant. Evidently, these allele-specific observations cannot be explained by linkage disequilibrium between the gene *STK15*/*Stk6* and a more important gene in the neighborhood[11].

Has the prey been captured?

As with another recently reported cancer modifier[7], evidence from mice does not yet include a polymorphic sequence: both the sensitive and the resistant strains have the allele encoding the Ile31 variant, but the sensitive strain overexpresses the kinase in normal tissues and in skin tumors. Regulatory polymorphisms are frequent but not yet systematically found at the sequence level[12]. The authors indicate ways in which contemporary mouse genomics/genetics can close this side of the argument. On the human side, population genetics pursued in collaboration with Bruce Ponder in Cambridge does not yet give significant evidence for association of the sensitive allele encoding the Ile31 variant with cancer incidence[13]. The allele encoding the biologically informative Ile31 variant is rare, compromising the search for significant association. Notably, an initial report of association of variation at human chromosome 20q13 with prostate cancer has been published by Stephen Thibodeau and his colleagues[14].

If this locus acts only as a modifier of neoplastic pathways, even across a broad spectrum of cancer histotypes, it may not show up as a primary susceptibility determinant but only as an outcome determinant. The apparent success in identifying this quantitative genetic modifier has depended on somatic variation at the locus. The non-autonomous modifiers[2] will be more elusive prey.

Surely this report will stimulate many investigators to test its claims, in the best tradition of science. The role of the centrosome in mitosis is restored to center stage[15,16].

1. Kinzler, K.W. & Vogelstein, B. *Cell* **87**, 159–170 (1996).
2. Gould, K.A. & Dove, W.F. *Proc. Natl. Acad. Sci. USA* **94**, 5848–5853 (1997).
3. Ewart-Toland, A. *et al. Nat. Genet.* **34**, 403–412 (2003)
4. Ruivenkamp, C.A. *et al. Nat. Genet.* **31**, 295–300 (2002).
5. Dietrich, W.F. *et al. Cell* **75**, 631–639 (1993).
6. Balmain, A. & Nagase, H. *Trends Genet.* **14**, 139–144 (1998).
7. Bischoff, J.R. & Plowman, G.D. *Trends Cell Biol.* **9**, 454–459 (1999).
8. Glover, D.M., Leibowitz, M.H., McLean, D.A. & Parry, H. *Cell* **81**, 95–105 (1995).
9. Sen, S., Zhou, H. & White, R.A. *Oncogene* **14**, 2195–2200 (1997).
10. Zhou, H. *et al. Nat. Genet.* **20**, 189–193 (1998).
11. Reich, D.E. *et al. Nature* **411**, 199–204 (2001).
12. Hudson, T.J. *Nat. Genet.* **33**, 439–440 (2003).
13. Dahlman, I. *et al. Nat. Genet.* **30**, 149–150 (2002).
14. Berry, R. *et al. Am. J. Hum. Genet.* **67**, 82–91 (2000).
15. Boveri, T. *The Origin of Malignant Tumours* (Williams and Wilkins, Baltimore, 1914).
16. Sibon, O.C. *Nat. Genet.* **34**, 6–7 (2003).