A New Generation of Mouse Models of Cancer for Translational Research

Cory Abate-Shen

This issue of *Clinical Cancer Research* contains a series of stimulating reviews that describe the benefits of using mouse models to study human cancer and the potential effect of these models for the treatment of patients with cancer. Each review is written by experts both in the generation of mouse models of cancer as well as the application of such models for translational research. All five reviews describe a new generation of genetically engineered mouse models that accurately recapitulate many features of human cancer and thereby provide valuable opportunities for drug discovery and other translational applications. In particular, Olive and Tuveson (1), focusing on mouse models of pancreatic cancer, discuss how such models can be used for drug discovery as well as the establishment of a "mouse hospital" to facilitate preclinical testing in mouse models. Fomchenko and Holland (2), focusing on mouse models of brain tumors, provide examples of their application in preclinical studies. Similarly, Carver and Pandolfi (3), focusing on mouse models of leukemia and prostate cancer, describe preclinical studies using these models. Degenhardt and White (4) describe models that enable investigations of the programmed cell death mechanisms in cancer and the applications of such models to the development of rational chemotherapy. Finally, Singh and Johnson (5) review mouse models of several types of cancer, discussing the value of these models for drug development from the industry standpoint. Although each review has a different focus and offers a unique perspective, their overriding theme is that many highly sophisticated models that recapitulate many aspects of human cancers are now available, and therefore, translational studies using such models are likely to have a meaningful effect for the treatment of patients with cancer.

However, the rapid expansion and widespread usage of mouse models of cancer has, not surprisingly, unearthed a certain amount of skepticism about their value and relevance for human cancer. Indeed, although we have witnessed a remarkable refinement of mouse models of cancer over the years, these models are still not "perfect" and may never be so, considering the significant species differences between mice and humans (6). However, we need to remember that mouse models are just that—they are models, which offer unique opportunities to investigate cancer mechanisms in genetically defined and environmentally controlled scenarios in the context of the tumor microenvironment. Importantly, many studies that are easily done using mouse models of cancer would not be feasible in humans. Therefore, mouse models are intended to complement, not replace, studies done in humans and, if effectively "credentialled" as discussed by Olive and Tuveson (1), can augment studies of human cancer. The reviews in this series are specifically focused on the application of mouse models of cancer for preclinical and translational studies; for more general discussions of mouse models of cancer, the reader is referred to previous reviews (7–10).

Evolution of Mouse Models of Cancer—Toward a New Generation of Models

Although the spontaneous occurrence of carcinoma in mice is rare, mice have become an attractive model for studying human cancer because of the ease of manipulating their genome. Although the earliest mouse models were derived from viral insertions, nowadays, when we refer to mouse models of cancer, we are typically referring to mice that have been genetically modified to express oncogenes or to delete tumor suppressor genes, either of which can lead to cancer phenotypes. Generally speaking, these genetically modified mouse models enable the investigation of cancer phenotypes in the context of the tumor microenvironment and an intact immune system. These are critical distinctions from the widely used xenograft models in which tumor cells or tissues are typically grown in immunodeficient mice, which, as argued by Olive and Tuveson (1), Fomchenko and Holland (2), and Carver and Pandolfi (3), limit their "predictive use" for drug development.

The original genetically engineered mouse models of cancer were engineered to express dominantly acting oncogenes, such as the SV40 T antigen, in particular compartments using tissue-specific promoters (e.g., refs. 11–13). Such mouse models were enabled by the availability of tissue-specific promoters driving oncogene expression. Although they are limited by the need for such promoters as well as practical issues about variability of transgene integration site, expression levels, and cell types of expression, these transgenic models established the feasibility of studying cancer phenotypes in genetically engineered mice and continue to provide a valuable resource for preclinical studies.

Complementing these gain-of-function transgenic models are loss-of-function models in which targeted gene deletion of tumor suppressor genes results in cancer phenotypes. Indeed, since the landmark studies showing that loss of function of *p53* could lead to development of cancer in mice (14, 15),

Author's Affiliation: The Cancer Institute of New Jersey, Center for Advanced Biotechnology and Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, New Jersey

Received 3/1/06; revised 3/28/06; accepted 5/25/06.

Grant support: National Cancer Institute Mouse Models of Human Cancer Consortium grant UO1-CA84294 and Department of Defense grant W81XWH-06-1-0035.

Requests for reprints: Cory Abate-Shen, Center for Advanced Biotechnology and Medicine, 679 Hoes Lane, Piscataway, NJ 08854. Phone: 732-235-5161; Fax: 732-235-5789; E-mail: abate@cabm.rutgers.edu.

doi:10.1158/1078-0432.CCR-06-0500

many subsequent studies have shown that the individual or combinatorial loss of function of tumor suppressor (or other) genes in mice can lead to cancer. Moreover, as a consequence of a veritable explosion in the technological advances of gene targeting in recent years (16), mouse models based on targeted alterations of the genome have become increasingly more common and significantly more sophisticated. Nowadays, the conditional as well as inducible deletion of tumor suppressor genes or activation of oncogenes in tissue-specific compartments have become the norm (see discussions in refs. 1–3). This has led to the emergence of a new generation of mouse models that are highly relevant for drug development and translational studies.

Opportunities and Limitations of Using Mouse Models for Preclinical and Translational Research

Nonetheless, despite these technological advances, there remain significant differences between cancer development in humans and in genetically engineered mouse models (6). One important distinction is that, in many genetically engineered mice, the genomic alteration(s) (i.e., the loss or gain of gene expression) typically occurs in the germ line or at least in a large portion of the cells, which contrasts with most instances of human cancer in which gene alterations are typically rare and stochastic. Therefore, as discussed by Fomchenko and Holland (2), most genetically engineered mouse models are more representative of human cancer predisposition syndromes rather than random tumorigenesis. They and others have used a somatic gene transfer approach (the *RCAS/tv-A* system) to circumvent this potential limitation (2). Another notable exception is the spontaneous activation of *Kras* following somatic recombination in the whole animal (17).

Does this difference in cancer development of most genetically engineered mouse models limit their use in studying human cancer? If one's intent is to study the evolution of the disease as it occurs in humans, then it very well might. However, if one's intent is to investigate the molecular mechanisms underlying a cancer phenotype based on a particular genetic alteration or to facilitate biomarker analyses, then perhaps not. Indeed, analyses of gene expression changes in relatively "homogeneous" mouse models can help to identify biomarkers that may have otherwise been obscured in more "heterogeneous" human cancer specimens. For example, comparison of gene expression profiles from a mouse model of lung cancer model based on activation of *Kras2* and human tumors enabled the identification of a *Ras* signature that was not identifiable by analyzing only the human tumor data (18).

Moreover, the relative homogeneity of cancer development in mouse models, relative to humans, can be of considerable benefit for drug testing. As discussed in the reviews by Degenhardt and White (4), Fomchenko and Holland (2), and Carver and Pandolfi (3), mouse models based on the perturbation of specific molecular pathways can enable a detailed interrogation of the involvement of such pathways in tumorigenesis as well as investigations of potential therapeutics that specifically target these pathways. Generally, cancer develops more uniformly and more rapidly in mouse models, which from an industry perspective can be highly advantageous for drug testing (5). Moreover, mouse models provide ready access to cancer tissue at all disease stages; this can greatly facilitate pharmacokinetic and pharmacodynamic studies (1, 5), thereby providing valuable information about whether a given agent is effective in the target tissue. Finally, the ability to monitor the consequences of drug delivery by *in vivo* imaging of mouse models (1, 2) can enable a quantitative assessment of the consequences of drug action for tumor development.

However, not all of the unique features of mouse models are advantageous either for interrogating human cancer or pursuing translational studies. Perhaps the most significant hindrance of mouse models is that relatively few develop metastases and even those that do tend to display metastases with different tissue specificity than seen in human cancer. This is of particular concern because most cancer lethality is a consequence of metastasis, and the availability of mouse models that facilitate investigation of therapeutics targeting metastatic disease would be highly advantageous.

Can this be overcome? It is certainly plausible that the genesis of metastases in mice and humans is so inherently different as to preclude their occurrence in most mouse models. However, a new generation of mouse models able to closely recapitulate the metastatic features of human cancers seems to be in evolution as exemplified by recently described mouse models of pancreatic cancer (19, 20).

Conclusions

We are approaching a new era in modeling cancer in mice. Although our models are still imperfect, they have become considerably more accurate in their ability to recapitulate human cancer and, thereby, have become increasingly more valuable and more widely used for preclinical and translational research. The critical next step will be to determine whether mouse models have significant predictive use for drug development and whether such use can be directly translated to human therapeutic applications. Considering recent successes in this arena (21), the outlook is very promising!

Acknowledgments

I thank all of my colleagues in the Mouse Models of Human Cancer Consortium, whose thoughtful discussions over the past 7 years provided the foundation for this review, and Michael Shen, Arnold Rabson, and Bob DiPaola for helpful comments on the manuscript.

References

1. Olive KP, Tuveson DA. A "mouse hospital" for preclinical testing of novel cancer therapeutics. Clin Cancer Res. In press 2006.
2. Fomchenko EI, Holland EC. Mouse models of brain tumors and their applications in preclinical trials. Clin Cancer Res. In press 2006.
3. Carver BS, Pandolfi PP. Mouse modeling in oncological pre-clinical and translational research. Clin Cancer Res. In press 2006.
4. Degenhardt K, White E. A mouse model system to genetically dissect the molecular mechanisms of tumorigenesis. Clin Cancer Res. In press 2006.
5. Singh M, Johnson L. Using genetically engineered mouse models of cancer to aid drug development: an industry perspective. Clin Cancer Res. In press 2006.
6. Rangarajan A, Weinberg RA. Opinion: comparative biology of mouse versus human cells: modelling human cancer in mice. Nat Rev Cancer 2003;3:952–9.
7. Van Dyke T, Jacks T. Cancer modeling in the modern era: progress and challenges. Cell 2002;108:135–44.

8. Holland EC. Mouse models of human cancer. Hoboken (NJ): John Wiley & Sons, Inc.; 2004. p. 475.

9. DePinho RA, Jacks T. Introduction. The laboratory mouse in cancer research. Semin Cancer Biol 2001; 11:175–6.

10. Bowman T, Symonds H, Gu L, Yin C, Oren M, Van Dyke T. Tissue-specific inactivation of p53 tumor suppression in the mouse. Genes Dev 1996;10:826–35.

11. Greenberg NM, DeMayo F, Finegold MJ, et al. Prostate cancer in a transgenic mouse. Proc Natl Acad Sci U S A 1995;92:3439–43.

12. Hanahan D. Heritable formation of pancreatic β-cell tumours in transgenic mice expressing recombinant insulin/simian virus 40 oncogenes. Nature 1985;315: 115–22.

13. Stewart TA, Pattengale PK, Leder P. Spontaneous mammary adenocarcinomas in transgenic mice that carry and express MTV/myc fusion genes. Cell 1984; 38:627–37.

14. Jacks T, Remington L, Williams BO, et al. Tumor spectrum analysis in p53-mutant mice. Curr Biol 1994; 4:1–7.

15. Donehower LA, Harvey M, Slagle BL, et al. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature 1992;356: 215–21.

16. Branda CS, Dymecki SM. Talking about a revolution: the impact of site-specific recombinases on genetic analyses in mice. Dev Cell 2004;6:7–28.

17. Johnson L, Mercer K, Greenbaum D, et al. Somatic activation of the K-ras oncogene causes early onset lung cancer in mice. Nature 2001;410:1111–6.

18. Sweet-Cordero A, Mukherjee S, Subramanian A, et al. An oncogenic KRAS2 expression signature identified by cross-species gene-expression analysis. Nat Genet 2005;37:48–55.

19. Aguirre AJ, Bardeesy N, Sinha M, et al. Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. Genes Dev 2003;17:3112–26.

20. Hingorani SR, Wang L, Multani AS, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell 2005;7:469–83.

21. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer Cell 2005;8:299–309.