Published in final edited form as:

J Vasc Interv Radiol. 2017 July ; 28(7): 1051–1052. doi:10.1016/j.jvir.2017.04.020.

Bigger Is Better: Refinement of an Animal Model of Hepatocellular Carcinoma and Transfemoral Arterial Embolization

Kelly Garcia, DVM, PhD, DACLAM and

Biologic Resources Laboratory, University of Illinois at Chicago, (MC533) 1840 West Taylor Street, Chicago, IL 60612

Dan Regan, DVM, DACVP

Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado.

Entities as disparate as computers, cell cultures, rodents, and nonhuman primates have been used as surrogates to investigate how human systems behave in normal and diseased states, from genotype to phenotype. Although much has and can be learned from these models, there are limitations that stem from the basic fact that all these systems are not exact replicas of humans. Most biomedical models are useful for studying discrete aspects of a disease but rarely allow investigation into every biochemical, genetic, and physiologic characteristic.

The most common model used in biomedical research is the mouse model. Many lines of transgenic mice develop tumors that share features of human malignancies, but they also exhibit dramatic phenotypic differences. Children with the *Rb* mutation develop retinoblastomas, whereas mice develop pituitary adenocarcinomas (1). *p53* null mice develop sarcomas, whereas human patients with Li-Fraumeni syndrome primarily develop carcinomas, and the mouse model displays different tissue specificity for metastasis (2). Differences in metabolic rate and dependence on cell signaling pathways might result in different responses to drugs (3). Finally, the small size of the laboratory mouse limits its usefulness for development of devices and instruments used in humans.

To accelerate biomedical research and drug discovery, it is imperative to optimize animal models. Optimization requires clearly defined goals. The National Research Council (4) established the following criteria to be considered when developing an ideal model: (a) the model is appropriate for the intended use (a specific disease model faithfully mimics the human disease and a model system is appropriate for the human system being modeled); (b) the model can be developed, maintained, and provided at a reasonable cost in relation to the perceived or potential scientific value; (c) it is of value for more than one limited kind of research; (d) it is reproducible and reliable so that the results can be confirmed; and (e) it is reasonably available and accessible.

Address correspondence to K.G.; kellygar@uic.edu.

Neither of the authors has identified a conflict of interest.

Tumor initiation, progression, and eventual metastasis are biologically complex, multifactorial processes (5,6). As such, developing and selecting animal models for cancer research and evaluation of novel therapeutic interventions requires thorough experimental validation. To maximize the likelihood of correlation between preclinical and clinical efficacy, this validation must demonstrate the relevancy of the model, must recapitulate the complex biology and pathogenesis of tumor development in the human patient, and must accurately predict other physiologic aspects such as drug pharmacology and toxicity (7).

It is now well known that the host microenvironment in which the tumor develops plays a critical role in shaping tumor growth and progression (5,8). Despite this, the continued use of preclinical models that disregard components of the tumor microenvironment, such as the extracellular matrix and immune cell infiltrates, remains as a likely disconnect between observed preclinical and clinical efficacy. Human hepatocellular carcinoma (HCC) is a prime example of a tumor histotype in which distinct features of the tumor microenvironment are of critical relevance when considering animal models of this disease. HCC develops in a background of chronic inflammation, hepatocellular injury, regeneration, and cirrhosis, and thus animal models that recapitulate this environment are essential to the evaluation and translation of novel therapeutic interventions for this disease (9).

The hepatocarcinogen diethylnitrosamine (DEN)-induced model of HCC is an established animal model that reliably recapitulates the complex phenotypic background of cirrhosis and arterial dependence that underlies the pathogenesis of the human disease (10,11). Compared with other xenograft and orthotopic models of HCC, the immune-competent, cirrhosis-inducing, and autochthonous nature of the DEN model likely results in a tumor microenvironment that nearly parallels that of human HCC (12). However, potential shortfalls of the DEN rat model of HCC are that most tumors induced by DEN harbor activating *H-ras* proto-oncogenes, rarely seen in humans (13–15), and a narrow therapeutic window exists between tumor induction and death owing to underlying hepatic dysfunction, which could significantly limit its utility in the evaluation of novel therapies (16).

The work of Kiefer et al (17) directly addresses this potential shortcoming, providing a means to significantly increase overall survival times in DEN-treated rats through selection of study animals based on initial body weight, while still maintaining a relevant background degree of hepatic cirrhosis. Furthermore, Kiefer et al refine a method of segmental transarterial embolization in their rat model, demonstrating a shorter, less complex, and more clinically relevant technique for embolization compared with some previously published methods (13), which, given the importance of locoregional therapies in the management of human HCC, provides an important advancement in small animal modeling of transarterial embolization. Taken together, the contributions of Kiefer et al toward the further characterization of the DEN rat model of HCC will provide both an increased window of opportunity and greater ease for the evaluation of novel translational therapeutics and their potential combination with transarterial embolization in this clinically relevant model of HCC.

With the recent developments of molecular-targeted and immune-targeted therapies in human oncology over the last decade, the continued refinement of an appropriate animal

model for the investigation of new drugs of this class and novel combinations thereof is critically important. The work of Kiefer et al provides a significant step in the right direction toward the continued refinement and improvement of a relevant animal model of HCC and femoral transarterial embolization, which will undoubtedly serve to improve the success of translational drug development for HCC.

ABBREVIATIONS

DEN	diethylnitrosamine
HCC	hepatocellular carcinoma

REFERENCES

1. Jacks T, Fazeli A, Schmitt EM, et al. Effects of an Rb mutation in the mouse. *Nature* 1992; 359:295–300. [PubMed: 1406933]
2. Jacks T, Remington L, Williams BO, et al. Tumor spectrum analysis in p53-mutant mice. *Curr Biol* 1994; 4:1–7. [PubMed: 7922305]
3. Frijhoff AF, Conti CJ, Senderowicz AM. Advances in molecular carcinogenesis: current and future use of mouse models to screen and validate molecularly targeted anticancer drugs. *Mol Carcinog* 2004; 39: 183–194. [PubMed: 15057870]
4. National Research Council. Biomedical Models and Resources: Current Needs and Future Opportunities. Washington, DC: National Academy Press; 1998.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144:646–674. [PubMed: 21376230]
6. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. *Cell* 2011; 147:275–292. [PubMed: 22000009]
7. Talmadge JE, Singh RK, Fidler IJ, Raz A. Murine models to evaluate novel and conventional therapeutic strategies for cancer. *Am J Pathol* 2007; 170:793–804. [PubMed: 17322365]
8. Quail D, Joyce J. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013; 19:1423–1437. [PubMed: 24202395]
9. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV-and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer* 2013; 13: 123–135. [PubMed: 23344543]
10. De Minicis S, Kisseleva T, Francis H, et al. Liver carcinogenesis: rodent models of hepatocarcinoma and cholangiocarcinoma. *Dig Liver Dis* 2013; 45:450–459. [PubMed: 23177172]
11. Gross C, Steiger K, Sayyed S, et al. Model matters: differences in orthotopic rat hepatocellular carcinoma physiology determine therapy response to sorafenib. *Clin Cancer Res* 2015; 21:4440–4450. [PubMed: 25995341]
12. Heindryckx F, Colle I, Van Vlierberghe H. Experimental mouse models for hepatocellular carcinoma research. *Int J Exp Pathol* 2009; 90: 367–386. [PubMed: 19659896]
13. Wang Q, Lin ZY, Feng XL, et al. Alterations in metastatic properties of hepatocellular carcinoma cell following H-ras oncogene transfection. *World J Gastroenterol* 2001; 7:335–339. [PubMed: 11819786]
14. Chen B, Liu L, Castonguay A, Maronpot RR, Anderson MW, You M. Dose dependent ras mutation spectra in N-nitrosoethylamine induced mouse liver tumors and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone induced mouse lung tumors. *Carcinogenesis* 1993; 14: 1603–1608. [PubMed: 8353844]
15. Stahl S, Ittrich C, Marx-Stoelting P, et al. Genotype-phenotype relationships in hepatocellular tumors from mice and man. *Hepatology* 2005; 42: 353–361. [PubMed: 15965925]
16. Gade TP, Hunt SJ, Harrison N, et al. Segmental transarterial embolization in a translational rat model of hepatocellular carcinoma. *J Vasc Interv Radiol* 2015; 26:1229–1237. [PubMed: 25863596]

17. Kiefer RM, Hunt SJ, Pulido S, et al. Relative initial weight is associated with improved survival without altering tumor latency in a translational rat model of diethylnitrosamine-induced hepatocellular carcinoma and transarterial embolization. *J Vasc Interv Radiol* 2017; 28:1043–1050. [PubMed: 28495453]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript