Alternative Animal Models for Carcinogenicity Testing - Evaluation of Gene-engineered Models -

Katsumi Fukamachi a)  Masumi Suzui a)  Jiegou Xu b)  Hiroyuki Tsuda b)

a) Department of Molecular Toxicology, Nagoya City University Graduate School of Medical Sciences
1 Kawasumi, Mizoho-cho, Mizuho-ku, Nagoya 467-8601, Japan

b) Nanotoxicology Project, Nagoya City University
3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Summary

Use of animals for the determination of carcinogenicity of compounds is still the most reliable method. The traditional approach for detecting carcinogens, the long-term (generally 2 years in rats) study in rodents, has the disadvantages of being expensive and time consuming. Furthermore, taking into account animal welfare considerations, attention has recently been concentrated on development of alternative methods to reduce testing time and animal number. For this purpose, various types of 2-stage carcinogenesis models and, more recently, examples featuring genetic-engineering have been developed. In this review, we concentrate on gene-engineered animal models (GEM) for evaluation of carcinogenicity and mutagenicity. Currently, the GEMs most commonly used are the rasH2, p53+/− and Tg.AC models. The rasH2 mouse appears to be the most appropriate for general carcinogenicity testing because of sufficient validation studies using known carcinogens. Other murine models, p53+/− and Tg.AC, need more validation studies, historic background data, unexpected tumor site, and tumor characterization. Rats with the same transgene as rasH2 mice are also promising because of documented induction of mammary carcinomas by a variety of carcinogens. Animal models for evaluation of mutagenesis are also more reliable than simple in vitro models, although examples are obviously required which allow a simplified detection method. Overall findings indicate that prediction of two-year rat bioassay outcomes with early assessment by GEMs may have the potential to increase the efficiency of strategies for identification of human carcinogens.