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Transgenic animals as tools in drug development

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Abstract

A transgenic animal can be defined as an organism that has undergone a stable modification of genotype as a result of genetic manipulation. Such animals are being increasingly employed as research and development tools by both academic and commercial institutions. The primary methods by which transgenic animals can be generated will be described. The relative merits of the approaches will be illustrated, as will their potential use in the discovery and development of novel therapeutic entities.

Introduction

The ability to manipulate the genotype of an animal has allowed a systematic investigation of a large number of fundamental biological phenomena in the context of the whole animal. The principal means by which transgenic animals are currently produced are pronuclear DNA microinjection, blastocyst microinjection of embryonic stem (ES) cells and replication-defective viral vector transduction (for a review see [1]).

The route chosen for a particular project will depend upon the type of biological question being addressed and the relative merits and limitations of the different methods. For example, while the ability to target specific regions of the genome in ES cells probably holds the most promise for the future, this technique is currently restricted to use in the mouse. In contrast, pronuclear microinjection has been employed in a number of different species, including commercially important animals such as the pig, goat, sheep and cattle. Viral vectors were the first means by which DNA was introduced into the germline; however, the technical limitations of this approach have restricted their use. In humans, where gene therapy by somatic transformation is beginning to bear fruit, viral-mediated DNA transduction remains the predominant route [2].

The widespread use of transgenics has greatly aided our understanding in many areas of biology, including investigations of possible mediators involved in inflammation [3–5]. Briefly, other areas include: (i) the definition of *cis*-acting DNA sequences involved in tissue-specific, developmentally regulated gene expression, e.g. novel promoter/enhancer combinations and locus control regions; (ii) investigation of the consequences of ectopic gene expression, e.g. oncogenesis; (iii) new insights into the influence of genome organisation on gene expression, e.g. genomic imprinting; and (iv) the opportunity to study developmental processes as a result of the fortuitous (insertional mutagenesis), selected (promoter/enhancer trap transgenes) or defined (homologous recombination) genetic lesions that can be generated using these techniques [1].

In some cases these investigations have resulted, by design or fortuitously, in the production of novel rodent models of human disease states that should prove invaluable in gaining a better understanding

of the underlying dysfunction in their human counterpart. Future developments along these lines may result in many of the existing animal models being replaced by such "designer" transgenics. In addition to the extensive transgenic work being performed in rodents, several groups are trying to exploit these technologies in commercially important agricultural species. Initial attempts to generate significant improvements in animal performance, e.g. in growth rate, meat quality, or by adding value to milk through the production of human proteins, have produced mixed results.

Transgenic rodents are already being evaluated in the pharmaceutical industry, e.g. as a generic source of novel immortalised cell lines [6] and as a means of evaluating more effectively the *in vivo* toxicity and mode of action of mutagenic agents [7, 8]. The ability to "humanise" rodents provides a major opportunity to replace the existing animal models with more refined small animal models, which, in turn, could lead to a reduction in overall animal usage. It is anticipated that, in the pharmaceutical industry, transgenics will have an impact on both the discovery and development of novel therapeutic entities by facilitating target identification and validation, and the development of more refined generic animal models in which to evaluate candidate pharmaceuticals.

References

[1] R. Jaenisch, *Transgenic animals.* Science *240,* 1468–1474 (1988).

[2] A. D. Miller, *Human gene therapy comes of age.* Nature *357,* 455–460 (1992).

[3] N. Sarvetnick, D. Liggitt, S. L. Pitts, S. E. Hansen and T. A. Stewart, *Insulin-dependent diabetes mellitus induced in transgenic mice by ectopic expression of class II MHC and interferon-γ.* Cell *52,* 773–782 (1988).

[4] R. L. Tepper, D. A. Levinson, B. Z. Stranger, J. Campos Torres, A. K. Abbas and P. Leder, *IL-4 induces allergic-like inflammatory disease and alters T cell development in transgenic mice.* Cell *62,* 456–467 (1990).

[5] R. E. Hammer, S. D. Maika, J. A. Richardson, J.-P. Tang and J. D. Taurog, *Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m: An animal model of HLA-B27-associated human disorders.* Cell *63,* 1099–1112 (1990).

[6] P. S. Jat, M. D. Noble, P. Ataliotis, Y. Tanaka, N. Yannoutsos, L. Larsen and S. Kiousis, *Direct derivation of conditionally immortal cell lines from an H-2K^b-tsA58 transgenic mouse.* Proc. Natl. Acad. Sci. *88,* 5096–5100 (1991).

[7] J. A. Gossen, W. J. F. de Leeuw, C. H. T. Tan, E. C. Zwarthoff, F. Berends, P. H. M. Lohman, D. L. Knook and J. Vug, *Efficient rescue of integrated shuttle vectors from transgenic mice: A model for studying mutations in vivo.* Proc. Natl. Acad. Sci. *86,* 7971–7975 (1989).

[8] S. W. Kholer, G. S. Provest, A. Fieck, P. L. Kretz, W. O. Bullock, J. A. Sorge, D. L. Putman and J. M. Short, *Spectra of spontaneous and mutagen-induced mutations in the lacI gene in transgenic mice.* Proc. Natl. Acad. Sci. *88,* 7958–7962 (1991).