International Journal of Animal Biotechnology & Applications
ISSN: 2455–7315 (online)
Vol. 2: Issue 1
www.journalspub.com

Transgenic Animals

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Abstract

A transgenic animal is one that carries a foreign gene that has been deliberately inserted into its genome. The foreign gene is constructed using recombinant DNA methodology. In addition to the gene itself, the DNA usually includes other sequences to enable it to be incorporated into the DNA of the host as well as to be expressed correctly by the cells of the host.

Keywords: applications, genetically modified organisms, transgenic animals

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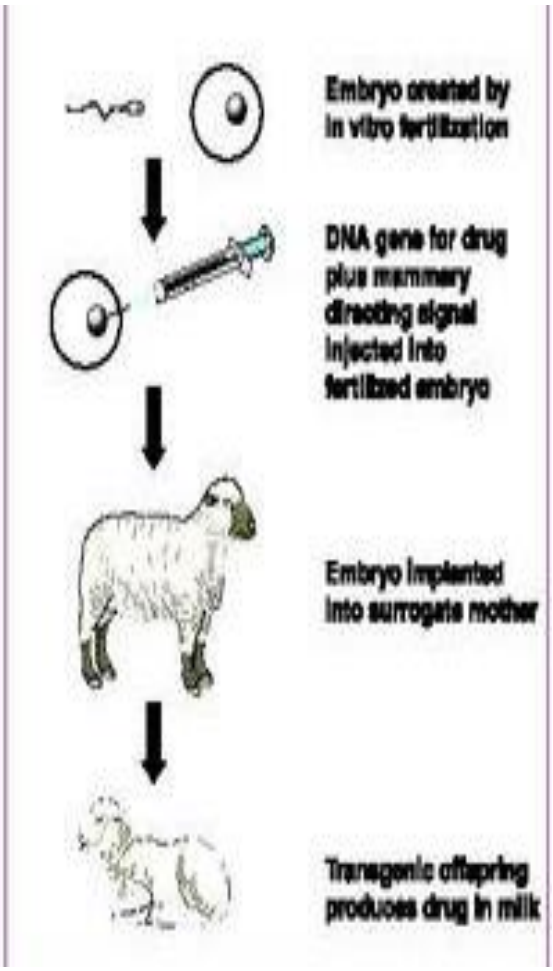
INTRODUCTION

Transgenic animals are animals (most commonly mice) that have had a foreign gene deliberately inserted into their genome. Such animals are most commonly created by the micro-injection of DNA into the pronuclei of a fertilised egg which is subsequently implanted into the oviduct of a pseudopregnant surrogate mother.[1-3] This results in the recipient animal giving birth to genetically modified offspring. The progeny are then bred with other transgenic offspring to establish a transgenic line. Transgenic animals can also be created by inserting DNA into embryonic stem cells which are then micro-injected into an embryo which has developed for five or six days after fertilisation, or infecting an embryo with viruses that carry a DNA of interest.[4-7] This final method is commonly used to manipulate a single gene, in most cases this involves removing or 'knocking out' a target gene. The end result is what is known as a ‘knockout’ animal.[2-5]

The process of genetically engineering animals is a slow, tedious, and expensive process. However, new technologies are making genetic modifications easier and more precise.



The first transgenic (genetically modified) animal was produced by injecting DNA into mouse embryos then implanting the embryos in female mice.

METHODS

The three principal methods used for the creation of transgenic animals are DNA microinjection, embryonic stem cell-mediated gene transfer and retrovirus-mediated gene transfer.[8-10]

1) **DNA microinjection**: This method involves the direct microinjection of a chosen gene construct (a single gene or a combination of genes) from another member of the same species or from a different species, into the pronucleus of a fertilized ovum.

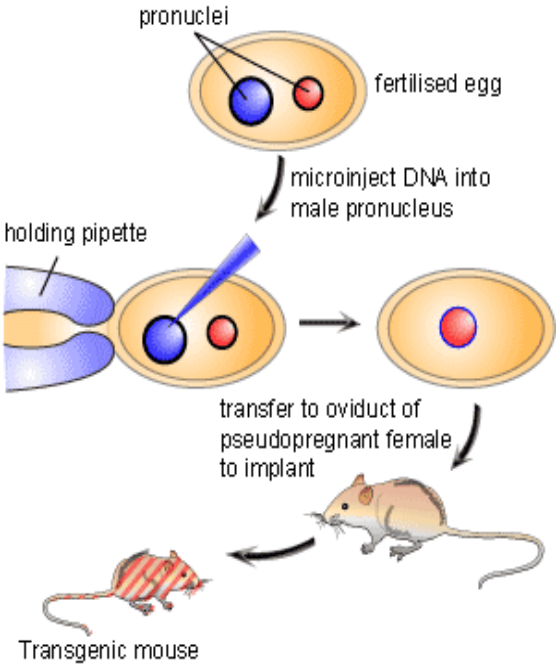
It is one of the first methods that proved to be effective in mammals (Gordon and Ruddle, 1981).

The introduced DNA may lead to the over- or under-expression of certain genes or to the expression of genes entirely new to the animal species.

The insertion of DNA is, however, a random process, and there is a high probability that the introduced gene will not insert itself into a site on the host DNA that will permit its expression.

The manipulated fertilized ovum is transferred into the oviduct of a recipient female, or foster mother that has been induced to act as a recipient by mating with a vasectomized male.

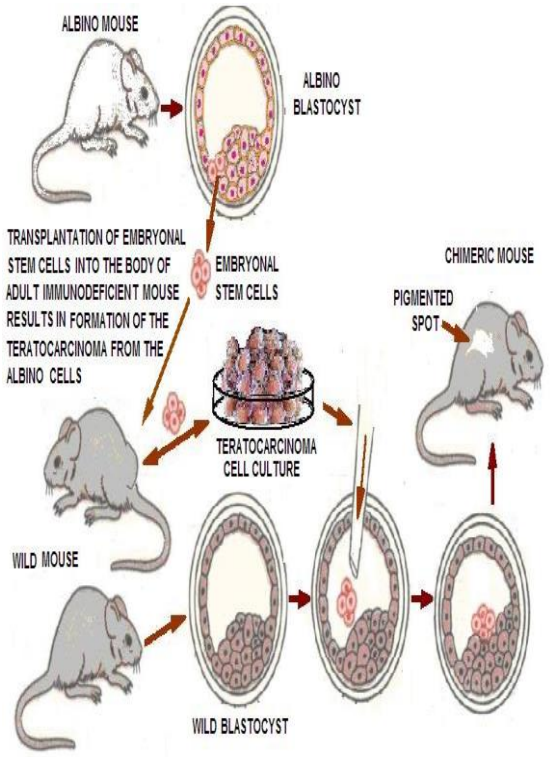
A major advantage of this method is its applicability to a wide variety of species.[8,9,11]



2) **Embryonic stem cell-mediated gene transfer:** This method involves prior insertion of the desired DNA sequence by homologous recombination into an in vitro culture of embryonic stem (ES) cells. Stem cells are undifferentiated cells that have the potential to differentiate into any type of cell (somatic and germ cells) and therefore to give rise to a complete organism. These cells are then incorporated into an embryo at the blastocyst stage of development. The result is a chimeric animal. ES cell-mediated gene transfer is the method of choice for gene inactivation, the so-called knock-out method.[12]

This technique is of particular importance for the study of the genetic control of developmental processes.

This technique works particularly well in mice. It has the advantage of allowing precise targeting of defined mutations in the gene via homologous recombination.



3) Retrovirus-mediated gene transfer: To increase the probability of expression, gene transfer is mediated by means of a carrier or vector, generally a virus or a plasmid. Retroviruses are commonly used as vectors to transfer genetic material into the cell, taking advantage of their ability to infect host cells in this way. Offspring derived from this method are chimeric, i.e., not all cells carry the retrovirus. Transmission of the transgene is possible only if the retrovirus integrates into some of the germ cells.[8,13,14]

For any of these techniques the success rate in terms of live birth of animals containing the transgene is extremely low. Providing that the genetic manipulation does not lead to abortion, the result is a first generation (F1) of animals that need to be tested for the expression of the transgene. Depending on the technique used, the F1 generation may result in chimeras. When the transgene has integrated into the germ cells, the so-called germ line chimeras are then inbred for 10 to 20 generations until homozygous transgenic animals are obtained and the transgene is present in every cell. At this stage embryos carrying the transgene can be frozen and stored for subsequent implantation.[15]

Genetically modified animals currently being developed can be placed into six different broad classes based on the intended purpose of the genetic modification:

- to research human diseases (for example, to develop animal models for these diseases);
- to produce industrial or consumer products (fibres for multiple uses);
- to produce products intended for human therapeutic use (pharmaceutical products or tissue for implantation);
- to enrich or enhance the animals' interactions with humans (hypo-allergenic pets);
- to enhance production or food quality traits (faster growing fish, pigs that digest food more efficiently);
- to improve animal health (disease resistance).

APPLICATIONS

- in medical research, transgenic animals are used to identify the functions of specific factors in complex homeostatic systems through over- or under-expression of a modified gene (the inserted transgene);[16]
- in toxicology: as responsive test animals (detection of toxicants);
- in mammalian developmental genetics;
- in molecular biology, the analysis of the regulation of gene expression makes use of the evaluation of a specific genetic change at the level of the whole animal;
- in the pharmaceutical industry, targeted production of pharmaceutical

proteins, drug production and product efficacy testing;

- in biotechnology: as producers of specific proteins;
- genetically engineered hormones to increase milk yield, meat production; genetic engineering of livestock and in aquaculture affecting modification of animal physiology and/or anatomy; cloning procedures to reproduce specific blood lines; [17]and
- developing animals specially created for use in xenografting.

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