ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 2(K), pp. 24593-24598, February, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

MODERN APPROACH OF TRANSGENIC ANIMALSAND THEIR APPLICATIONS IN PROSPECT OF BIOTECHNOLOGY- A REVIEW

Tariq A.L*

Department of Biotechnology, Government Degree College Beerwah-193411, Kashmir

DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1690

ARTICLE INFO

Article History:

Received 05th November, 2017
Received in revised form 21st December, 2017
Accepted 06th January, 2018
Published online 28th February, 2018

Key Words:

Transgenic animals, Transgenic methods, Benefits, Limitations, Ethics,

ABSTRACT

The transgenic animals are those animals in which the genetic arrangements are changed by insertion of foreign genes, the produced modified animals are called transgenic animals and process is known as transgenesis. The transgenic effectiveness and precise regulation of gene expression are the significant limiting factors in the production of transgenic animals. Transgenesis may involve whole organisms, rather than individual cells and there may be in vivo alteration of body function. There are many methods used for the production of transgenic animals such as DNA microinjection, embryonic stem cell-mediated gene transfer, gene knock out method, retrovirus-mediated gene transfer and Somatic Cell Nuclear Transfer. The transgenic animals have numerous applications in scientific biological models, animals improving Livestock, Research, Disease Models of Alzheimer's Mouse, Huntington's Mouse, Xeno-transplanters, Recombinant therapeutic proteins, Blood substitutes, Antibodies and transgenic animals, Carcass composition and growth enhancement, in the aquaculture industries, Production of pharmaceuticals in transgenic animals. Many technical methods have been used for the detection of transgenic products such as southern blotting technique, northern blotting, quantitative Real-Time reverse transcriptase polymerase chain reaction, western blotting, enzyme linked immunoabsorbent assays and green fluorescent protein. The transgenic animals show both negative and positive impacts in the modern era of the biological science.

INTRODUCTION

The first transgenic experiment was performed in mice (Gordon *et al*., 1980). After couple of years the progressive transgenic technology made pathway to execute transgenesis in other mammals viz rabbits, pigs, sheep and cattle (Hammer *et al*., 1985, Pursel *et al*., 1987, Rexroad *et al*., 1989, Roschlau *et al*., 1989). Modern development technology in animal gene transfer techniques are microinjection method, embryonic stem cell mediated gene transfer, retroviral vector method, sperm mediated gene transfer method, somatic cell nuclear transplantation method and nuclear transfer. These techniques can deliver a better stage to produce transgenic animals for research medical sciences, breeding new animal varieties; promote the livestock production and improvement of nutrients and volume in animal products (Lai *et al*., 2006; Wheeler *et al*., 2010).

PRODUCTION OF TRANSGENIC ANIMALS

There methods used for the production of transgenic animals are DNA microinjection, embryonic stem cell-mediated gene transfer, gene knock out method, retrovirus-mediated gene transfer and, Somatic Cell Nuclear Transfer.

DNA MICROINJECTION

DNA microinjection method was first developed successfully used for the first time in 1980 (Gordon *et al*., 1980). In this technique the young virgin female animal are allowed to superovulation by administration of follicle stimulating hormones and human chronic gonadotropin. The superovulated animal produces 30 to 35 eggs. The female animal are mated with males and scarified on the next day. The fertilized eggs are removed from the fallopian tubes. The micromanipulation is done by using the microinjection needle and holding a pipette. The DNA is injected into the male pronucleus of the fertilized egg and kept for overnight incubation to develop two cell stages. After incubation these cells are implanted microsurgically into the oviduct active foster mother. This results in the recipient animal giving birth to genetically modified offspring.

Corresponding author:* **Tariq A.L
Department of Biotechnology, Government Degree College Beerwah-193411, Kashmir

Benefits of DNA microinjection

This technique is very simple, inexpensive and applied to variety of species and more size of DNA can be inserted into recipient animal

Limitations of DNA microinjection

The success rate of producing transgenic animals is very low and inserted gene may not insert itself into a site on the host DNA that will permit its expression thus technique cannot be used into the cell at later development stage. The manipulations of oocytes/ embryos/ the disruption of parental DNA at the integration site of the gene construct can also influence the normal development of the transgenic animal.

Embryonic stem cells

Embryonic stem cells mediated gene transfer method based on findings of Gossler *et al*., (1986);Capecchi, (1994). The embryonic stem cells are pluripotent cells, establish in the inner cell mass of embryos at the blastocyst stage of progress. These cells have not yet differentiated and retain the ability to develop into any type of tissue during the embryonic and foetal development. DNA can be hosted into the embryonic stem cells in vitro. Embryonic stem cells grown at blastocyst stage, containing the desired DNA are incorporated into the host's embryo and then embryo implanted in the uterus of a surrogate mother, resulting in a chimeric animal.

Gene knock-out

The technique uses homologous recombination of DNA to permit particular targeting of DNA in embryonic stem cells. Uncertainty the homologous sequence to be introduced into the cell carries a mutation or a gene from another species, the new sequence will replace the specific targeted gene. This is the method of choice for gene inactivation therefore named as knock-out method, particular important for the study of the genetic control of developmental processes.

Benefits of embryonic stem cell technique

This technique is relatively efficient in homologous recombination in comparison to other animal cells. The gene targeting involves inducing the embryonic stem cell to remove one of its own genes and replace it with a modified version of the same gene and allows testing for transgenes at the early cell stage. This helps to detect precisely mutations in the gene via homologous recombination

Limitations of embryonic stem cell technique

The production, characterization and maintenance of pluripotent Embryonic stem cells lines very difficult.

Retrovirus-mediated gene transfer

Retrovirus-mediated gene transfer method based on findings of Jaenisch (1976). 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 because of their ability to infect host cells. A retrovirus is a virus that carries its genetic material in the form of RNA rather than DNA. The code in the viral RNA is reverse transcribed to produce DNA, which is then incorporated into the host cell. The offspring derived from this method are chimeric, i.e., not all cells carry the retrovirus or an organism consisting of tissues or parts of diverse genetic constitution. Transmission of the transgene is possible only if the retrovirus integrates into some of the germ cells.

Benefits of retroviral gene transfer method

This technique is simple, retroviruses are unable to infect human cells and small piece of DNA can be integrated with minimal disruption of host DNA. It readily integrates and passes through the germ lines allowing for their propagation into subsequent generations.

Limitations of retroviral gene transfer method

This is unstable to insert large size of the foreign DNA, risk of retroviral contamination in the products, losing of some regulatory sequences and some of the cells in the tissues of an organism receive the genetic change while the other cells without the desired addition

Transgenesis by Somatic Cell Nuclear Transfer

Somatic cell nuclear transfer (SCNT) involves the removal of a nucleus from a somatic cell, most likely a skin cell, and the implantation of that nucleus into an enucleated egg by microinjection. After the nucleus has been transferred, the egg is developed into a blastocyst, and implanted into a surrogate mother. The resulting offspring is genetically identical to the donor of the skin cell nucleus. This somatic cell nuclear transfer process was used to create the worlds first cloned mammal, Dolly the sheep (Li *et al*., 2009). With respect to transgenesis, the injected nucleus can also be engineered to be transgenic. The nucleus can be prescreened before the organism is developed to ensure its uptake of the transgene (Nuclear Transfer Technology). This method produces an incredible strain on a cell because it is completely reprogrammed, but the end result will be a 100% transgenic animal. This gives them the ability to create patient specific pluripotent cells, which could then be used in therapies or disease research (Lo and Parham, 2009; Lomax and Dewitt, 2013; Peraand Trounson, 2013). The potential applications and uses of SCNT technology like production of transgenic goat for production of quality milk and meat are discussed (Abdullah *et al*., 2011).

Sperm-mediated gene transfer

In the year 1971, the first evidence of mammalian spermatozoa being able to take up and transfer exogenous DNA was demonstrated by Bracket *et al*. (1971).Sperm cells are exposed to foreign DNA, which binds to the surface of sperm through specific protein-protein interactions. There is currently a general agreement that only two steps in the processes are well-established and fully reproducible: (i) the spontaneous interaction between sperm cells and foreign DNA molecules, and (ii) delivery of spermbound DNA to oocyte at fertilization. At present research has been carried out to determine the appropriate conditions to use when incubating DNA with sperm (Lavitrano *et al*., 2006). This method is now being hopefully perceived as avaluable technique for transgenic animal production. To increases the effectiveness of sperm uptake of DNAby various approaches are being taken. One is to attach there combinant DNA to the sperm head via an antibody amalgamated to the DNA (Chang *et al*., 2002).

Liposome's mediated gene transfer technology

Liposome is small bodies consisting of membrane-like lipid layers surrounding hydrous compartments. Cationic liposome was used to increase the transfection efficiency of sperm cells. Association of the cationic liposome/DNA complexes with sperm cells may allow DNA to be carried into oocytes at fertilization (Bachiller *et al*., 1991). However, sperm motility and fertilizing capability of spermatozoa was lower at the higher concentration of liposome as assessed by microscopic observation. The recent report that BSA, a major serum protein, could prevent the cellular uptake of liposome/DNA complexes in cells (He *et al*., 2009).

Benefits of Liposome's gene transfer

The high transgenic rates were reported more recently in mouse F11%) and F2 (37%) offspring via testis mediated gene transfer (TMGT) using liposome treated plasmid DNA

Limitation of Liposome's gene transfer

Furthermore, the existence of several different types of liposome makes it difficult to make general predictions as to the likelihood of success, in the absence of specific empirical studies.

Linker (receptor) based method

The process of linking the exogenous DNA to the head of the sperm was reported by using the monoclonal antibody (Chang *et al*., 2002). The antibody is a positively charged basic linker protein; it binds to negatively charged DNA via ionicinteractions. These interactions specifically bind exogenousDNA to sperm in a precise way. DNA can bind to polycations in a strong but noncovalent manner forming soluble complexes. DNA coupled with antibodies or antibody fragments offers the ability to internalize the complexes viareceptor-mediated endocytosis (Varga *et al*., 2000).

Restriction enzyme-mediated integration (REMI): Restriction enzyme-mediated integration involves the transformation of cells with a mixture of plasmid DNA, linearized with a restriction enzyme, along with a restriction enzyme that is capable of generating compatible cohesive ends in the genome. Restriction enzyme-mediated integration has proven useful for genetic screens and for placing genetic and molecular markers at particular points in the genome. Plasmids were linearized with a restriction enzyme to generate single-stranded cohesive ends and then introduced in vitro into decondensed sperm nuclei using restriction enzyme-mediated integration.

APPLICATIONS OF TRANSGENIC ANIMALS

Transgenic animals as Scientific-Biological Models

This is very wide-ranging group of transgenic animals used to understand particular protein functions in vivo and mechanisms is vital for developing any successful transgenic animal to benefit society. As more of the mechanisms underlying biological systems become clear, our ability to regulate these natural pathways increases dramatically. A transgenic monkey engineered to express jellyfish green fluorescent protein to study primate gene expression (Chan *et al*., 2001), a smart mouse that over-expresses the NR2B subunit of the glutamate receptor to learn faster and retain memories better than wild type mice (Tang *et al*., 1999) and knockout mice used to study the developmental effects of specific proteins.

Transgenic animals improving Livestock

Transgenic cattle produce more meat for human consumption and transgenic sheep that grow higher quality and quantity of wool. Transgenic fish shows increased growth rate, improved flesh color and increased disease resistance than the natural fish. Transgenic cows produce more milk or milk with less lactose or cholesterol and therapeutic proteins in their milk, which include hormones, antibodies, vaccines, growth factors and blood clotting factors. Therapeutic proteins are used to treat human diseases.

Transgenic animals in Research

In cancer research OncoMouce or Harvard mouce are carrying an oncogene significantly increases the mouse's susceptibility to cancer and thus makes the mouse suitable for cancer research. The transgenic animals are used for detection of toxicants, study of mammalian developmental genetics and molecular biology analysis of the regulation of gene expression and evaluation of a specific genetic change occurring in entire animal.

Transgenic animals in Disease Models

Disease models are produced to mimic specific aspects of a human disease, to aid our understanding of disease onset and to serve as a method of rapidly screening potential therapies on a model other than humans. In these models, human genes implanted animals to allow them to mimic certain aspects of a human disease. This creates nearly identical symptoms in the host animal that a human would exhibit, allowing scientists to test new medications and treatments without risking human lives. Both Alzheimer's disease and Huntington's disease have each been modeled in mice and other animals, paving the way for greater understanding of the molecular mechanisms underlying these devastating diseases.

Alzheimer's Mouse

Transgenic pigs used as an animal model of human diseases like Alzheimer's disease, cardiovascular diseases, cystic fibrosis, cancer and diabetes mellitus (Aigner *et al*., 2010).The vaccine has already moved into human clinical trials, where other disease model-inspired treatments have joined it. These models could lead to a greater understanding of what causes Alzheimer's disease and therefore, how to prevent. The Elan Pharmaceuticals created a vaccine capable of removing amyloid from brains (Schenk *et al*., 1999).

Huntington's Mouse

Huntington's disease is a neurodegenerative disorder classified as triplet repeat disorder because it is characterized by excessive repetition of 3 nucleotides CAG (Sathasivam *et al*., 1999). Normally, the Huntingtin gene (HTT) contains a segment within the coding region containing anywhere from 3-30 CAG trinucleotide repeats. Patients with Huntington's disease undergo an expansion of this section, resulting in 35-121 repeats, which lead to abnormal production of polyglutamine and nuclear aggregates (Gurney, 2000). The potential benefits of this transgenic application in monkeys will help scientists to accurately target Huntington's in humans.

Xenotransplanters

In order to transplant a donated organ, it must be histocompatible with the recipient. Complete compatibility can rarely be found, so immunosuppressive drugs are usually given to the transplant patient to prevent an immune response. Over the past 2 decades, the number of organ transplants conducted in the United States each year has increased dramatically (Yang and Sykes(2007). As the demand for viable organs rises, the supply from donors cannot keep up. In 1996, 20,000 transplant procedures were done in the US, yet approximately 50,000 persons were left awaiting organ donations at the end of that year (Pearson and Chapman, 1998). Thus in 2002, scientists created pigs in which the galactosyltransferase gene has been knocked out, so the organs do not have galactose on their surface (Lai *et al*., 2002).

Medical Applications

Milk-producing transgenic animals are especially useful for medicines. The milk of transgenic cows, sheep and goats contain nutritional supplements and pharmaceuticals products such as insulin, growth hormone and blood anti-clotting factors .Transgenic milk used for treatment of devastating diseases such as phenylketonuria and cystic fibrosis. Transgenic milk is a more nutritionally balanced product than natural milk and could be given to babies and the elder peoples with special nutritional and digestive requirements. A transgenic cow produces a substance to help human red cells grow. Human gene therapy involves adding a transgene to the genome of a person carrying defective copies of the gene. First recombinant protein of animal origin was human antithrombin produced by the transgenic goats was the used as a drug for the clinical use in humans (Moura *et al.,* 2011).

Recombinant therapeutic proteins

Several novel therapeutic proteins have been derived from the mammary gland of transgenic animals. Thetransgenic livestock serve as potential bioreactors for the production of valuable proteins like antithrombinIII, tissue plasminogen activator and antitrypsin. Glycosidase has beenproduced in the milk of transgenic rabbits, which is used inthe treatment of Pompes diseases (Vanden Hout *et al*., 2001).

Blood substitutes

Transgenic swine has been developed that produce functional hemoglobin which has the same oxygen binding capacity as that of normal human hemoglobin and that could be purified from porcine blood (D'Agnillo, and Chang 1988).

Antibodies and transgenic animals

Different varieties of monoclonal and recombinant antibodies were produced in transgenic goats and cattle (Meade *et al*., 1999; Grosse-Hovest *et al*., 2004).

Carcass composition and growth enhancement

Growth hormone and insulin like growth factors genes have been expressed at various levels in transgenic animals. Transgenic cattle and salmonfish have been produced that contains foreign geneconstructs. The introduction of chicken ski gene has caused muscular hypertrophy in case of pigs and cattle (Bowen *et al*., 1994). The acid meat gene or Rendement Napole gene has been involved in low processing yields of pork thereby affecting the quality of meat in pig. Other genes like GHreleasing factor, IGF binding proteins also play a majorrole in the modification of growth.

Transgenics in the aquaculture industries

Fish and shellfish tend to be highly fecund, producing a large quantity of gametes. The first successful gene transfer experiment in fish occurred in 1985 in China. ADNA was createdby using the human growth hormone under control of the mouse metallothionein promoter then injected into the germinal disc of an early-stage goldfish Carassius auratus embryo while other groups in Norway themicroinjection procedures preferred. Brem *et al*.(1988) was the first to produce a commercially important fish Nile tilapia, Oreochromis niloticus bearing a human growth hormone transgene, again under the control of the mouse metallothionein promoter. Recently, in Drosophila, zebra fish and rats direct embryo injection of engineered zinc-finger nuclease (ZFN) encoding mRNA/DNA has been used to generate heritable knockout mutations at specific loci engineered a line of Japanese abalone Haliotis divorsicolor suportexta which expresses Chinook salmon growth hormone(Carroll 2008; Geurts *et al*., 2009;Tsai *et al*. 2000).

Production of pharmaceuticals in transgenic animals

In January 2004, GTC Biotherapeutics submitted a market authorization application to the European Medicines Agency for ATryn®, a recombinant form of human antithrombin produced in the milk of transgenic goats. This was the first product derived from a transgenic animal to be submitted for formal regulatory approval in Europe or the USA. Milk is presently the most mature system to produce recombinant proteins fromtransgenic organisms. The production of therapeutic proteins from transgenic animals usually involves their expression from mammary gland specific promoters to drive secretion of the transgene into milk. Blood, egg white, seminal plasma and urine are other theoretically possible systems, but all have drawbacks. Biologically activeproteins in blood may alter the health of the animals(Houdebine and Louis-Marie, 2009).

ETHICS OF TRANSGENIC TECHNOLOGY

There are care concerns if new processes and products fail to gain consumer acceptance because of moral concerns. Genetically altering the cells of an animal, thus side effects could result from altering genes. Animal suffering affected by the expression of transgenes inducing neurodegenerative or tumor diseases. The foreign genes affect the host and yield a lot of threats tospecies diversity and ecological balance (Miao, 2013).

METHODS FOR TRANSGENE DETECTION

Many methods for the detection of a transgene or products have been developed. Southern blotting is a technique that detects a specific DNA sequence in a complex mixture of DNA. So for example, this technique can detect the presence and copy number of a transgene inserted in the genome of an animal. Northern blotting is another technique used to determine the expression of a transgene. The quantitative Real-Time Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR)is another very effective method for detecting transgene mRNA. Western blotting in this case cellular protein is electrophoresed.

The membrane is hybridized to an antibody against the transprotein, and a signal indicates the presence of the transprotein. Enzyme Linked Immunoabsorbent Assays (ELISAs) also screen for the production of a transprotein.Green Fluorescent Protein (GFP) is the golden child reporter for expression. GFP can be fused with the transgene, so when the transgene is expressed so is GFP.

Common Curb of Transgenic animals

- The transgenic animal creation is a challenging, prolonged and costly procedure.
- Transgenic technique is not faultless with low survival rates of transgenic animals.
- It usually leads to functional disorders, mutagenesis and breeding problems.
- This technique is undeveloped stage which means it requires further studies.
- The joining efficiency of external genes at the determined site is low and unstable.
- The effect of the intrinsic gene creating abnormalities in animals is unclear.

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How to cite this article:

Tariq A.L.2018, Modern Approach of Transgenic Animalsand Their Applications In Prospect of Biotechnology- A Review. *Int J Recent Sci Res.* 9(2), pp. 24593-24598. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1690

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