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Potential Applications of Genetic Engineered (Transgenic) Animals in Medical Biotechnology for Human Healthcare

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Abstract

Genetic engineering is a thoughtful modification process of animal's genome using recombinant-DNA technology for generating transgenic animals. Transgenic animals are genetically altered animals having the desired traits. Genetically engineered animals have a significant medical application for human healthcare by making the transgenic animal models of human disease for studying of gene function; manufacturing of transplant organs; and production of safe and complex recombinant human protein-based drug, blood and vaccine products with higher expression and low cost for the treatment and prevention of human disease. The first two commercially accessible therapeutic agents isolated from the milk of transgenic animals are C1 esterase inhibitor (Ruconest®) and anti-thrombin III (ATryn®), which encourages that a novel recombinant protein will be created and become available for practical use in the near future. So that, transgenic animals will provide a pharmacological revolution for discovery and development of drugs, clinical trials of xeno-transplant human organs or xenotransplantation that will be the unchoice option to diminish the growing gap between demand and severe shortage of appropriate organs for recipient human patients with serious organ failure. In this context, the principal objective of this review paper was to assessed the current challenges and future perspectives of transgenic animals in medical biotechnology for human healthcare, and also address the question: What potential benefits and risks are in the creation of transgenic animals in the real world?

Keywords: Transgenic • Genetic Engineering • Recombinant Protein • Xenotransplantation

Introduction

Genetic engineering technology has been experienced for studying of gene functional properties, and presently it's one of the fastest growing areas in the field of biotechnology for creating genetically engineered animals. It is based on a process that integrates the exogenous (i.e. foreign genes) from either similar or different species into the recipient animal's genome. These transferred foreign genes (i.e. transgenes) are inherited and expressed by their next generation or offspring [1,2], the whole procedure for creating the transgenic animal is called transgenesis. Genetically engineered animals are also described as transgenic, genetically modified, genetically altered, genetically manipulated, and biotechnology-derived animals that can be produced by a deliberate modification or altering of their endogenous genomic DNA using recombinant DNA technology, against spontaneous mutation [3-5]. Furthermore, for producing transgenic animals, scientists have been commonly used several methods through recombinant DNA technology with different efficiencies such as pronuclear DNA micro-injection, Embryonic Stem (ES) cells-mediated, retrovirus-mediated gene transfer, sperm-mediated gene transfer, and Somatic Cell Nuclear Transfer (SCNT), which are primarily needed to transfer the foreign DNA sequence into the recipient organism genome, that has been genetically altered to have specific desired features it would not have [1,6,7].

After the first ever recombinant DNA technology laboratory experiment that performed and created transgenic mouse in 1973 [8], several transgenic animals such as transgenic goats, rabbits, pigs, sheep, chickens and cattle have been created. Besides the noticeable agricultural and industrial applications, the creation of genetic engineered animals is crucial in a wide range of medical applications such as for transgenic models of human disease in biological and medical research with the concern of finding solutions or investigations for human disease and *in vivo* studying of gene function, expression and its regulation; for the identification and validation of new therapeutic targets; serve as bioreactors for biopharmaceutical production of recombinant human proteins secreted in their mature systems with considerably larger amounts and at much minima costs than proteins produced in normal synthesis process that protect organisms/humans against several neuro-generative disease and genetic disorders; and production of transgenic xenograft organs by xenotransplantation [9-12]. So that, genetic engineering technology will be one of the most vital areas of biotechnology to the near future. Currently, most of the medicines are synthetically produced and will continue with great quality and quantity in future. Even though it is an interesting field with a wide range of applications; it has controversies, doubts, challenges, and which needs further investigation to advance the technology [10,13,14]. In the above context, the main objective of this review paper was to assess the current challenges and future prospects of transgenic animals and their potential applications in medical biotechnology for human healthcare system.

Literature Review

Historical overview of genetic engineering

Since the 1970s, the direct transfer of DNA has been performed from one organism to another organism and this process is called as genetic engineering technology. The idea of genetic engineering is the direct manipulation or modification of an organism's genome using certain biotechnological techniques such as recombinant DNA technology through human interventions to get their desired traits as they wanted. The first genetically modified animals was transgenic mouse produced by Rudolf Jahnish in 1973 using DNA microinjection into the male pronuclear of zygotes [8] followed the transgenic sheep (i.e. dolly) in 1996 by Scottish scientists at the Rollin Institute in Edinburgh Scotland using Somatic Cell Nuclear Transfer Technique (SCNT)

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using cells taken directly from early embryonic nuclei [15], and later several transgenic animals including transgenic rabbits, mice, cat, goats, pigs, sheep and cattle have been created through effective DNA recombinant techniques by the introduction of a foreign DNA or transgenes into the host animal. This incorporation of foreign DNA should exclude any mutagenesis.

Methods to generate transgenic animals

The creation of genetic engineered/transgenic animals can be operated by the following several DNA recombinant based techniques with different efficiencies, which are;

- Pronuclear DNA microinjection; is a successful method for producing genetically engineered/transgenic animals until now. It is simply a process of transferring of foreign DNA containing the genes of interest directly from donor of the same or different species into the pronucleus of zygotes or fertilized ovum (i.e. because of its large size the male pronuclei of embryos are excellent and admirable) on a single cell followed by transfer of embryos into the oviduct of a foster recipient female, or a pseudo pregnant surrogate mother [3,16].
- As the transgene enters the nucleus, linear DNA has been integrating into the genome of cell lines that transcriptionally inactive gene-poor region. In a single cell embryo, up to 200 to 500 copies of the injected gene construct could integrate into one genomic site [3]. The early integration of the inserted transgenes into the host embryonic genome is important to ensure that transgenic DNA in all cells of the host. However, this process is a random incorporation, and has a high possibility that the introduced transgene will not insert itself into the host DNA sites that will permit its gene expression.
- The expression level of the integrated transgene has been examined by the original transgenic animals and their offspring, in order to obtain females producing recombinant DNA proteins in milk from the original male organisms [17]. Primarily, this method was tested on mice and now applicable to produce a wide variety of species including transgenic mice, rabbits and pigs, but ordinarily not used due to its tediousness and the limited number of cells that can be held (Figure 1).

Ethical issues in transgenic technology

Nowadays, globally the people have asked the regulatory challenges and ethical issues in transgenic animals and their products.

The first concern area is the animal welfare and the safety concern or life span of an individual transgenic animal. Even though humans may benefit from the transgenic animals, the animal itself may not benefit [2]. Ethical concerns related to animal welfare often involves the sacrifice during surgical procedures for the creation of new transgenic animals, for instance the oocyte and blastocyst donor females may be induced to super-ovulate and/or subcutaneous injection of hormones and genetically engineered embryos may be surgically implanted to the oviduct of recipient women.

Transgenic animals often exhibit variable or uncontrolled expression of the inserted transgenes inducing tumors or neurodegenerative diseases, resulting in severe health problems, illness and death. This unnecessary suffering of the animals could result from modifying or altering of an animal's genome [18,19]. This issue needs to be considered by all stakeholders, that ensuring all concerning bodies are aware of the ethical issues at stake and can make a valid contribution to the current debate regarding on the formation and use of transgenic animals. Here, biotechnologists can play a central role in carrying out such monitoring, especially in the research setting in order to follow the animal welfare when new transgenic animal strains are being created.

A second area of concern is the transgenic products fail to gain public acceptance including consumers due to moral concerns, the boundary constructed between what is considered 'natural' and 'unnatural'. The 'unnatural of an individual' crossing of species boundaries becomes problematic when higher life forms are involved [14]. Some scientists, governments and religious organizations oppose the future possibility of fabricating transplantable organs and recombinant human protein-based drugs from transgenic animals. The genetic engineering of animals may also put their moral principles at risk.

Another greatest concern is the potential risk of xenotransplantation that an infectious agent such as Porcine Endogenous Retrovirus (PERV) may be transferred with the transgenic organ to the recipient and then from recipient to public members, may be leading to epidemic. However, there is no current evidence that will be pathogenic. Using GE-based biotechnology, it may be

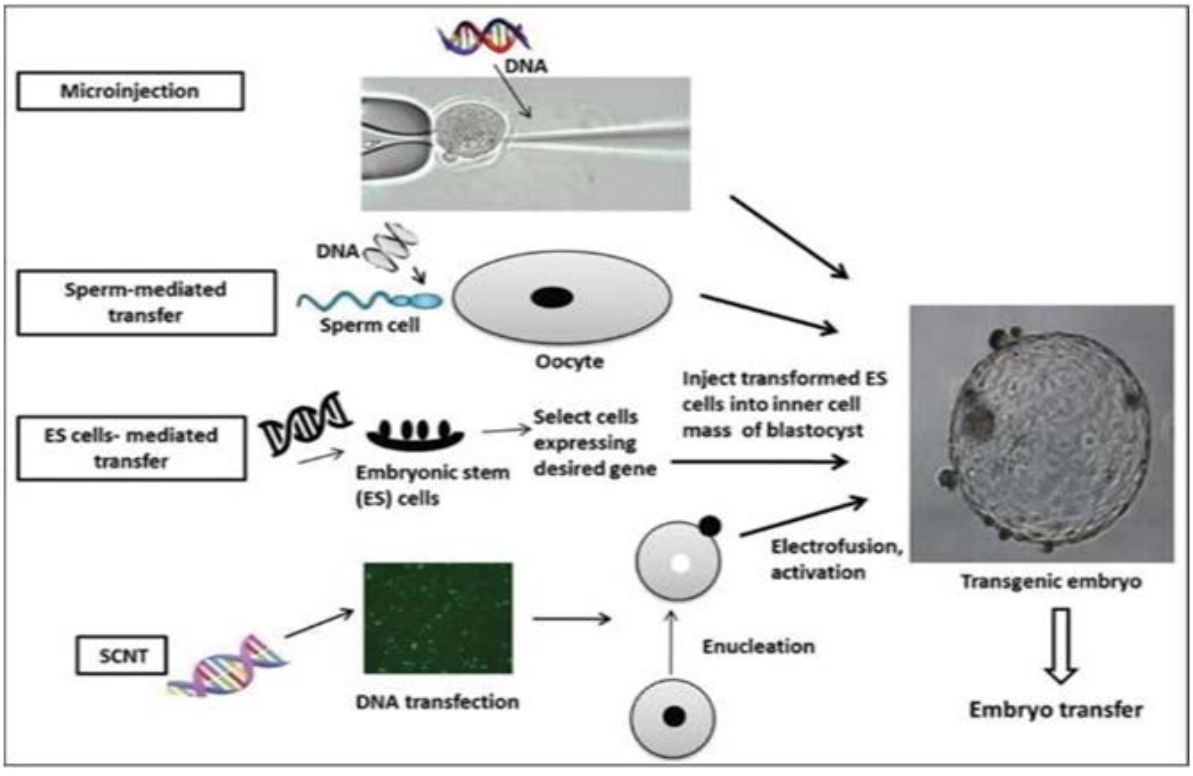

Figure 1. Methods for the creation of transgenic animals.

possible to generate pigs that are free of PERV virus in the near future through addressing deliberately in a scientific manner, in order to fulfill the increasing demand for transplantable organs with minimal risk.

Scientists have suggested that national regulatory authorities should be reconsidering guidelines on the care of animals used in research and better design of informative clinical trials of xenotransplantation in many countries, but not universally accepted and it is unclear which regulatory agencies consider current evidence to be sufficient for moving forward with clinical xenotransplantation [9,10]. It is likely that public acceptance of genetically engineered animal products will be an important step in determining when and what types of genetically engineered animals will appear on the commercial market. Nevertheless, the use of transgenic animals has the capacity to overcome the current and future needs in medicine and is now a necessity rather than a matter of choice that could alleviate the current shortage of human organs for transplantation chimeras by using various biotechnological techniques. Few perhaps would disagree that the technology may be forging ahead faster than consideration of the ethical concerns it raises. There is no doubt in the future, global public especially consumers and/or transplantable organ waiters will accept and gain this exciting benefit in areas of GE-based biotechnology. The current delay of a transplantable organ clinical trial because of the potential risk of logically unknown microorganisms would be illogical and unreasonable, since there will always be an 'unknown' to any scientific endeavor.

Discussion

Genetic engineering is a 21st century discipline for producing genetic engineered/transgenic animals by introducing the exogeneous foreign DNA sequence into animals' genome by using recombinant DNA technology for humankind. The techniques for obtaining transgenic animals of medical interest are still inefficient with low success rates. New and exciting techniques being developed will continue to enlarge the usefulness of the transgenic recombinant DNA technology.

Nowadays, the need for public health is urgent issue. Accordingly, transgenic animals will play a significant contribution to human healthcare benefits in the biomedical area, through the production of novel and valuable pharmaceutical recombinant human proteins from mostly their milk for treatment of human diseases and as a source of xenografts [5]. However, considerable effort and time are a limiting factor to generate the transgenic animal, and also consideration should be given to ethical concern regarding animal welfare, human health and public or consumer acceptance. In coming years, high number production of transgenic animals will be needed and are promising not only safer, lower-cost protein-based drugs in medical practice to minimize the attrition rate in clinical trials, but also a paradigm shift from a high quantity model to a high quality drug making the transition from discovery into development and meet the growing global transplantable organ demand that can provide substantial perfections over today's medicines in public health benefits. However, the number of companies involved in the production of pharmaceutical recombinant human proteins and xenograft is expected to be increase in the near future.

Transgenic mouse disease model is the one currently dominated model available for use in biomedical research, but the paradigm shifting will be difficult with only this [19]. It is not only important to note that the development of new gold standards large transgenic animal models of human disease will be utilized increasingly in the near future, but also will need to gain public acceptance. The most important priority of working with transgenic animals is that the public acceptance of the recombinant technology for confident purchasing and using the transgenic products. So that, the global science-based regulatory process that results in approvals will enhance consumer confidence and acceptance of products from genetic engineered animals, and development of universal harmonization of the regulation process [20]. The human health benefits will now be realized based on the science-based regulatory framework for governing how these animals will provide biomedical consumer benefits, but the challenges ahead are not simple.

Currently, high number transgenic pigs are already exist, most of which are being tested in preclinical pig-to-NHP xenotransplantation models which is a key step toward further clinical study [10]. With recent achievements of the xenotransplantation technology and gaining of experience in preclinical research, the first-in-human clinical trial may be possible and will hold great promise in the near future, providing a solution to help the thousands of people who may die waiting for a severe shortage of human transplant organ. New gene-editing technologies enable the production of multiple transgenic pigs in shorter periods of time and greater efficiency with different immunosuppressive therapies for the effective transplantation of organs. The greatest potential risk in xenotransplantation will benefit individuals while possibly putting the population at risk of infection. However, if the technology leads to great benefits to individuals, we have a moral obligation to accept a small risk to the community with taking all possible steps to minimize that risk. We should be reasonable in relation to the potential benefit to the patient side.

Conclusions

Even though, transgenic animals have a wide range of medical applications, many challenges from the animal welfare, socio-cultural and religious obstacles or public acceptance and technical inefficiency are headache for the recombinant technology. Therefore; the following recommendations should be forwarded to overcome the above challenges:

- Much systematic and organized works to be done on generating public awareness to avoid the socio-cultural and religious/public acceptance problems, and to keep moral values of transgenic animals.
- Biotechnologists should acquire basic knowledge, further investigation and research to improve the recombinant techniques and increase their successes rate.
- Both governmental and non-governmental organizations should develop international harmonized guidelines energetic to create transgenic animals.
- The number of companies involved in the production of recombinant pharmaceutical recombinant human proteins and xenografts should be increase. This will result from the improvement of the different animal systems.

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Competing interests

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