Knockout mouse

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1. Introduction

Generally, DNA was first transferred by design into an organism and expressed as protein, therefore the potential of the tool that was being discovered must be found quickly by the scientist. Early experiments were limited to bacteria and viruses, but soon after the field of experiments were enlarged to those on animals and plants. (E. Hill, 2002).

This topic, “ knockout mouse” relates to the field of genetic engineering which further delves into a more specific technique called transgenic technology. “ Knockoutscience. com”(2009) analyses that transgenic technology refers to the alteration of a certain genomic DNA of an organism in genetic engineering. As the result, both offspring of a transgenic organism and the parents (homozygous) will share the same genotype. The most common type of transgenic organism used in research is the knockout mouse, thoughknockout rats andknockout rabbits have also been developed.

A knockout mouse defines a mouse which is being genetically engineered by turning off one or more genes through a process called gene knockout. “ Genome. gov “ also explains that a knockout mouse is a laboratory mouse in which researchers have inactivated, an existing gene by replacing it or disrupting it with an simulated piece of DNA. The loss of gene activity often causes changes in a mouse’s phenotype, which includes appearance, activities and other observable physical and biochemical characters.

“ Knockoutscience. com” (2009) also elucidates that it has become routine to develop knockout mice with disruptions in specific genes. By observing the

resulting phenotype, scientists are able to view the effects of this gene disruption from these knockout mice. It is true to say that the phenotype is a direct result of the gene knockout and can offer evidences as to the biological role of the gene, but rarely the phenotype can also be the result of compensatory or indirect effects of the gene knockout. Sometimes the result obtained in a phenotype can be completely unrelated to the disrupted gene. Additionally, some gene knockouts create alethal phenotypewhere the organism fails to develop in utero, making in vivo studies exceedingly difficult.

It was claimed that this technique may help to solve dopamine-related neurological illnesses.(Carol A. T, 1996) The technique allows transgenic animals that lack of a certain gene or its associated protein product to grow. In experiments with mice, researchers were able to knockout the animals' dopamine transporters, causing the mice to behave as if they had been given huge doses of cocaine or amphetamine.

Walinski. H(2009) states that knockout mice have different way of uses. First, the specific functions of particular genes can be tested and the regulation of these particular genes can be observed. The effects of a particular gene can be determined by examining what is happening in anin vivo model, we are able to determine the effects a particular gene may have. These effects would be impossible to observe in a culture dish.

Another useful application of knockout technology is in biomedical research and drug development. Knockout mouse can be used to study the evolution of thousands of genetically based diseases at the molecular level in order to

seek for the best medications that act on that gene. For Example, Lili. X and Asok. C (2005) both agree that Duffy positive and Duffy knockout mice have revealed both human malaria parasite Plasmodium vivax and mouse malaria parasite Plasmodium yoelii by using parasite invasion. Furthermore, the knockout technology may lead to the discovery of the next generation of blockbuster therapies for curing numerous diseases based on novel targets from the human genome.

2. Background Genetics

Timeline for the key events in the history of knockout mouse

1900 – Japanese fancy mice became mutant resources for mouse genetics.

1915- The first verterbrate linkage (mapping) was discovered between albino (c) and pink-eyed dilution (p) loci in the mouse.

1923- Discovery of X-ray induced mutations in mouse before the phenomenon was confirmed in fruit-flies.

1980- Specific-locus tests were conducted extensively in the mouse with various chemical mutagens, including N-ethyl-N-nitrosourea (ENU).

1981-1991- knockout mice are established.

1981- The first embryo stem (ES) cell was identified in the mouse. Martin Evans and Matt Kaufman in Cambridge, U. K., isolate mouse embryonic stem cells, which can develop into the full range of tissues.

1982-Transgenic mouse technology was established through the generation of the “ giant mouse” mutant.

1985- Introduction of the Cre-loxP system by Brian Sauer act as temporal control of transgenic gene expression.

1987- Mario Capecchi's team at the University of Utah describes a method for making knockout mice, as does Oliver Smithies's group at the University of Wisconsin.

1989- First knockout mouse was made by combining ES cell and gene-targeting technologies.

2007- International Knockout Mouse Consortium was organized and the Banbury II meeting was held in Brussels, Belgium. Nobel Prize for Physiology and Medicine was awarded for the development of mouse knockout techonologies.

3. Genetic Technique

There are several method to produce knockout mouse, such as gene deletion, homologous recombination method, pronuclear microinjection and gene targeting. However, only gene targeting will be mentioned herein.

Gene Targeting is the elimination or alteration of a gene's function. One of the advantages of gene targeting is a mutant allele can be mended by substituting a wild-type allele over the mutant one in its normal chromosomal location, and such technique known as gene replacement. In this way, both position effect and the DNA rearrangements associated with ectopic insertion can be prevented, as a single replication of the gene is inserted in its normal chromosomal environmental. (Griffiths. A and Susan R. Wessler, etc, 2008).

4. Social Issues

Recently, the evaluation of animal and human welfare as it may be affected by biotechnology is becoming a hot issue. The lack of an conscience and the information of the processes involved is one of the most important fact. (Marie. B, 1997)

Marie. B (1997) also states that the moral evaluation process is complicated by the fact that many techniques and developments in biotechnology are appropriate for patent. Some of the biotechnologists are reluctant to reveal appropriate information is understandable.

Therefore, education concerning transgenic animal care and utilize is indeed very importance, involving the careful consideration of the reasons for manipulating the genome of any organism as genetic engineering is a dangerous and sensitive social issue. (Marie. B, 1997)

Pros and Cons of Knockout Mouse

Advantages

Disadvantages

Provides important clues about what that gene normally does because human share many genes with mice. (Genome. gov, 2009)

Limitation of the utility of knockout mice as models of human disease. (Walinski. H, 2004)

Gives better understanding and observation of the characteristics of knockout mice. (Genome. gov, 2009)

The lack of adult mice limits studies to embryonic development and makes it more difficult to determine a gene’s function in relation to human health. (Genome. gov, 2009)

Gives information that can be used to better understand how a similar gene may cause or contribute disease in human. (Genome, 2009)

The gene that being examined might serve a different function in adults than in developing embryos, giving a false information. (Genome, 2009)

Useful in studying and modeling different kinds of cancer, obesity, heart disease, diabetes, arthritis, substance abuse, anxiety, aging and Parkinson disease.

Fails to produce an observable change in a mouse or may even produce a different characteristics from those observed in humans in which the same gene is inactivated. (Genome. gov, 2009) Offers a biological context in which drugs and other therapies can be developed and tested.

Producing custom knockout mice is very expensive. It can be from 3000 to as much as 30, 000 (Walinski. H, 2004)

Useful in drug development and helps to discover the next generation of blockbuster therapies for curing numerous diseases based on novel targets from the humane genome. (Walinski. H, 2004)

The cost of equipping and maintaining such a facility is usually very high. (Walinski. H, 2009)

5. 0: Conclusion

In conclusion, it is clear that knockout mouse offer a lot of benefits for us. Therefore, a thorough discussion of biotechnology issues is needed, as concurrence must be practiced as to protect transgenic animals. The field of transgenic animal biotechnology is likely to rise as the techniques develop further and will link to more applications by using many more animal species. Thus, it is important that the welfare and ethical concerns must continue to evolve. (Marie. B, 1997) In short, technology essentials together with thoughtful ethical decision-making are equally important to maintain the balance of living creatures.

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