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Editorial

Toward A Transgenic Dog as a Human Disease Model

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Introduction

Even though transgenic mouse models have been widely used as disease models in biomedical research, organs size, genetic and physiological differences between human and rodents have put limitations on applying the rodents study to the human [1,2]. In contrary, the dog is a relevant model for human diseases and therapeutics because it is more similar to humans than mice in body size, longevity, behavior and physiology. In addition, dogs have been considered as one of the most invaluable animals in the research field of drug discovery [3,4]. The dog nucleotide sequences are highly conserved with human sequences in cancer candidate genes owing dogs to be used for translational clinical trials for new drug discovery [5-8].

Above all, the dog has emerged as a powerful genetic tool for study human disease. Of the nearly 617 known hereditary diseases described in the dog, more than the half (328) have a counterpart in the human (e.g. Alzheimer disease, cardiomyopathy, muscular dystrophy or prostate cancer; see http://omia.angis.org.au/home/ accessed June 2013). Moreover, dogs are exposed to the same environmental factors as humans, which is of great importance because numerous common inherited human diseases (e.g. asthma, diabetes, epilepsy and various types of cancer) involve complex interactions between genes and the environment [9,10]. Recently, dog genome sequencing [11,12] makes the dog as a model for the study of the genetic basis of diseases and the mechanism of disease occurring. Moreover, dog offers unique evolutionary replicates than can be mined by molecular tools to undercover the genetic basis on phenotypic traits [13].

For profound understanding of human disease, transgenic animals which express or delete a target gene are more effective than the natural model animal. The most difficult challenge in generating transgenic animal models in large animals has been in obtaining viable germ cells and Embryonic Stem Cells (ESCs). However, recent successes in creating transgenic animals [14-19] using Somatic Cell Nuclear Transfer (SCNT) technique which targeted modification of the genome of the donor cells gave promise to future generation of genetically modified models in large animal including dogs [20,21].

In dog, the first cloned puppy (a male Afghan puppy named Snuppy) was born in 2005 via SCNT using adult fibroblasts [22]. From that birth onwards, our group generated lots of canine clones from a variety of donor cells: male and female, adult and fetal fibroblasts, young and aged donor dogs, small and large breeds, and even from genetically modified cells [20,21, 23-29]. Recently, transgenic puppies were born following nuclear transfer from fetal canine fibroblasts transfected with the Red Fluorescent Protein (RFP) gene [20] or Green Fluorescent Protein (GFP) conditionally expressed by doxycyclin administration (Tet-on) [21]. The transgenic cloned animals of having identical genomic background are extremely valuable for biomedical research, in which the transgenic SCNT technique is worth enough.

Nevertheless, those who interested in obtaining canine clones and expect a perfect phenotypic copy should be made aware of the diversity of phenotypes that may occur in animals obtained from donor cells with the same genotype. Marked differences in anatomy, coat characteristics, behavior and performance have been reported among animals obtained from the same cellular source in cattle, horses, cats and pigs [30, 31].

Stem cells derived from cloned and TG dogs and its differentiation capabilities

In the last decade, knowledge of mesenchymal stem cells (MSCs) has evolved rapidly; their immunomodulatory properties and paracrine interactions with specific cell types in damaged tissues and promising results in some clinical applications have made these cells an attractive option for the treatment of certain diseases. Canine Adipose-Derived Mesenchymal Stem Cells (cASCs) represent an easy and effective source of stem cells for dogs. In our laboratory, we isolated the cASCs from both normal and transgenic cloned dogs and effectively showed an osteogenic, adipogenic, myogenic, neurogenic and chondrogenic differentiation capabilities [32]. In canine SCNT, cloned dogs were generated by nuclear transfer using cASC [32], these outcomes suggest that cASCs could be a useful tool as nuclear donor cells for SCNT as well as clinical applications.

Current progress in generating disease model dog

On the basis of the previous successful cloning of RFP or GFP transgenic dogs, we are now producing transgenic dogs for application to the neuronal degenerative Alzheimer's disease (AD). Although the pathogenesis of AD has been a subject of intensive research for the last several decades worldwide, treatment or preventive measures have so far produced no breakthrough because of the lack of appropriate AD models. Mouse models have a limitation for AD research because the irreconcilable species gap between rodents and humans has impeded the research itself as well as the translation of findings from rodent studies to human cases. As an alternative to the mouse model, a preliminary study was conducted to produce a dog that expresses a neuron-specific transgene in brain by SCNT. As result, the transgenic dog expressing the RFP transgene in neural cells of the brain under human synapsin 1 promoter was generated [33], indicating that the human synapsin promoter is functional. Currently, we are performing a study to produce a brain neural-specific AD related-transgene expressing dog, which will be a pivotal animal model for neurodegenerative AD.

Conclusion

Dogs have organ sizes comparable to those of humans, generally cohabitate with human beings, receive exceptional medical care and nearly similar genetics; all makes the dog regarded not only as a pet, but also in some way as the modern mouse, which creates a definite need for generating transgenic dogs as human disease models.

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