Pig and mouse transgenesis for animal disease models

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ABSTRACT

The PhD dissertation was carried out at Institute of Human Genetics, Faculty of Health Sciences, University of Aarhus, and Department of Genetics and Biotechnology, Danish Institute of Agricultural Sciences.

Transgenic animals can be used to study the pathogenesis of human diseases. Until now micee have been the most widely used species in such animal models. However, the pig has come into consideration due to its genetic, anatomical and physiological similarity to man.

The aim of this PhD dissertation was to develop techniques for the production of transgenic pigs and mice as models for human genetic diseases. The thesis has two major projects: 1) Development of a technique for production of transgenic pigs by a somatic cell nuclear transfer technique, *handmade cloning*, and 2) Development of a mouse model for studies on mitochondrial quality control.

In Project 1, the *handmade cloning* technique was developed for production of transgenic pig embryos with expression of green fluorescence protein as a marker gene. The suitability of the technique has been investigated by transfer of cloned pig embryos to recipient sows (work in progress). The perspectives of the *handmade cloning* technique are production of genetically modified pigs as models for various human genetic diseases, as well as analysis of transgenes in different cellular lineages differentiating from cloned embryos. At present the development of models for Alzheimer's disease, atherosclerosis, mitochondrial stress disorders and psoriasis, are in progress.

In Project 2, transgenic mice containing variants of the human short chain Acyl-CoA dehydrogenase (SCAD) gene were produced. The transgenic mice had expression of the variant genes at the RNA level but not at the protein level, and the result indicate that SCAD folding variants are degraded extremely rapidly by the mouse brain mitochondrial protein quality control system. This is in agreement with the fact that no disease phenotype developed in the transgenic mice. The indicated amazing efficiency of the mouse protein quality control system in the degradation of SCAD folding variants should be further substantiated and investigated, since it might save the animal from potential dominant negative disease causing effects.