Stem Cell Research in Minipigs: a Potential Model for Mimicking Human Disease

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Stem cell research has developed into a huge research topic that has grown and widened significantly in the past few years. This is evident by the expansion of stem cell research conferences and increasing numbers of delegates, as well as an increase in the number of scientific publications. This expansion is largely due to promising developments in the transplantation of adult stem cells for disease treatment, and a relatively new breakthrough: the production of a new type of stem cell, the induced pluripotent stem cell. These latter cells are stem cells that look and behave very similarly to embryonic stem cells. The advantage of induced pluripotent stem cells is that they do not come from an early embryo. In fact, they can be made from almost any type of adult cell in the body. These cells are "reprogrammed" into embryonic stem cells by introducing a number of key genes into the cells, which changes their cell identity and turns them into an embryonic stem cell. These cells overcome the ethical barrier of embryonic stem cells whereby an embryo must be sacrificed in order to produce them. This remains a controversial issue in many countries around the world and has now been apparently and potentially resolved.

Why are embryonic and induced pluripotent stem cells so important for researchers? Because they have the ability to form any cell type of the body. This can be performed simply by adding a few specific cues when culturing these cells. This means that these cells are able to produce beating cardiomyocytes for treating cardiac disease, to produce insulin cells for treating diabetes, and to produce brain cells for potentially treating a number of brain-related diseases. Therefore, these cells have the capability to be used for cell transplantation to replace diseased or lost cells in the body. In fact, there are phase 1 clinical trials currently in progress using embryonic stem cells for treating spinal cord injury and for treating Stargardt's macular dystrophy. These remarkable induced pluripotent stem cells are the current object of focus of my research, which is primarily performed using the pig as a model.

Many people often question why I use the pig as a research model, since stem cell research is traditionally performed using either mice or human-derived cell lines. I think the best answer to this is that in Denmark we love pigs! There are considerably more pigs in Denmark than human beings. In fact, pigs outnumber humans 5 to 1. As Denmark has an enormous export production of pork and pork products, Danes prize their pigs, which also play an important economic role for the country's GDP. The pig is also considered a good, alternative model to the human. It is a large mammal and more similar to human beings (in many organs, both histologically and physiologically), than the well-characterised small mammal, the mouse.

The current focus of my research is to produce induced pluripotent stem cells from a transgenic minipig. This minipig was produced by cloning (also known as somatic cell nuclear transfer), and was designed to carry a human gene, which is inherited by a cohort of people who develop an early onset of Alzheimer's disease. The hope is that this animal will develop Alzheimer's in a manner similar to humans. This transgenic animal model was first produced in 2007 by a number of Danish researchers from the Foulum Research Centre (Faculty of Agricultural Sciences, University of Aarhus), together with researchers from the Department of Human Genetics (University of Aarhus) and the University of Copenhagen. The main research principle is to study pathological features of the disease in the stem cells and the cells derived from them (i.e. neurons) in order to determine whether these cells carry clues about the underlying mechanism of the disease. Can we see how these cells are unhealthy and die after we guide them from being stem cells into neurons? Therefore can we understand more about the disease, which may lead to breakthroughs for better treatment in the future? If these cells do display and recapitulate typical characteristics of the disease, can these cells be used in screening for new and better drug compounds and medicines? These questions remain the hallmark of the current research. Moreover, we are working with non-transgenic pigs and minipigs, to produce induced pluripotent stem cell lines from animals considered "healthy" to determine whether these cells can form the specific neurons that are lost in Alzheimer's disease. Another key research question being investigated is whether these neurons display typical characteristics of the neurons found in the brain. If we can produce identical or similar neurons, these could be envisioned for future cell transplantation into the aging transgenic minipigs (or other models of Alzheimer's disease).

STEM CELL RESEARCH IN MINIPIGS

Induced pluripotent stem cells (iPSC) have been produced successfully in the pig and minipig by a number of different research groups.

CELL LINE AND CELL BACKGROUND	PIG BREED	SENIOR AUTHOR AND LOCATION
iPSC from fetal fibroblasts	Pig (breed unknown)	Michael Roberts, University of Missouri (USA)
iPSC from embryonic fibroblasts	Tibetan minipig	Duanquing Pei, Guangzhou Institutes of Biomedicine and Health (China)
iPSC from adult ear fibroblasts	Danish Landrace	Lei Xiao, Shanghai Institutes for Biological Sciences (China)
iPSC from adult ear fibroblasts	White landrace x Large white	Juan Carlos Izpisua Belmonte, Salk Institute for Biological Studies (USA)
iPSC from mesenchymal stem cells	Pig (breed unknown)	Steven Stice, University of Georgia (USA)

One of the problems entailed in producing good animal models of Alzheimer's disease has been that, despite the ability to integrate the known human mutated genes which trigger the disease, these animals tend to lack the full pathological features of the disease. Traditionally, mouse models of Alzheimer's disease have been produced. Zebra fish and rabbits have also been used, but less widely. Aging in mice is also significantly different from aging in humans. The lifespan of a mouse is roughly two years. Whether these animals are a suitable organism for studying the process of aging is hotly debated by researchers. Given the fact that it has been difficult to produce an animal model displaying all the hallmark features of the disease, it has been quite difficult to identify the disease mechanisms, thereby limiting the extent of potential breakthroughs for new and better treatments.

Alzheimer's disease is the most common form of dementia and no cures are currently available. It is therefore important to look to better, alternate disease models, which may mimic the disease more closely to that observed in humans. The pig (being a large mammal) is therefore a good alternative candidate to consider. In so doing, we may just be able to gain a little more insight into Alzheimer's disease, which could lead to the development of better medicines and possibly breakthroughs, as well as pave the way for developing a cure.