Department of Genetic Disease Research (Lysosomal Storage Disease)

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General Summary

The Donated Department of Genetic Disease Research (Lysosomal Storage Disease [LSD] Research Center) was established in April 2008. The main topic of research is the basic pathogenesis of genetic diseases, especially LSDs. In particular, the pathogenesis of central nervous system (CNS) involvement in LSDs is a difficult problem. To understand the pathophysiology of CNS events, we attempted to generate induced pluripotent stem (iPS) cells from mucopolysaccharidosis (MPS) VII mice and to differentiate them into neuronal cells. For Fabry disease and Pompe disease, we generated iPS cells from model mice and differentiated them into cardiac cells.

Research Activities

1. Our aim is to establish novel treatment procedures, such as enzyme replacement therapy (ERT), chaperon therapy, new anti-oligonucleotide therapy (PTC), and cell therapy/gene therapy.

1) Hematopoetic stem cell transplantation

Hematopoetic stem cell transplantation was performed to treat Hurler disease, Hunter disease, Gaucher disease, Krabbe disease, and metachromatic leukodystrophy.

2) ERT

Six LSDs can now be treated with ERT.

3) Small molecules:

Substrate deprivation therapy and chaperon therapy was performed with butylnojirimycin (miglustat), Genz , and N-octyl-4-epi-beta-valienamine.

4) Gene Therapy

Gene therapy was performed with viral vectors (including adeno-associated viruses, adenoviruses, retroviruses, and lentiviruses), *ex vivo, in vivo* gene therapy.

5) Cell Therapy

Cell therapies involved neural stem cell therapy performed by means of intraventricular or intravenous injections, intranvenously administered mesenchymal stem cell therapy, fibroblast-derived iPS cells (Yamanaka, 2007), embryonic stem cells, and microglial cells. Among these treatments, we explored ERT and gene therapy in human and animal models, particularly in Pompe disease mice, using lentivirus vectors.

2. Establishing new iPS cells from various LSDs: We successfully derived iPS cells from the skin fibroblasts of twitcher, Fabry, and Sly mice. To derive iPS cells from tail-tip fibroblasts and mouse embryonic fibroblasts, 4 factors were inserted (hKlf4, hSox2, hc-Myc, and hOct), and Myc was deleted (Mao et al., 2008).

3. Evaluating the long-term efficacy of ERT for LSDs: Enzyme uptake in Gaucher disease occurs through a mannose receptor—mediated system. High mannose-6-phosphate—enriched enzymes are taken up at a high rate. Antibody formation will also inhibit the uptake of enzymes by cells. The relation to antibodies is the most important factor for ERT.
4. New treatments for CNS involvement in LSDs and other genetic diseases
Generally, ERT is not effective for treating neurological improvement, but we have performed intrathecal administration of enzymes into MPS II mice.
5. New screening procedures for LSD with dried blood spots and other techniques
We have attempted to develop procedures for screening for the development of Pompe disease with dried blood spots.

Publications

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