Department of Genetic Diseases and Genome Science

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General Summary

The main research topics in the Department of Genetics and Genome Science are the basic pathogenesis of genetic diseases, particularly, lysosomal storage diseases (LSDs), and the development of therapies for LSDs. Of our research topics, the pathogenesis of central nervous system (CNS) involvement in LSDs is the most important. To understand the pathophysiology of CNS events in LSDs, we generated induced pluripotent stem (iPS) cells from mucopolysaccharidosis (MPS) VII mice and caused them to differentiate into neuronal cells. We also generated iPS cells from a mouse model of Pompe disease and caused them to differentiate into skeletal muscle cells. We can produce disease models of various LSDs using iPS technology. Recently, we generated iPS cells from human patients with Gaucher, Fabry disease, and Pompe disease. Furthermore, we treated CNS involvement of LSDs by means of intrathecal injection of enzymes into MPS II mice. Intrathecal injection of enzymes was extremely effective for treating the CNS involvement of lysosomal diseases. These findings indicate that intrathecal treatment is feasible for treating the CNS in various LSDs.

Research Activities

1. iPS cells from various LSDs are important research tools for understanding the pathophysiology of LSDs and can also be applied to the treatment of LSDs. We successfully generated iPS cells from Pompe mice by means of tail-tip fibroblasts, mouse embryonic fibroblasts, and 3 factors: Klf4, Sox2, and Oc2/4t. The iPS cells differentiated into skeletal muscle cells. Pompe skeletal muscle cells showed massive accumulation of glycogen in lysosomes surrounded by a single membrane unit. We also generated iPS cells from patients with Gaucher disease, Fabry disease, and Pompe disease.
2. Development of treatment procedures for LSDs

Establishing novel treatment procedures for the CNS involvement of LSDs is our most important project. One procedure is intrathecal or intraparenchymal injection of enzymes into MPS II mice. We found that intrathecal injection produced significant elevations of enzyme activities in various regions of the brain and in other organs, such as the liver, spleen, kidney, and heart. Furthermore, histological improvement in the brains of MPS II mice was also observed.

3. The screening for LSDs with dried blood spots is an important technology for the early diagnosis and treatment of patients with Fabry, Pompe, and MPS I, II, IV, and VI. We used the fluorometric assay method to establish the dried blood spot method for the early diagnosis of Pompe disease, Fabry disease, Morquio syndrome (MPS IV), and MPS VI. Furthermore, we recently established a dried blood spot diagnostic method for Wolman disease.

4. Development of gene and cell therapy: Basic research using lentiviral vectors or adeno-associated vectors in a mouse model of MPS II was performed to develop gene and cell therapies for human LSDs, including Pompe disease, Fabry disease, and MPS VII.
5. Pathological analysis and generation of iPS cells from LSDs
We revealed the ultrafine structural characteristics of iPS cells from human Pompe disease, Fabry disease, and MPS.
6. Educational activities for patients with LSDs
We held educational seminars for patients with Fabry disease 3 times this year and plan to continue doing so in the future.
7. We organized seminars about genetic diseases (including LSDs) for medical students 3 times this year and held a public seminar in the Tokyo area.
8. International symposium of gene therapy
This symposium, held on January 17, 2012, was attended by about 120 persons. The aim of the meeting was to encourage international cooperation for the establishment of a gene therapy system for genetic diseases.
9. Educational activities about LSDs
To increase recognition of LSDs by physicians, medical students, and the general public, we are creating a pamphlet, holding patient seminars, organizing research meetings, and creating websites.

These activities are very important in the future
In the study of LSDs, research on iPS cells, screening methods, and educational programs have achieved much, internationally and in Japan, and have led to beneficial social, scientific, and academic outcomes.

Inspection and evaluation
Screening with blood spot methods have contributed to the early diagnosis of patients at high-risk for LSDs in Japan. In collaboration with the Department of Gene Therapy, Institute of DNA Medicine, we accomplished several of these topics. In the study of LSDs, research on iPS cells, screening methods, and educational programs have achieved much, internationally and in Japan, and have led to beneficial social, scientific, and academic outcomes.

Research achievements
Intrathecal administration of enzymes could be very useful for treating CNS manifestations of LSDs, such as MPS II. Furthermore, iPS technology will contribute to our understanding of the pathogenetic mechanism of LSDs.

Publications

Nishiyama Y, Shimada Y, Yokoi T, Kobayashi H, Higuchi T, Eto Y, Ida H, Ohashi T. Akt inactivation induces endoplasmic reticulum stress-independent autophagy in fibroblasts from patients with Pompe disease. *Mol Genet Metab.* 2012; **107:** 490-5.
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CD3 antibodies modulates the immune response to an infusion of α-glucosidase in mice. *Mol Ther.* 2012; **20:** 1924-31.

Higuchi T, Shimizu H, Fukuda T, Kawagoe S, Matsumoto J, Shimada Y, Kobayashi H, Ida H, Ohashi T, Morimoto H, Hirato T, Nishino K, Eto Y. Enzyme replacement therapy (ERT) procedure for mucopolysaccharidosis type II (MPS II) by intraventricular administration (IVA) in murine MPS II. *Mol Genet Metab.* 2012; **107:** 122-8.