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. Among them, the pathogenesis of central nervous system (CNS) involvement in LSDs is the most important research subject. To understand the pathophysiology of CNS events, we generated induced pluripotent stem (iPS) cells from mucopolysaccharidosis (MPS) VII mice and differentiated them into neuronal cells. We also generated iPS cells from model mice of Pompe disease and differentiated them into skeletal muscle cells. We can produce disease models of various LSDs using iPS technology. Furthermore, we treated CNS involvement of LSDs by means of intrathecal injection of enzymes into MPS II mice. These findings indicate that intrathecal treatment is feasible to treat the CNS in various LSDs.

Research Activities

1. Development of treatment procedures for LSDs

To establish novel treatment procedures for 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 correction in the brain was observed.

2. The iPS cells from various LSDs might provide insights into the pathophysiology of LSDs and might be used to treat them. We successfully generated iPS cells from Pompe mice using tail-tip fibroblasts and mouse embryonic fibroblasts. With 3 factors—Klf4, Sox2, and Oc2/4t—we caused the iPS cells to differentiate into skeletal muscle cells. Pompe skeletal muscle cells showed massive accumulation of glycogen in lysosomes surrounded by a single membrane unit.

3. The screening for LSDs with dried blood spots is an important technology for the early diagnosis and treatment of patients with various LSDs. We used the fluorometric assay method to establish the dried blood spot method for the early diagnosis of Pompe disease, Fabry disease, Morquio syndrome, and MPS VI.

Publications

Ohashi T, Iizuka S, Shimada Y, Eto Y, Ida H, Hachimura S, Kobayashi H. Oral administration of recombinant human acid a-glucosidase reduces specific antibody formation against enzyme in mouse. *Mol Genet Metab* 2011; **103:** 98–100. Epub 2011 Jan 27.

Iida T, Shiba H, Misawa T, Ohashi T, Eto Y. Immunogene therapy against colon cancer metastasis using an adenovirus vector expressing CD40 ligand. *Sugery* 2010; **148:** 925–35.

Kobayashi H, Takahashi-Fujigasaki J, Fukuda T, Sakurai K, Shimada Y, Nomura K, Ariga M, Ohashi T, Eto Y, Otomo T, Sakai N, Ida H. Pathology of the first autopsy case diagnosed as mucolipidosis typeIII α/β suggesting autophagic function. *Mol Genet Metab* 2011; **102:** 170–5.

Meng XL, Shen JS, Kawagoe S, Ohashi T, Brady R, Eto Y. Induced pluripotent stem cells derived from mouse models of lysosomal storage disorders. *Proc Natl Acad Sci U S A* 2010; **107:** 7886–91.

Kyosen SO, Iizuka S, Kobayashi H, Kimura T, Fukuda T, Shen JS, Shimada Y, Ida H, Eto Y, Ohashi T. Neonatal gene transfer using lentiviral vector for murine Pompe disease: long term expression and glycogen reduction. *Gene Ther* 2010; **17:** 521–30.

Okuyama T, Tanaka A, Suzuki Y, Ida H, Tanaka T, Cox GF, Eto Y, Orii T. Japan Elaprase Treatment (JET) study: idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II). *Mol Genet Metab* 2010; **99:** 18–25.

Eto Y. Single gene disorder: recent advances of research(in Japanese). *Nippon Rinsho* 2010; **68 Suppl 8:** 117–28.