Department of Neuroscience
Division of Neuropathology

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General Summary

Our research projects have concerned neurodegenerative disorders caused by intracellular accumulation of abnormal proteins. We are also studying mouse models of neurodegenerative disorders and autopsy cases by means of standard methods of morphologic analysis and molecular biological analysis.

Research Activities

Expression of hydroxyindole-O-methyltransferase enzyme in the human central nervous system and in pineal parenchymal cell tumors

Pineal parenchymal tumor (PPT) cells usually show immunoreactivity for synaptophysin, neuron-specific enolase, neurofilament protein, class III α-tubulin, tau protein, PGP9.5, chromogranin, serotonin, retinal S-antigen, and rhodopsin, but these markers are not specific for PPTs. Melatonin is produced and secreted mainly by pineal parenchymal cells; hydroxyindole-O-methyltransferase (HIOMT) catalyzes the final reaction in melatonin biosynthesis. We hypothesized that HIOMT could serve as a tumor marker of PPTs and investigated HIOMT localization and HIOMT expression in samples of normal human tissue and in PPTs, primitive neuroectodermal tumors, and medulloblastomas. In normal tissue, HIOMT was expressed in retinal cells, pineal parenchymal cells, neurons of the Edinger-Westphal nucleus, microglia, macrophages, thyroid follicular epithelium, principal and oxyphil cells of the parathyroid gland, adrenal cortical cells, hepatic parenchymal cells, renal tubule epithelium, and enteroendocrine cells of the stomach and duodenum. The expression of HIOMT was also found in all 46 PPTs examined. The proportions of HIOMT-immunoreactive cells successively decreased in the following tumors: pineocytoma, PPT of intermediate differentiation, and pineoblastoma. A few HIOMT-immunoreactive cells were observed in 1 of 6 primitive neuroectodermal tumors and in 23 of 42 medulloblastomas. These results indicate that immunohistochemical staining for HIOMT may be useful in the diagnosis of PPTs and be a prognostic factor in PPTs.

Neuropathology of Fabry knockout mice

Fabry disease is a rare X-linked recessive disorder caused by mutations in the alpha galactosidase A gene (GLA). As the result, globotriaosylceramide (GL3) and related glycosphingolipids accumulate in the lysosomes of many tissues and lead to organ failure. In this study, we investigated histopathological changes in GLA knockout mice and compared them with those in human Fabry disease. Male GLA knockout mice

were evaluated microscopically, ultramicroscopically, and immunohistochemically with an anti-GL3 antibody. GL3 accumulated in a variety of cells, including vascular endothelial cells, perithelial cells, and smooth muscle cells throughout the body. The storage material had a lamellar structure. Cells storing GL3 included proximal kidney tubule cells and macrophages and fibroblasts in a variety of organs. In the nervous system, GL3 accumulated in the cytoplasm of neurons in the trigeminal motor nuclei, solitary nuclei, spinal cord, trigeminal ganglions, dorsal root ganglia, and gastrointestinal tract. Electron microscopy revealed that the lamellar structure was present in axons and Schwann cells of peripheral nerves in the skin but not in the sciatic nerves. GL3 also accumulated in the cells of the pituitary gland, adrenal medulla, and spermatogenic cells. In a 67-year-old man with Fabry disease, GL3 immunoreactivity was observed in the neurons of the posterior nuclei of the hypothalamus and the dorsal motor nuclei of the vagus of the central nervous system and in a variety of cells, including cardiac muscle and renal glomeruli, of organs in which GL3 storage was not found in mice. We have demonstrated that GLA knockout mice show GL3 accumulation in the neurons and the axons of the nervous system, especially in the peripheral nerves of the skin.

Expression analysis of NCKX1 and phactr2 in a cellular model of spinocerebellar ataxia type 7

Spinocerebellar ataxia type 7 (SCA7) is a polyglutamine disease caused by polyglutamine expansion within a causative protein, ataxin-7. SCA7 is characterized by accentuated degeneration of the cerebellum and retina. Recent evidence suggests that ataxin-7 regulates transcription and that aberrant regulation of transcription is related to the pathogenesis of SCA7. We developed inducible PC12 cell lines expressing mutated/normal ataxin-7 (H111: ataxin-7-Q100, F127: ataxin-7-Q10). Expression array analysis using H111 demonstrated that about 300 genes decrease expression, with induction of mutated ataxin-7. Of these genes, we selected Na/Ca-K exchanger 1 (NCKX1) and phosphatase and actin regulator 2 (phactr2) and evaluated gene expression levels with the real-time reverse transcriptase-polymerase chain reaction. The expression of both genes decreased chronologically, only when mutated ataxin-7 was induced. NCKX1 regulates the intracellular calcium concentration of rod cells in the retina. Phactr2 is related to synapse plasticity in the Purkinje cells of the cerebellum. Suppression of the genes indicates that fluctuating expression of these genes could be related to the retinal and cerebellar degeneration in SCA7.

Publications

Akiyama N, Ohno Y, Fukuda T, Manome Y, Saito S. Enhancing activity of N-glycosylation for constitutive proteins secretions in non-polarized cells. *Biochem Biophys Res Comm* 2009; **381:** 612–8.

Fukumitsu N, Suzuki M, Fukuda T, Kiyono Y. Multipoint analysis of reduced ^{125}I-meta-iodobenzylguanidine uptake and norepinephrine turnover in the hearts of mice with MPTP-induced Parkinsonism. *Nucl Med Biol* 2009; **36:** 623–9.

Kaku S, Ishii T, Hasegawa Y, Fukuda T, Abe T. Multiple dural AVF occurring in the time and place of transverse-sigmoid sinus: A case report and discussion from the standpoint of histopathological and clinical medicine (in Japanese). *Nosocchu* 2009; **31:** 111–6.

Kyosen SO, Iizuka S, Kobayashi H, Kimura T, Fukuda T, Shen J, 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. Epub 2009 Dec 24.

Janer A*[1]*, Werner A*[2]*, Takahashi-Fujigasaki J, Daret A*[1]*, Fujigasaki H*[3]*, Takada K, Duyckaerts C*[4]*, Brice A*[1]*, Dejean A*[2]*, Sittler A*[1] *(*[1]*INSERM, UMRS 975,* [2]*INSERM U579, Inst Pasteur,* [3]*Musashino Redcross Hosp,* [4]*Salpetriere Hosp, Neuropathol). SUMOylation attenuates the aggregation propensity and cellular toxicity of the polyglutamine expanded ataxin-7. *Human Mol Genetics* 2010; **19:** 181–95.

Yamaoka M*[1]*, Akiyama M*[1]*, Yuza Y*[1]*, Yokoi K*[1]*, Yokokawa Y*[1]*, Matsushima S*[1]*, Fujigasaki J, Chiba S (Jikei Univ Dep Neuropathol), Kohno M (Jikei Univ Dep Clin Lab Med), Ida H*[1] *(*[1]*Jikei Univ Dep Pediatr). Disseminated Absidia corymbifera Infection in a 14-Year-Old Girl with Burkitt Lymphoma (Stage IV). *Jpn J Pediatr Hematol* 2010; **24:** 43–6.

Reviews and Books

Takahashi H, Hano H, Shiraishi T, Fukuda K, Fukuda T, et al. (Translation) Robbins and Cotran Atlas of Pathology. In: Klatt EC, editor. Tokyo: Elsevier Japan; 2009. p. 447–86.