Department of Pathology
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General Summary

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

Research Activities

Granulocyte colony stimulating factor producing solitary fibrous tumor

Introduction: Rare cases of granulocyte colony stimulating factor (G-CSF)-producing tumors exhibit leukocytosis due to G-CSF production and have an extremely poor prognosis. We histopathologically evaluated a G-CSF-producing solitary fibrous tumor. The patient was 39-year-old man who underwent resection of an extra-axial well-circumscribed right frontal convexity extracerebral dural-based tumor 60 mm in diameter. Biopsy of the tumor revealed a solitary fibrous tumor, characterized by staghorn vessels and a patternless architecture with hypercellular tumor cells, which had eosinophilic cytoplasm and a nucleus immunoreactive to signal transducer and activator of transcription 6. After surgery the patient was treated with radiation therapy. When the patient was 44 years old, 2 nodular tumors with a diameter of 10 mm appeared in the lung. At the age of 49 years, the patient complained of fever and abdominal pain and was found to have multiple metastatic tumors in the lungs, liver, kidneys, and adrenal gland. The white blood cell count was 70,500/μL (it had been 7,400/μL 5 years earlier), and the serum G-CSF concentration was 283.0 pg/mL. Biopsies of the liver and kidney tumors revealed a metastatic solitary fibrous tumor. Two weeks after being admitted to the hospital, the patient died of multiorgan failure. Tumor cells obtained when the patient was 39 and 49 years old expressed G-CSF, G-CSF receptor, and B-cell lymphoma 2 (bcl-2). The diagnostic criteria for G-CSF-producing tumors include: (1) a marked increase in leukocyte count, (2) elevated G-CSF activity, (3) a decreased leukocyte count following tumor resection, and (4) verification of G-CSF production in the tumor. This case fulfilled the criteria for G-CSF-producing tumors except for criteria 3. Expressions of G-CSF, G-CSF receptor, and bcl-2 in this tumor suggest that G-CSF itself has an effect on tumor cell growth and the inhibition of apoptosis. The prognosis of patients with G-CSF-producing tumors is usually poor, regardless of the primary organs. We should evaluate G-CSF and G-CSF receptor in solitary fibrous tumors.

Increase in messenger RNA level of subunit c of mitochondria ATP synthase in the central nervous system in a mouse model of prosaposin deficiency disease

Introduction: The pathophysiological changes of the central nervous system (CNS) in prosaposin knockout mice accompanied the degeneration of neurons and axons with organelle changes and the activation of ubiquitin-proteasome and autophagy-lysosome systems. In the CNS of prosaposin knockout mice 9 to 31 days old, the number of subunit c of mitochondria ATP synthase (SCMAS)-immunoreactive neurons increased in proportion to the number of amino-cupuric-silver-impregnated neurons. The accumulation of SCMAS might be induced by an increase in transcription of SCMAS messenger (m) RNA or a depletion of SCMAS degradation. This study investigated the mRNA level of SCMAS in the CNS of prosaposin knockout mice.

Material and methods: We analyzed the level of alternatively spliced SCMAS mRNA variants (ATP5G1, AT5G2, ATP5G3a, and ATP5G3b) in the CNS of wild-type and prosaposin knockout mice 9 to 29 days old with the real-time cycleave polymerase chain reaction using specific primers and probes.

Results: The levels of alternatively spliced SCMAS mRNA variants (ATP5G1, AT5G2, ATP5G3a, and ATP5G3b) all showed the same tendency. In wild-type mice, the level of SCMAS mRNA decreased in proportion to age. On the other hand, the level of mRNA increased in proportion to age in prosaposin knockout mice.

Discussion: SCMAS is a candidate for amino-cupric-silver-impregnated material in the CNS of prosaposin knockout mice. We reported the accumulation of SCMAS in the neuronal cytoplasm of neuronal ceroid lipofuscinoses, Niemann-Pick disease type C, Fabry disease, mucolipidoses, methylenetetrahydrofolate reductase deficiency, and mucopolysaccharidoses types I, II, and VII. In the CNS of prosaposin knockout mice, the increased level of alternatively spliced SCMAS mRNA variants would induce the accumulation of SCMAS-immunoreactive cells in proportion to an age of 9 to 29 days. The reason for increased SCMAS mRNA transcription is still unknown. The increase of ATP synthase might be induced by the depletion of ATP because of organelle dysfunction and the activation of ubiquitin-proteasome and autophagy-lysosome systems. We should investigate whether ATP decreases and whether SCMAS degradation is depleted in prosaposin knockout mice.

Publications

Kobayashi H, Ariga M, Sato Y, Fujiwara M, Fukasawa N, Fukuda T, Takahashi H, Ikegami M, Kosuga M, Okuyama T, Eto Y, Ida H. P-Tau and Subunit c Mitochondrial ATP Synthase Accumulation in the Central Nervous System of a Woman with Hurler-Scheie Syndrome Treated with Enzyme Replacement Therapy for 12 Years. *JIMD Rep.* 2018; **41:** 101-7.

Fukasawa N, Fukuda T, Nagaoka M, Harada T, Takahashi H, Ikegami M. Aggregation and phosphorylation of α-synuclein with proteinase K-resistance in focal α-synucleinopathy predominantly localized to the cardiac sympathetic nervous system. *Neuropathol Appl Neurobiol.* 2018; **44:** 341-4.

Komatsu T, Matsushima S, Kaneko K, Fukuda T. Perivascular enhancement in anti-MOG antibody demyelinating disease of the CNS. *J Neurol Neurosurg Psychiatry.* 2019; **90:** 111-2.