Department of Pathology
Division of Neuropathology

Hiroshi Hano, *Professor and Director*
Junko Fujigasaki, *Assistant Professor*
Takahiro Fukuda, *Assistant Professor*

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 morphologic analysis and molecular biological analysis.

Research Activities

Pathophysiological study of neuronal organelles in lysosomal disorders
Objective: This study investigated the pathophysiology of neuronal organelles in lysosomal disorders.
Material and methods: We analyzed the central nervous system of mouse models of Niemann-Pick disease type C and prosaposin deficiency with immunohistochemical techniques and antibodies against early endosome antigen 1, trans-Golgi network protein 38 (Golgi apparatus), cytochrome c oxidase subunit IV (mitochondria), calnexin (endoplasmic reticulum), S6 ribosomal protein, lysomsomal-associated membrane antigen 2, and catalase (peroxisome).
Results: In the central nervous system neurons of Niemann-Pick disease type C and prosaposin-deficiency mice, swollen lysosomes accumulated. Structurally preserved peroxisomes and Golgi apparatuses decreased slightly in number. Mitochondria, endosomes, endoplasmic reticulum, and ribosomes decreased markedly in number.

An autopsy case of frontotemporal lobar degeneration with motor neuron disease (primary lateral sclerosis type)
Flaccid dysarthria developed in a 68-year-old man. At age 69 years, he acted in a conspicuously selfish manner and exhibited forced laughter with mild dementia (Hasegawa Dementia Scale, Revised: 22 of 30). He showed upper motor neuron signs, including hyperreflexia, spasticity, Babinski sign, and paralysis. He died of pneumonia at 71 years of age. A postmortem examination of the brain, which weighed 1,150 g, revealed degeneration of the corticospinal tract with complete loss of Betz cells. The affected frontal and temporal cortices showed diffuse neuronal loss, with microvacuolar change and phosphorylated 43-kDa transactivation response DNA-binding protein (pTDP43)-positive neuronal cytoplasmic inclusions and pTDP43-positive dystrophic neurites in all cortical layers. No pTDP43-positive neuronal intranuclear inclusions could be detected. There was no obvious lower motor neuron loss or Bunina bodies in the hypoglossal nucleus or spinal cord, whereas the fragmentation of Golgi apparatuses was observed in lower motor

neurons with pTDP43-positive inclusions.

An autopsy case of Chagas disease

An 80-year-old Japanese–Brazilian man had lived in urban areas of Brazil and moved to Japan at 62 years of age. He was admitted with a complaint of somnolence. Diffusion-weighted magnetic resonance imaging showed multiple areas of high signal intensity in the deep white matter. Physical examination revealed megacolon. *Trypanosoma cruzi* organisms were identified in the blood. He died of chronic Chagas disease. A postmortem examination of the brain, weighing 1,320 g, revealed infiltration of macrophages, lymphocytes, and plasmacytes into perivascular areas and *T. cruzi* organisms in intravascular and perivascular areas and in the cytoplasm of astrocytes, macrophages, and neurons. Neuronal loss and ischemic cerebral changes and demyelination were also observed. Chagas disease has a long incubation period and is often refractory to treatment. Awareness that Chagas disease is now found in places far from areas of Latin America where it is endemic is important because it leads to the development of strategies to prevent potential sources of transmission.

Nuclear inclusions and Cajal bodies in spinocerebellar ataxia 7

Spinocerebellar ataxia 7 (SCA7) is an autosomal dominant neurodegenerative disorder characterized by cerebellar ataxia and retinal degeneration. SCA7 is caused by a polyglutamine expansion in ataxin-7. The pathologic hallmark of SCA7 is the formation of neuronal intranuclear inclusions (NIIs) and accumulation of mutated ataxin-7. Nuclear functional domains related to the formation of NIIs, especially promyelocytic leukemia nuclear bodies, could be accumulation sites of the pathological ataxin-7 with expanded polyglutamine. Cajal bodies, which have been implicated in RNA-related metabolic processes, might be related to the formation of NIIs in SCA7. In this study, we examined the relation of Cajal bodies and NIIs in the brains humans and mice with SCA7. Coilin, a molecular marker of Cajal bodies, were attached to or entrapped in ataxin-7-positive NIIs in the human and mouse brains. The protein survival of motor neurons, a marker of Gemini of Cajal bodies, is also found in the NIIs. These findings indicate that alteration of RNA metabolism might be related to the pathogenesis of SCA7.

Publications

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