Department of Pathology
Division of Neuropathology

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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

Accumulation of subunit c of mitochondria ATP synthase in the central and peripheral nervous systems in human lysosomal diseases

Objective: This study investigated the accumulation of subunit c of mitochondria ATP synthase (SCMAS) in the central nervous system in lysosomal disorders.

Material and methods: We used SCMAS immunohistochemistry to analyze the central and peripheral nervous systems of Niemann-Pick disease type C, mucopolysaccharidoses types I and II, neuronal ceroid lipofuscinoses, Gaucher disease, Fabry disease, mucolipidoses types II and III. An antibody against SCMAS was raised in rabbits with keyhole limpet hemocyanin-fused DIDTAAKFIGAGAATVGVAC. An affinity-purified anti-SCMAS antibody was purified from rabbit sera with glutathione S-transferase-DIDTAAKFIGA binding column.

Results: In the central and peripheral nervous systems of lysosomal disorders, the numbers of SCMAS-immunoreactive neurons increased in proportion to the amico-cupuric-silver-impregnated neurons.

Discussion: SCMAS is reported to accumulate in the neuronal cytoplasm of neuronal ceroid lipofuscinoses and mucopolysaccharidoses types I and II. We found neuronal SCMAS accumulation in the central and peripheral nervous systems of Niemann-Pick disease type C, Fabry disease, and mucolipidoses. The accumulation of SCMAS suggests that a disturbance of ATP synthase might cause the neuronal deaths in lysosomal disorders.

A biopsy case with Nocardia farcinica brain abscess

A 72-year-old man with Gerstmann syndrome had left parietal ring-enhanced lesions in magnetic resonance images of the brain. Formalin-fixed paraffin-embedded (FFPE) tissue of the lesion showed branching filamentous rod-shaped bacteria marked with Grocotte, Gram, and Kinyoun stains. To identify bacteria, we applied 16S ribosomal RNA (rRNA) gene sequencing in FFPE tissue. The extraction of DNA was performed with the GeneRead DNA FFPE kit (Qigen, Venlo, the Netherlands) following the manufacturer's

instructions. Primers (5′-GTTTGATCCTGGCTCA-3′ and 5′-TACCAGGGTATCTA-ATCC-3′) were used for the first 800 bp and primers (5′-GGATTAGATACCCTGGTA-3′ and 5′-CGGTTACCTTGTTACGACTT-3′) were used for the last 800 bp of the 16S-rRNA gene. The annealing temperature was 58˚C. BigDye Terminator v3.1 cycle sequencing kits and an ABI PRISM 310 genetic analyzer (Thermo Fischer Scientific, Waltham, MA, USA) were used to determine DNA sequences. The 16S rRNA gene sequences obtained were compared with the GenBank databases (http://www.ncbi.nlm.gov/BLAST/) and identified as being from the bacterial species Nocardia farcinica. The bacterial identification rates for paraffin tissue sections were 18% to 70%. For the treatment of bacterial infection, the 16S-rRNA DNA sequences of bacterial species should be evaluated in lesions.

A 132-day-old male neonate with ectodermal dysplasia examined at autopsy

A male neonate was born to a 40-year-old gravida 1 mother after frozen embryo transfer. The pregnancy was complicated by umbilical artery regurgitation and amniotic membrane peeling, and the child was delivered prematurely with cesarean section at 32 weeks' gestation. Birth weight was 1,089 g. Multiple congenital malformations were noted at birth and included alopecia of the scalp, anhydrosis, hyperkeratosis, inguinal herniation, and a ventricular septal defect. The neonate died of sepsis, and autopsy revealed enlarged lateral cerebral ventricles with periventricular white matter necrosis. The results of exome sequencing identified mutations of epidermal growth factor receptor as a cause of ectodermal dysplasia.

Publications

Sengoku R, Matsushima S, Murakami Y, Fukuda T, Tokumaru AM, Hashimoto M, Suzuki M, Ishiwata K, Ishii K, Mochio S. ^{11}C-PiB PET imaging of encephalopathy associated with cerebral amyloid angiopathy. *Intern Med*. 2014; **53:** 1997-2000.