Japan Academy Prize to:

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for "Peroxisome Biogenesis and its Role in the Pathogenesis of Human Peroxisome-Deficiency Disorders"

Outline of the work:

Peroxisomes are single-membrane-bound organelles occurring in the cells of eukaryotes. Peroxisomes contain approximately hundred different enzymes that catalyze the reactions of various metabolic pathways, including H_2O_2 metabolism, β-oxidation of very long-chain fatty acids, and the synthesis of ether-phospholipids called plasmalogens. The functional importance of peroxisomes in humans is represented through the manifestation of peroxisome deficiency or peroxisome-biogenesis disorders (PBDs), the most identifiable being Zellweger syndrome.

Cells with a specific genetic defect that affects a certain biological process and/or a cell phenotype are generally called "cell mutants" and act as a highly useful tool in genetic, biochemical, and cell biology studies. To investigate peroxisome biogenesis and PBDs, Dr. Yukio Fujiki and colleagues have isolated and established a model system comprising 13 different complementation groups (CGs) of Chinese hamster ovary (CHO) cell mutants defective in peroxisome biogenesis. Gene-cloning through a forward genetic approach utilizing a rapid, functional complementation assay of CHO cell mutants, led to the isolation of *PEX* genes, which encode peroxins required for peroxisome assembly, thus invaluably contributing to the cloning of genes involved in the pathogenesis of PBDs. The identification of such genes in all 14 CGs, together with a homology-based screening of the human expressed sequence tag database using yeast *PEX* genes, is complete.

Peroxins are divided into the following three groups: 1) peroxins including Pex3, Pex16, and Pex19 that are responsible for the biogenesis of the peroxisome membrane via the Classes I and II pathways; 2) peroxins that participate in matrix protein import; and 3) Pex11β that coordinates with other factors including DLP1, Mff, and Fis1 is involved in the peroxisomal division. In the matrix protein import pathway, newly synthesized proteins harboring the peroxisome targeting signal type 1 or 2 are recognized by Pex5 or Pex7 in the cytoplasm and are imported into the peroxisomes via a complex translocation machinery. Pex5-PTS1 and Pex5L-Pex7-PTS2 protein complexes (Pex5L is a longer form of Pex5), initially target the docking complex consisting of Pex14 and Pex13. They are then translocated to RING complexes comprising Pex2, Pex10, and Pex12 after the release of cargos. In the terminal step, Pex1 and Pex6, which belong to the AAA ATPase-family, mediate the export of Pex5 for which its Cys-ubiquitination is essential. While addressing the important issue of the production and supply of energy-rich GTP for the division of peroxisomes, Dr. Fujiki and colleagues discovered a novel nucleoside diphosphate kinase-like protein termed DYNAMO1 in a lower eukaryote, which also has a homolog "NME3" in mammalian cells. Deficiencies of Pex11β, DLP1, or NME3 induce abnormal morphological changes in the peroxisomes and/or mitochondria and are associated with a dysfunctional central nervous system.

PBDs manifest as neurological deficiencies of the central nervous system, including defective neuronal migration and abnormal cerebellum development. To investigate the underlying mechanisms, Dr. Fujiki's group established a new PBD model termed Pex14**Δ**C/**Δ**C mouse defective in a functional Pex14 due to a truncated C-terminal. The Pex14**Δ**C/**Δ**C mouse showed a malformation of the cerebellum including the impaired dendritic development of Purkinje cells. This was a result of an elevated level of brain-derived neurotrophic factor (BDNF) together with the enhanced expression of TrkB-T1, a dominant-negative isoform of the BDNF receptor. The BDNF-TrkB pathway is essential for cerebellar morphogenesis and its dysregulation leads to the pathogenesis of the cerebellum-defects in PBDs. In the peroxisome-deficient cells, abnormal cytosolic redox states due to a wrongly localized catalase induce the secretion of BDNF.

Several findings by Dr. Fujiki and his group made recently have advanced our understanding of the biology, physiology, and metabolic deficiencies due to the functional defects in peroxisomes. Cooperativity in cell-defense mechanisms active against oxidative stress involves the localization of the proapoptotic effector "BAK" to the peroxisomes, which alters their membrane permeability, thus resulting in the export of catalase to the cytoplasm. They also provided evidence for the dynamic and highly regulated dual subcellular localization of catalase in the peroxisomes and the cytosol by suppression of catalase import involving the phosphorylation of Pex14.

Plasmalogens are a unique family of glycerophospholipids that contain a vinyl-ether bond. Synthesis of plasmalogens is initiated in the peroxisomes but completed in the endoplasmic reticulum. Plasmalogens are either absent or severely reduced in various organs of PBD patients. A reduced level of plasmalogens in the brain has been reported in Alzheimer's disease, Parkinson's disease, and schizophrenia. Dr. Fujiki's group reported that plasmalogen biosynthesis is regulated spatiotemporally through a feedback mechanism that senses the levels of plasmalogens in the inner leaflet of the plasma membrane and regulates the stability of fatty acyl-CoA reductase 1 (Far1), the rate-limiting enzyme of the plasmalogen biosynthesis pathway. They also observed that the dysregulation of plasmalogen synthesis impairs cholesterol synthesis in cells and the brain, resulting in the reduced expression of genes such as those for mRNA encoding myelin basic protein, a phenotype found in the cerebellum of plasmalogen-deficient mice. Thus, plasmalogen homeostasis is tightly linked to cholesterol homeostasis.

List of Main Publications (*, Corresponding author)

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