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Peroxisome homeostasis, dysfunctions and disorders

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Cellular homeostasis is regulated by orchestrating the functions of organelles in response to the extracellular stimuli and/or intracellular signals. To elucidate the highly organized functions of intracellular organelles, peroxisome, a single membrane-bounded essential organelle has been used as a model compartment in mammalian cells. Peroxisomes are present in a wide variety of eukaryotic cells and they function in various metabolic pathways, including β-oxidation of very long chain fatty acids and the synthesis of ether-lipids such as plasmalogens. The functional consequence of human peroxisomes is highlighted by fatal genetic peroxisome biogenesis disorders (PBD) such as Zellweger syndrome (ZS). We successfully isolated a dozen Chinese Hamster Ovary (CHO) cell mutants defective in peroxisome biogenesis and identified PEX genes encoding peroxisome biogenesis factors termed peroxins, including PEX2, PEX6, PEX12, PEX26, by means of the genetic phenotype-complementation of CHO cell mutants. We also unveiled the roles of peroxins in peroxisomal membrane assembly including targeting mechanism of nascent C-tailed anchored proteins, matrix protein import and division. We are now focusing on the peroxisomal membrane targeting mechanism of nascent C-tailed anchored proteins. Physiological consequence of plasmalogens is highlighted by PBDs. Ablation of plasmalogen homeostasis is reported in several neurological diseases including Alzheimer's disease. In cells from PBD patents, plasmenylethanolamine is remarkably reduced and phosphatidylethanolamine is increased. We have shown that plasmalogen biosynthesis is regulated by modulating stability of fatty acyl-CoA reductase (Far1) and that plasmalogen homeostasis plays an important role in cholesterol synthesis. Moreover, plasmalogens located in the inner leaflet of plasma membrane are sensed for monitoring cellular plasmalogen level.

Biography

Yukio Fujiki and his colleagues investigate cellular homeostasis involving subcellular organelles such as peroxisome. His lab tackles the problems involving membrane assembly, matrix protein import, morphogenesis and homeostasis of peroxisomes. His group successfully identified and isolated more than a dozen *PEX* genes including the first Zellweger gene *PEX2*. He and his colleagues unveil the roles of peroxins in peroxisome biogenesis and the pathogenesis of PBDs from the viewpoint of dysregulation of peroxisome homeostasis.

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