Japan Academy Prize to:

Takao SHIMIZU
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for "Studies on Lipid Mediators and Phospholipid Metabolism"

Outline of the work:

Dr. Takao Shimizu has worked for almost 30 years on lipid metabolism and lipid mediators. He has made historically seminal discoveries and significant contributions to the development of this field. Summarized below are his contributions.

1. Biosynthetic pathway: Characterization of 5-lipoxygenase and related enzymes involved in the leukotriene biosynthesis

Leukotrienes (LTs) were found in the late 70's to have potent proinflammatory and vasoconstrictive activities. While their structures and precursors were identified, LTs' biosynthetic pathway from arachidonic acid had remained elusive. In 1982, Dr. Shimizu and his collaborators isolated and characterized 5-lipoxygenase, which incorporates O2 molecules at the C5-position of arachidonic acid and catalyzes subsequent dehydration to produce LTA4. Since then, other downstream enzymes have been isolated and cDNA-cloned by Shimizu's group and others. Enzyme regulation, especially phosphorylation and Ca-dependent translocation have also been demonstrated. Dr. Shimizu further demonstrated the metabolic inactivation pathway of these biologically active compounds.

2. Biosynthetic pathway: Characterization and elucidation of *in vivo* roles of cytosolic phospholipase A2α (cPLA2α)

Dr. Shimizu, then became interested in arachidonate release from membrane glycerophospholipids, which is catalyzed by intracellular Ca-dependent cytosolic phospholipase A2α (cPLA2α). He established mice deficient in cPLA2α, and conclusively demonstrated that the enzyme is involved in various pathologies (e.g., bronchial asthma, multiple sclerosis, thromboembolism, rheumatoid arthritis) as well as in multiple physiological responses (e.g., reproduction, synaptic plasticity). In collaboration with pharmaceutical companies, Dr. Shimizu is currently developing cPLA2α inhibitors, as a new therapeutic target for various inflammatory and immunological disorders.

3. Discovery and characterization of lipid receptors

In 1991, Dr. Shimizu succeeded in the molecular cloning of a G-protein coupled receptor (GPCRs) for platelet-activating factor (PAF), which was the first successful cloning of lipid bound GPCRs. Since then, more than 30 different types of lipid GPCRs have been identified. Dr. Shimizu and his collaborators isolated 7 among the 30. He, then, established receptor-deficient mice and analyzed their various phenotypes. It was clarified that lipid mediators are deeply involved at the onset and propagation of various inflammatory diseases, by enhancing cytokines and immune cells.

4. Dynamics of membrane phospholipids

Arachidonic acid and many other polyunsaturated fatty acids are esterified at the sn-2 position of glycerophospholipids, and phospholipase A2 is a key enzyme that cleaves the ester bond to yield arachidonic acid and lysophospholipids. Lysophospholipids are further reacylated to produce mature glycerophospholipids. Although the existence of lysophospholipid acyltransferases was postulated in 1958, no molecular information had thus far been available. In 2006, Dr. Shimizu discovered lysophosphatidylcholine acyltransferase (LPCAT1) from the lung, and consequently identified 20 putative genes involved in acyltransferase reaction and membrane remodeling. This discovery by Shimizu's and other groups opens a new field of investigation into how membrane asymmetry and diversity are produced and their biological outcomes.

5. Comprehensive analyses of lipid mediators and membrane lipids

Dr. Shimizu further devised a new method to determine a variety of lipid mediators (about 30 different molecules) simultaneously using liquid-chromatography-mass spectrometry with high sensitivity and high precision. He also optimized the technique to measure quantitatively membrane phospholipids with different fatty acid compositions. Using these newly established methods, a simultaneous determination of lipid mediators and precursor phospholipid composition will be analyzed in cells under normal and stimulated conditions.