[S5-3] [4/18/2003(Fri) 15:10-15:50/Maple Hall]

Lysophosphatidic Acid and Lysophosphatidylserine, New Bioactive Lysophospholipids

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Phospholipids function as major components of biological membranes as well as precursors of biologically active lipid messengers. It is well known that arachidonic acid attached at the sn-2 position of phosphoglycerides serves as a precursor of prostaglandins and leukotrienes.Recently, it has been recognized that lysophospholipids such as lysophosphatidic acid, sphingosine 1-phosphate, lysophosphatidylserineand monoglyceride also function as lipid messengers with a variety of biological activities. In this symposium, I would like to focus on the biological activities, associated diseases and synthetic enzymes of lysophosphatidic acid and lysophosphatidylserine, which were studied extensively in our laboratory. The biological activities of lysophosphatidic acid (LPA) so far identified include platelet activation, smooth muscle contraction, cell proliferation and cell motility. LPA evokes its effect through G-protein

coupled receptors (GPCRs). Members of this family include three GPCRs belonging to the EDG family, EDG2, EDG4 and EDG7. We isolated and characterized EDG7 (J.B.C 274(1999)27776). In contrast to the other two receptors which are activated by both 1-acyl LPA and2-acyl LPA with equal potency, EDG7 is activated by only 2-acyl LPA. It has also been shown that vascular smooth muscular cells per sedramatically proliferate by the action of 2-acyl LPA but not by 1-acyl LPA, suggesting the involvement of EDG7 on smooth muscular proliferation. Migration of cultured fibroblasts is stimulated by LPA(both 1-acyl and 2-acyl LPAs). We have demonstrated that fibroblasts isolated from EDG2 knockout mice show no migration whatsoever in response to LPA, although they migrate efficiently by the action of PDGF, indicating that the migratory stimulus evoked by LPA is mainly mediated by EDG2. Among the three LPA receptors, EDG2 is most abundantly expressed in normal colon epithelial cells. However, whenthese cells show malignancy, the major isoform receptor expression

changes from EDG2 to EDG4. This may suggest that EDG4 is involved in colon cancer growth and metastasis development. In contrast to the extensive analysis of mechanisms underlying LPA signaling mediated by LPA receptors, the enzymes that regulate LPA production are poorly understood. We have recently cloned the lysophospholipase D which catalyzes the production of LPA from lysophosphatidylcholine (J.Cell Biol. 228(2002)227). Lysophospholipase D is synthesized as a type II transmembrane ectoenzyme and then released from the cell by cleavage of the 12th amino acid external to the transmembrane domain. Unexpectedly, it was found that lysophospholipase D is identical to autotaxin (ATX). ATX was originally identified as a tumor cell motility-stimulating factor isolated from melanomacell supernatants. ATX dramatically increases chemotaxis and proliferation of various cancer cells in the presence of lysophosphatidylcholine, a substrate of this enzyme. Lysophosphatidylcholine is abundantly present in the plasma, and we found that some cancer cells secrete significant amounts of lysophosphatidylcholine. Therefore,we speculate that autocrine or paracrine production of LPA contributes to tumor cell motility, survival and proliferation. It also provides potential novel targets for therapy of some forms of cancer. It has long been postulated that lysophosphatidylserine stimulates histaminerelease from rat peritoneal mast cells triggered by IgE receptor cross-linking in vitro. However, it was not clear if this phenomenon also occurs in vivo. Lysophosphatidylserine may be produced by theaction of phospholipase A on phosphatidylserine and in fact we havecloned phosphatidylserine-specific phospholipase A1 (PS-PLA1) (J.B.C. 272(1997)2192) from mammals. PS-PLA1 is a 55-kDa secretoryprotein and homologous to mammalian lipases such as lipoprotein lipase and pancreatic lipase. It only hydrolyzes phosphatidylserine but not triglycerides. Expression levels of this enzyme are greatly enhanced in various organs upon stimulation by endotoxin, suggestingits involvement in inflammation and shock. We have demonstrated that PS-PLA1 stimulates histamine release from mast cells in vitro (J.Biol. Chem. 276(2001)29664) and most recently showed that in PS-PLA1 knockout mice, mast cell activation is greatly diminished as examined by the passive cutaneous anaphylaxis test. These data indicatethat PS-PLA1 is relevant in the production of lysoPS. This substance stimulates mast cell activation in vivo. Therefore, substances that inhibit the function of PS-PLA1 may be useful as novel anti-allergic drugs in future.