[S2-1] [10/17/2002 (Thurs) 10:50~11:20/Hall B]

In Vivo Roles of Lysophospholipid Receptors Revealed by Gene Targeting Studies in Mice

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Lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P) are bioactive lysophospholipids (LPs) that act as mediators in various cellular processes, such as cell growth, differentiation, survival, motility, and cytoskeletal reorganization (1,2). LPA and S1P are both abundant in serum and are produced by activated platelets and other cell types. From recent studies, they are recognized as extracellular ligands for a family of cognate G protein-coupled receptors (GPCRs), which are encoded by *lpa*$_{1/2/3}$ and *s1p*$_{1/2/3/4/5}$ genes (1-3). Three of these genes, *lpa*$_1$, *lpa*$_2$ and *lpa*$_3$, encode high-affinity LPA receptors, whereas the remaining five genes, *s1p*$_1$, *s1p*$_2$, *s1p*$_3$, *s1p*$_4$, and *s1p*$_5$, encode GPCRs that specifically interact with S1P or sphingosylphosphorylcholine (SPC). These LP receptors couple to multiple classes of heterotrimeric G proteins ($G_{i/o}$, $G_{q/11/14}$, G_s, and $G_{12/13}$) and activate various ligand-induced signal transduction pathways (4). Some of the signaling events that follow LP receptor activation include stimulation of serum response element and subsequent transcriptional events, activation or inhibition of adenylyl cyclase, activation of mitogen-activated protein kinase, intracellular Ca^{2+} mobilization, phospholipase C (PLC) activation, and stress fiber formation (1,2,4,5).

The *lpa* and *s1p* genes are widely expressed in various mammalian organ systems, such as cardiovascular, nervous and reproductive systems, and their expression patterns are regulated throughout development. The *lpa*/*s1p* gene homologs are also found in *Xenopus* (6) and zebrafish. The widespread existence of LPs in many mammalian tissue types, the pleiotropic nature of their biological effects, and the unique spatio-temporal expression patterns of *lpa*/*s1p* genes, combine to confer upon the LP signaling system a capability to exert diverse physiological actions in the whole organism. LPA and S1P are implicated in processes as divergent as shaping neuronal morphology, cell-cell communication, tumor invasion, angiogenesis, wound healing and embryonic development.

Despite a growing understanding of LP receptors and their signaling systems, there has been

a lack of direct evidence for their physiological roles in intact animals until recently.The generation of receptor-null mice allows direct examination of the systemic roles of LP receptors *in vivo* as well as further elucidation of LP receptor-specific signaling pathways in receptor-null primary cells.

In this symposium, we will present our results obtained from series of LP receptor-null mice we developed, detailing receptor-specific cellular signaling through LPs (7-10).

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