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VIEWPOINT

Lysophospholipids and Their G Protein-Coupled Receptors in Biology and Diseases

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The following set of Prospects is dedicated to bioactive lysophospholipids (LPLs) and their G protein-coupled receptors (GPCRs), which influence the development, functions, and diseases of every mammalian organ system. From their origins as growth factors, whose effects were inhibited by Pertussis toxin, lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P), and related LPLs have emerged as a major class of intracellular messengers and extracellular mediators. Two decades of intensive research has elucidated many elements of the biochemistry of generation and biodegradation of LPLs, led to the cloning of their subsets of GPCRs, and established the tools necessary for sophisticated biological research, with much more to come. On this foundation, present efforts now can progress to more complex analyses of biology, development of pharmacological agents selective for relevant enzymes and LPL GPCRs, and delineation of the pathophysiological roles of each LPL-GPCR axis in diseases.

Although the principal characteristics of the LPL-GPCR family resemble those of many other ligand-GPCR axes, several distinctive features enhance interest in the mechanisms of their physiological and pathophysiological effects. These are the focus of the first six Prospects that appear in this issue. The pathways of biosynthesis and metabolism, and the constellation of GPCRs with LPL specificity exhibit extreme diversity. Biologically important consequences are individual cellular patterns of expression of both ligands and receptors. Unique mechanisms permit full expression and signaling activity of the GPCRs in many types of cells despite significant occupancy by high ambient concentrations of ligand, which would lead to downregulation in most other systems. Numerous intracellular events subject to evolving interpretation include messenger functions for activation of and signal transduction by other receptors, perinuclear, and intranuclear localization, and agonist interactions of S1P with calcium channels and of LPA with the nuclear transcription factor peroxisome proliferator activating factor-gamma (PPAR-gamma).

The contributions of LPLs to normal organ development, survival, re-modeling, and regeneration are the subject of Prospects seven to ten. The first of this series describes a need for multiple G protein-coupled pathways in control of development and promotion of survival, and possible pathologic consequences of abnormal signaling by one or more of these cascades. The next discusses evidence from developmental model systems that signals from LPL GPCRs are central in embryogenesis and that abnormal signaling results in defects in development. The last two prospects of this sequence outline evidence that LPL GPCR-generated signals may determine the genesis, migration, and differentiation of neurons peripherally and in the neocortex.

The final five Prospects which will be published in JCB 92:6, will address several aspects of the involvement of LPL-GPCR axes in integrated normal physiology and in disease states, with particular reference to the cardiovascular and immune systems, and to cancer. In the cardiovascular area, S1P GPCR signals are critical for maintaining integrity of endothelial barriers through actin reorganization-dependent increases in cell–cell and cell–matrix adherence and other mechanisms. Several S1P-GPCR axes promote cardiomyocyte resistance to hypoxia directly and mediate much of the protective effect of ischemic pre-conditioning. LPA is found in the core of atherosclerotic

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plaques from which its release can activate platelets and cause acute vascular occlusion. LPA also has been shown recently to be a major mediator of vascular remodeling. It elicits vascular smooth muscle cell de-differentiation and neointima formation largely through a novel agonist activity on PPAR-gamma. These exciting findings provide a GPCR-independent pathway for LPA and possibly S1P contributions to atherosclerosis. Each of these cardiovascular effects will be susceptible to manipulation by LPL GPCR- and potentially PPAR-selective pharmacological agents.

Human and mouse T cells selectively express $S1P_1$ and $S1P_4$ GPCRs, of which $S1P_1$ transduces S1P promotion of survival, stimulation of chemotaxis, and inhibition of other diverse immune functions. The capacity of the S1P-$S1P_1$ axis to control T cell efflux from the thymus, lymphoid homing and distribution in non-immune tissues, and their resultant ability to detect and respond to some antigens have been confirmed by showing that FTY720, an S1P GPCR-acting drug, successfully blocks autoimmunity in rodents and prevents renal allograft rejection in humans. Recent results have strongly implicated LPA-GPCR systems in ovarian cancer. The cancer invasion factor autotaxin, which augments cancer cell migration, has been shown to be identical to the lysophospholipase D that produces LPA. The ability of ovarian cancers, but not breast cancers, to produce large amounts of LPA correlates with their higher than normal content of autotaxin and possibly with lower than normal levels of degrading lysophospholipid phosphatases. That mice expressing LPA-high ovarian levels of transgenic LPA2, similar to those in human ovarian cancers, show follicular hyperplasia and secrete elevated amounts of known markers for ovarian cancer also supports a role for the LPA-LPA_2 GPCR axis in oncogenesis. Again, LPL GPCR-selective pharmacological agents will establish these relationships with practical relevance.

It is hoped that the clarity, current contents, broad biological orientation, and pathophysiologic context of these prospects will make them valuable to those working in the field as well as those in other areas with conceptual or mechanistic relationships to ligand-GPCR systems.