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Introduction: lipids as regulators of cell function

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Abstract. It is becoming increasingly clear that lipids are key regulators of cellular function and that these effects are quite diverse. First, the lipid environment in the cellular membrane bilayer is important in maintaining the normal function of receptors, enzymes, transporters and so on that are localized in the membrane. Phosphoinositides are important regulators of signalling molecules. Lipid metabolites formed by a number of enzymes including the cyclooxygenases, lipoxygenases and P450s also mediate important cellular functions. Fatty acids and lipid metabolites can also activate the nuclear peroxisome proliferator-activated receptors. Finally, a wide variety of lipid molecules are generated nonenzymatically by free-radical mechanisms that also exert potent biological effects in a wide variety of organs. Presented are a series of eight reviews that broadly cover all of these topics in some detail.

Key words. Phosphoinositides; cyclooxygenase; P450; lipoxygenase; isoprostanes; lipoxin; polyisoprenyl phosphate.

It is becoming increasingly clear that lipids play key roles in regulating cellular function. Notably, the cell membrane comprises a lipid bilayer, and contained in this bilayer are a variety of different receptors, transporters, enzymes and ion channels whose normal function is maintained by the composition of lipids and structure of the bilayer. Lipids formed by the cyclooxygenase and lipoxygenase pathways also are important in regulating a number of diverse cellular functions in an autocrine and paracrine fashion, such as angiogenesis and tumor growth. Fatty acids also activate the nuclear peroxisome proliferator-activated receptors, which induce transcription of a variety of target genes. Metabolites of P450 metabolism of arachidonic acid also mediate important cellular functions. Moreover, phosphoinositides are important lipids that regulate a number of signaling pathways. And finally, a number of interesting prostaglandin-like and related compounds have been discovered to generated by a nonenzymatic free-radical-induced mechanism which has been found to exert potent biological actions.

Bruce Levy and Charles Serhan outline their novel discovery of polyisoprenyl phosphates as natural anti-inflammatory lipid signals. They discovered that presqualene diphosphate (PSDP) inhibits superoxide generation by neutrophils, representing a stop mechanism for the activation of neutrophils. They discuss the role of lipoxins in inhibiting neutrophil function and the potential for long-lived analogs of PSDP and lipoxins as potential antiinflammatory therapeutic agents, and they describe intricate interactions of agonists of neutrophil activation, and the formation and effects of PSDP and lipoxins. Also described is the proposed molecular basis for the action of PSDP, namely direct inhibition of phospholipase D.

Jesper Haeggström and Anders Wetterholm review the biochemistry, molecular biology and cell biology of key enzymes in the leukotriene cascade. The discovery of leukotrienes by Samuelson and colleagues was a landmark achievement that opened up a new pathway of arachidonic acid metabolism that has been shown to have great importance in inflammatory and allergic conditions. Leukotriene B_4 is one of the most powerful leukocyte chemoattractants known, and the peptidoleukotrienes contract smooth muscles, most potently in the peripheral airways in the lung and in the microcirculation. Understanding the complexities of the enzymes involved in leukotriene biosynthesis provides insights into how these pathways are regulated and how they may be modulated pharmacologically.

Sean Colgan summarizes what is currently known about lipid mediators in epithelial cell-cell interactions. The downregulation of lipoxins on neutrophil migration and integrin expression is discussed as well as epithelial cell cytokine release. In contrast, it has been found that prostaglandins are capable of enhancing chemokine

release from enpithelial cells. Moreover, prostaglandins produced by fibroblasts can promote Cl^- secretion in intestinal epithelial cells. Interestingly, 6-keto-$PGF_{1\alpha}$ has also been shown to activate epithelial cell eletrogenic Cl^- secretion. Finally, the role of cyclooxygenase-2-derived prostaglandins in epithelial cell function is discussed.

Alex Toker reviews the role of phosphoinositides in signal transduction. Signalling through phosphoinositides has been shown to regulate a variety of important cellular functions, including cell growth and proliferation, apoptosis, cytoskeletal changes, insulin action and vesicle trafficking. A growing list of proteins which interact directly with distinct phosphoinositides is detailed. Recent advances in phosphoinositide signalling and the regulation of phosphoinositide metabolism by lipid kinases, phosphatases and phospholipases is reviewed. Finally, the role of these lipids in regulating signalling pathways and cell function is discussed.

Jorge Capdevila and colleagues review microsomal cytochrome P450 metabolism of arachidonic acid and eicosanoids. Both NADPH-dependent epoxygenation and NADPH-independent pathways of metabolism of fatty acids are discussed. P450-catalyzed ω-oxidation of prostaglandins is also outlined. Finally, the large number of biological actions that have been identified for epoxyeicosatetraenoic acid derivatives are reviewed.

Walter Wahli reviews transcriptional effectors of fatty acids and their derivatives in activation of peroxisome proliferator-activated nuclear receptors (PPARs). The structural organization and ligand-binding domain are discussed. Activation of α-, β-, γ-PPAR subtypes by fatty acids is outlined. Finally, the modulation of the transcriptional activity of PPARs endocrine status of the cell is detailed.

The role of angiogensis on tumor viability and metastasis is a topic of considerable interest. Daotai Nie and Kenneth Honn review the regulation of antiogenesis by arachidonic acid metabolites. A detailed discussion of the process of angiogenesis and factors involved in its regulation as well as how tumors promote neovascularization is provided. The role of cyclooxygenases 1 and 2, and 12-lipoxygenase in angiogenesis and the potential of inhibitors of these enzymes as anticancer, antiangiogenic therapeutic agents is outlined.

Finally, I have reviewed the area of isoprostanes and related compounds formed via the isoprostane pathway. The biochemistry of the formation of these compounds is detailed. The value of measurements of F_2 isoprostanes to assess oxidative stress status *in vivo* is highlighted. The biological actions of compounds mediated by interaction with receptors and receptor-independent actions of other compounds due to their chemical reactivity is also discussed. Finally, the formation of isoprostane-like compounds from fatty acids other than arachidonic acid is outlined.

In summary, we have enlisted experts in various fields of lipid biochemistry and biology to review in detail a number of important areas relating to the regulation of cellular function by lipids. Much has been learned and discovered in these areas over the last several years, but many tantalizing questions remain for future investigation.