thematic review series

The Role of Phosphoinositides in Signaling and Disease: Introduction to the Thematic Review Series

Vytas A. Bankaitis[1,*] and George M. Carman[†]

[1] E. L. Wehner-Welch Laboratory,* Department of Molecular and Cellular Medicine, Texas A&M Health Science Center, College Station, TX 77843; and Rutgers Center for Lipid Research,[†] New Jersey Institute for Food, Nutrition, and Health, Rutgers University, New Brunswick, NJ 08901

Phosphatidylinositol is a metabolic precursor of phosphoinositides, and these lipids collectively define a major component of the eukaryotic intracellular chemical signaling program. In that regard, phosphoinositide metabolism is a major mechanism used by eukaryotic cells to convert their membrane surfaces into what are, in effect, high-definition signaling screens. Even subtle derangements in the flux or physical organization of phosphoinositide metabolism result in deleterious consequences, such as disease in multicellular eukaryotes. Although the signaling power of phosphoinositides has been appreciated since the 1970s, these lipids continue to surprise with regard to the diverse ways they are used as intracellular signals, and how specific pools of these lipids are dedicated to particular biological outcomes. Precisely how this small cohort of molecules is translated to control literally hundreds of biological outcomes remains incompletely understood. In a perhaps related matter, it is also curious that the number of enzymes dedicated to synthesis and degradation of phosphoinositides is greater than the number of substrate molecules. Why cells would invest a multitude of pathways for production of the same phosphoinositides remains an open question. Finally, the issue of nuclear phosphoinositide signaling is enjoying exciting new progress that opens up new questions regarding the enzymology of phosphoinositide signaling and metabolism in nonmembraneous environments.

To update ongoing scientific research in these areas, we have assembled a series of seven timely reviews that discuss the structure, function, and regulation of enzymes responsible for the synthesis and degradation of phosphoinositides, as well as the roles phosphoinositides play in cell physiology, health, and disease. A goal of this thematic series is to highlight poorly understood, and under-discussed, aspects of phosphoinositide biology. The first three reviews deal with specific issues surrounding regulation of phosphoinositide synthesis and downstream effector biology and biochemistry, followed by two that discuss mechanisms of phosphoinositide degradation by lipid phosphatases and their roles in disease. The focus then shifts to the nucleus for the last two reviews where topics of phosphoinositide metabolism in the nuclear matrix are discussed.

The VPS34 phosphatidylinositol kinase phosphorylates phosphatidylinositol to produce phosphatidylinositol 3-phosphate. The enzyme product recruits specific proteins to the membrane that regulate sorting pathways like endocytosis and autophagy. Ohashi, Tremel, and Williams provide a comprehensive and detailed discussion about the structural aspects of VPS34 and complexes formed with accessory/regulatory proteins along with their regulation by posttranslational modifications. In the second review, Grabon, Bankaitis, and McDermott provide a comprehensive review of the expanding phosphatidylinositol transfer protein field with a discussion of the basic concepts as to how these proteins function within biological contexts. In particular, the review posits that phosphatidylinositol transfer proteins act as nanoreactors to amplify and diversify phosphatidylinositol 4-kinase and the function of its product, phosphatidylinositol 4-phosphate. GOLPH3 is a peripheral membrane protein localized to the Golgi and its vesicles, but its purpose has been unclear. Kuna and Field discuss how GOLPH3 binds specifically to phosphatidylinositol 4-phosphate, which functions at the Golgi to promote vesicle exit for trafficking to the plasma membrane and the role of this function in cancer.

Phosphoinositide phosphatases metabolize various phosphoinositides to generate a host of lipid second messenger molecules. The review by Ramos, Ghosh, and Erneux summarizes current knowledge on phosphoinositide-5-phosphatases and their signaling interplay with the PTEN phosphoinositide 3-phosphatase and other phosphoinositide-phosphatase enzymes, and also covers their roles in tumor promotion and suppression. The focus of the review by Staiano and DeMatteis is the kidney, whose function requires phosphoinositide signaling to direct appropriate cell polarization, filtration, solute reabsorption, and extracellular signal transduction. Genetically engineered animal models and the study of human genetic diseases such as Lowe syndrome/Dent disease 2 and Joubert syndrome are highlighted.

To whom correspondence should be addressed.
e-mail: vytas@tamhsc.edu

DOI https://doi.org/10.1194/jlr.E091355

A relatively high percentage of nucleoplasm-associated phosphoinositides exists in a poorly understood nonmembrane state stabilized by nuclear proteins. Bryant and Blind discuss the discoveries of nuclear proteins that solubilize and complex phosphoinositides, along with enzymes that act upon and remodel these complexes. The authors propose clinical opportunities for using these complexes as biomarkers, diagnostics, and therapeutics.

Phosphoinositide-specific phospholipase C enzymes are involved in signaling pathways related to critical cellular functions, such as cell cycle regulation, cell differentiation, and gene expression. The review by Ratti, et al. discusses the roles of the nuclear form of these phospholipase C enzymes in a number of disorders, including cerebral, hematological, neuromuscular, and fertility disorders.