

MULTIPLE APPROACHES TO STUDY THE COMPLEX REGULATORY FUNCTIONS OF PHOSPHOINOSITIDES

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Phosphoinositides (PIs) make up only a small fraction of cellular phospholipids, yet emerge as one of the most important group of signaling molecules in the cell. PIs are the precursors of important second messengers, but they also serve as regulatory molecules on their own rights by controlling the recruitment and function of protein signaling complexes in specific membrane compartments. PIs are involved in processes that mediate the metabolic, proliferative and antiapoptotic effects of hormones, the trafficking of molecules between the various organelles, and in those controlling exo- and endocytosis. PIs are regulators of almost all ion channels and transporters and are also implicated in nuclear signaling events. Thus, the versatility of inositide-based signaling is almost unparalleled in biology, and only the GTP-binding proteins bear similarity in their ubiquitously important regulatory roles. A multiplicity of inositol lipid kinases and phosphatases that phosphorylate/dephosphorylate the various positions of the inositol ring of phosphatidylinositol have been identified, and some of the inositide phosphatases have also been linked to human diseases. Over the years, it has become evident that the sites of inositide formation are spatially and temporally restricted and new methods are needed to explore the complexity of inositol lipid dynamics in living cells. In this lecture we will review our novel molecular tools to study the spatial and temporal aspects of phosphoinositide signaling and their application to studies in G protein-coupled receptor functions. We will also show our most recent data and new approaches to study the mechanism of formation and actions of inositol 1,4,5-trisphosphate in cells stimulated by Ca^{2+} mobilizing receptors and to follow the trafficking of the G-protein-coupled AT1 angiotensin receptor.