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Phosphoinositides Chemistry and Biology – A 40-Year Retrospective

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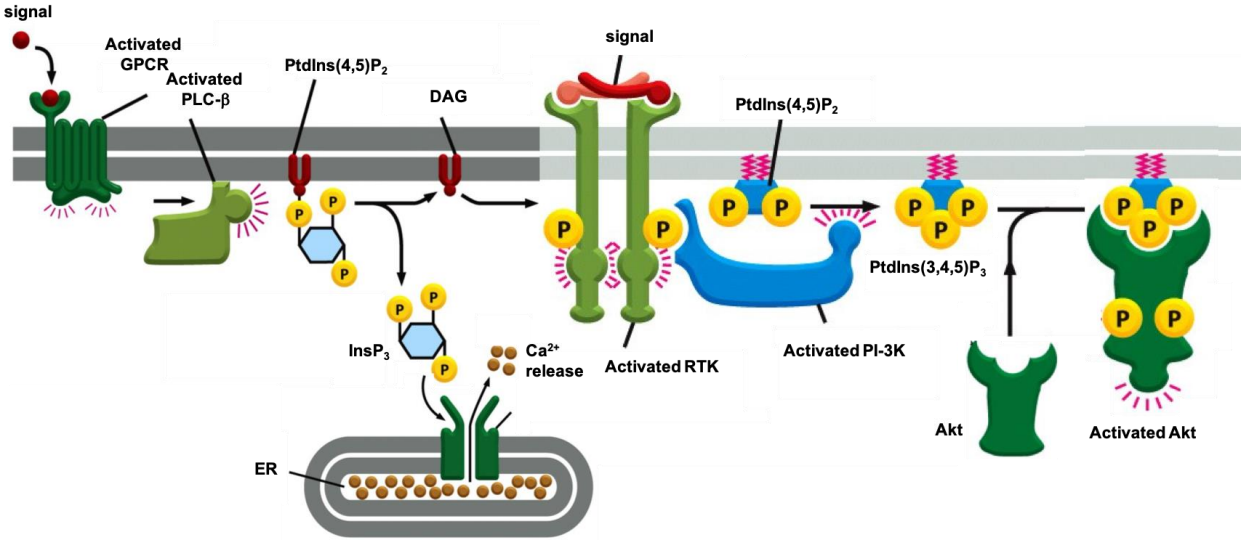
Although reports of vigorous turnover of inositol phospholipids in response to various stimuli started to appear already in the 1950s, only in the early 1980s the existing knowledge enabled formulation of a hypothesis that a large number of cellular receptors function through mobilization of internal Ca^{2+} stores by an action of inositol 1,4,5-trisphosphate ($InsP_3$).[1] This new cytosolic second-messenger was generated from a membrane constituent phosphatidylinositol 4,5-bisphosphate ($PtdIns(4,5)P_2$) by a new phosphodiesterase, $PtdIns(4,5)P_2$-specific phospholipase C (PLC). Following this discovery, a burgeoning new field of cell physiology has emerged that showed $InsP_3$ signaling is utilized by a great number of transmembrane and intracellular receptors. A few years later, another general cellular signaling scheme was discovered involving inositol lipids themselves, such as phosphatidylinositol 3,4,5-trisphosphate ($PtdIns(3,4,5)P_3$).[2]



These discoveries created a demand for synthetic alternatives of natural inositol phospholipids and inositol phosphates. In addition, investigation of molecular details of signaling pathways required synthetic analogs of natural phosphoinositides modified to achieve certain desired functions, such as membrane permeability (caged inositol phosphates), visualization of membrane trafficking (fluorescent analogs of inositol lipids), identification of proteins interacting with inositol phosphates (photoaffinity labels), and studies of mechanisms of enzymes involved in inositol turnover (hydrolysis-resistant analogs), to name just a few.

In this presentation, the main synthetic approaches from different laboratories will be discussed, including the author's own. Furthermore, it will be shown how the availability of the analogs of synthetic phosphoinositides facilitated advances in this field.

[1] M. J. Berridge, R. F. Irvine, *Nature*, **1984**, *312*, 315-20.
[2] K. R. Auger, L. A. Serunian, S. P. Solthoff, P. Libby, L. C. Cantley, *Cell*, **1989**, *57*, 167-75.