Phosphatidylinositol and inositol phosphate metabolism

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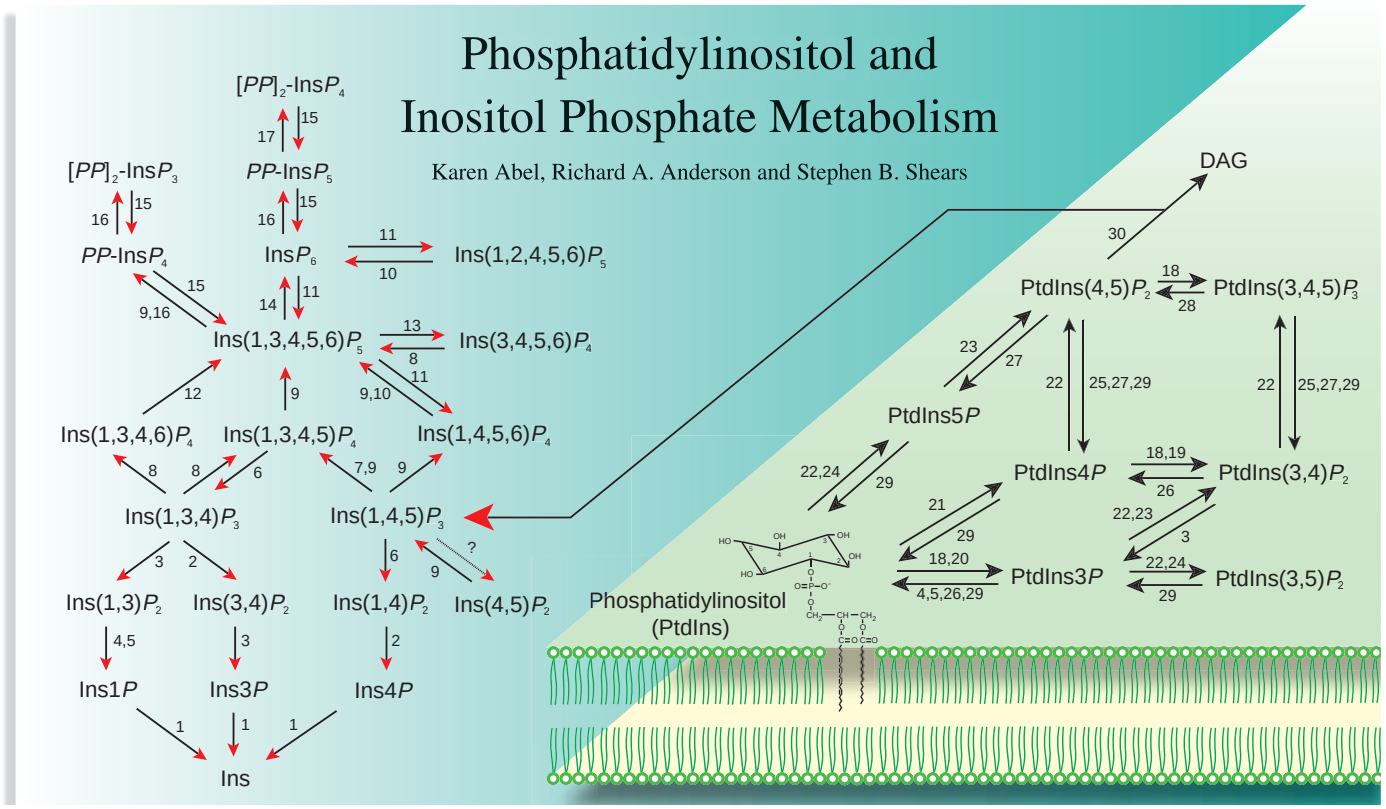
The six carbons that comprise the inositol ring can be phosphorylated in a combinatorial manner, generating a truly astonishing range of inositol phosphates and inositol lipids. Yet, somehow, the cell can distinguish and utilize several of these metabolites to specifically regulate a variety of signal transduction processes. These important actions have infiltrated so many areas of cell biology that reviews on these metabolites are abundant (Rameh and Cantley, 1999; Anderson et al., 1999; Majerus et al., 1999; Irvine and Schell, 2001; Shears, 1998). However, it can be difficult to digest all of this information fully without a clear appreciation of the complex enzyme reactions involved in their synthesis and metabolism. Our goal has therefore been to assimilate current understanding of these metabolic pathways into a single figure that we hope is user-friendly.

It can be intimidating to be confronted by the nomenclature that is used to describe these inositol-based metabolites; some inaccuracies in usage can also add to the confusion. So a brief technical explanation is warranted. The naked *myo*-inositol building block has six hydroxyl groups; the hydroxyl attached to the 2-carbon is axial to the plane of the ring, and the remaining hydroxyls are equatorial. The carbons are numbered in an anticlockwise direction when the ring is viewed from above. Substitution of three of the hydroxyls with phosphates at positions 1, 4 and 5 produces inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3). A small number of the inositol phosphates are diphosphorylated (i.e. pyrophosphorylated). For example, [*PP*]$_2$-InsP_4 has two diphosphate groups and four monophosphate groups. Note that *PP*-InsP_5 and [*PP*]$_2$-InsP_4 are often colloquially described as InsP_7 and InsP_8 but scientific rectitude forced us to avoid this usage (since it would clearly be confusing if *PP*-InsP_4 were called InsP_6). Our figure is ambiguous concerning the placement of the diphosphate groups around the inositol ring, since, for most of this subgroup of metabolites, we lack this information (and there is evidence that these may vary across the phylogenetic spectrum). In the inositol lipids, the diacylglycerol is attached through a diester group at position 1. These lipids were originally introduced as phosphoinositides, but sometimes this strictly lipidic term is incorrectly used to include inositol phosphates. Inositides is an alternative collective noun for both the lipids and the phosphates that was introduced by Robin Irvine.

As for the enzymes, where possible, we have tried to avoid terminology that exaggerates the promiscuity of certain enzymes. For example, the commonly used inositol polyphosphate 1-phosphatase is replaced here by the more discerning Ins(1,3,4)P_3 / Ins(1,4)P_2 1-phosphatase, because Ins(1,3,4)P_3 and Ins(1,4)P_2 are the only 1-phosphate



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containing inositol phosphates that this enzyme attacks. We also draw attention to a new proposal here that the enzyme originally denoted as an InsP_6 kinase ought to be renamed diphosphoinositol polyphosphate synthase, out of deference to the fact that it also actively places a diphosphate on InsP_5.

Another problem we were forced to confront was to judge the significance in vivo of some of the flexible substrate specificities that have been observed in vitro. The kinetics of some of these reactions present convincing cases that certain enzymes are truly promiscuous inside the cell. But there are also other examples where multi-substrate utilization may not so much reflect an in vivo situation but instead depend more on assays being performed with excessive quantities of enzyme, as well as being given sufficient time and patience from the experimenter. Of course, we cannot be too dismissive, because regulatory factors may change enzyme specificity in vivo. Nevertheless, what we have presented here reflects our understanding of what most workers in the field will agree to. We hope it meets with their approval.

References

Anderson, R. A., Boronenkov, I. V., Doughman, S. D., Kunz, J. and Loijens, J. C. (1999). Phosphatidylinositol phosphate kinases, a multifaceted family of signaling enzymes. *J. Biol. Chem.* **274**, 9907-9910.

Irvine, R. F. and Schell, M. (2001). Back in the water: the return of the inositol phosphates. *Nat. Rev. Mol. Cell Biol.* (in press).

Majerus, P. W., Kisseleva, M. V. and Norris, F. A. (1999). The role of phosphatases in inositol signaling reactions. *J. Biol. Chem.* **274**, 10669-10672.

Rameh, L. E. and Cantley, L. C. (1999). The role of phosphoinoistide 3-kinase lipid products in cell function. *J. Biol. Chem.* **274**, 8347-8350.

Shears, S. B. (1998). The versatility of inositol phosphates as cellular signals. *Biochim. Biophys. Acta* **1436**, 49-67

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