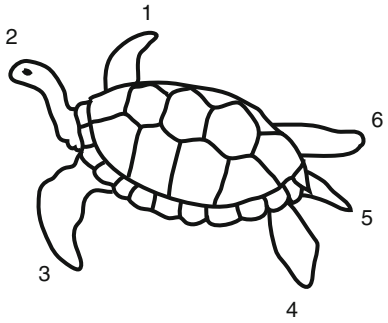
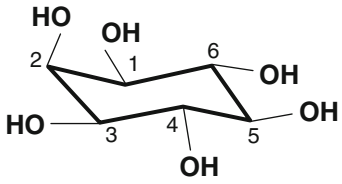
Glossary

A glossary of terms is provided for readers who are not experts of the inositol lipid field.

***myo*-Inositol:** This is one of nine possible stereoisomers of inositol which is a cyclohexanehexol. *My*o-inositol is the most commonly occurring stereoisomer in nature, therefore, the IUPAC-approved abbreviation "Ins" refers to *myo*-inositol (Nomenclature Committee of the International Union of Biochemistry, 1989, http://www.chem.qmul.ac.uk/iupac/cyclitol/myo.html). The conformation of *myo*-inositol is the so-called "chair" conformation with five equatorial and one axial hydroxyl groups. This conformation, and the numbering of the hydroxyls have been best visualized by Agranoff (1978) who compared the ring to a turtle and the hydroxyls to the appendages. Here, the numbering starts with the right front flipper going counterclockwise. The head of the turtle then corresponds to the axial hydroxyl at the 2nd position. It is notable that *myo*-inositol has an axis of symmetry going through the 2nd and 5th carbons. The numbering used refers to the D-enantiomers but it is important to remember that because of this symmetry D-Ins1*P* is the same as L-Ins3*P* and, therefore, isomers (such as Ins1*P* and Ins3*P*) that are enantiomeric twins cannot be separated with conventional HPLC methods.



Agranoff's turtle



myo-inositol

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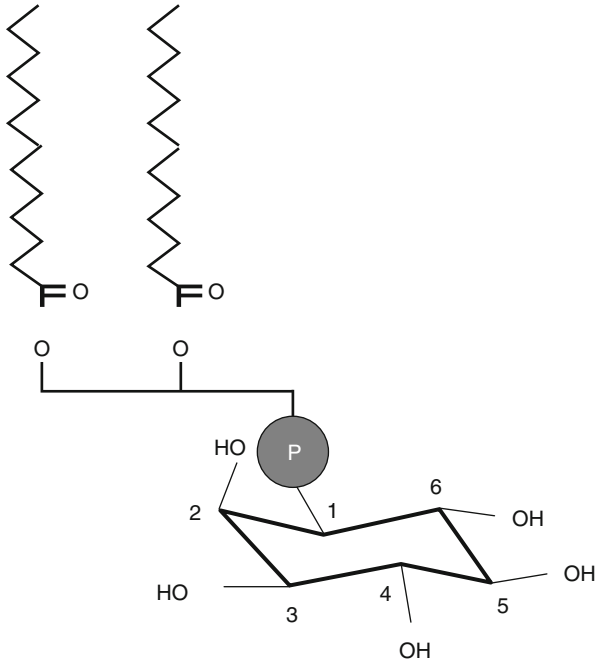
Phosphatidylinositol: This is the base molecule for all phosphoinositides. The recommended abbreviation is PtdIns (http://www.chem.qmul.ac.uk/iupac/misc/phos2t8.html#t4) but the early literature often uses "PI" as the abbreviation. This short form is still in use in the context of kinases that phosphorylate PtdIns or its phosphorylated derivatives, such as in PI 3-kinases or PI 4-kinases. PtdIns consists of a diacylglycerol backbone in which the 1- and 2-positions of the glycerol are most often esterified with a stearoyl- and arachidonyl- fatty acid chains, respectively, and the *myo*-inositol ring is linked to the 3rd- position of the glycerol via a phosphodiester bond formed with the 1st hydroxyl of inositol. PtdIns can be phosphorylated in all but the 2nd and 6th positions of the inositol ring, giving rise to the seven known phosphoinositides.



PtdIns

Polyphosphoinositides: This refers to any of the further phosphorylated PtdIns regardless of the number and positions of the phosphate groups. Sometimes they are abbreviated as PPIs but mostly in the 80's literature but this is still the recommended abbreviation (see in Michell et al. 2005).

Phosphoinositides: This is a term often used to designate collectively PtdIns and all of its phosphorylated derivatives regardless of their isomerism. "PI" is the abbreviation used lately for phosphoinositides but it often causes confusion so it should be avoided. There is no consensus abbreviation for this term that includes both PtdIns and the PPIs. The individual forms of PPIs are abbreviated specifying the

positions phosphorylated on the inositol ring. For example, phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2] is a double phosphorylated PtdIns with positions 4- and 5- phosphorylated.

It is worth pointing out here a few rules about the terminology: the numbers on the inositol ring are not "primed", since there is no other ring in the structure that would require the use of "prime" to discriminate the rings (as opposed to multiring structures such as the nucleosides). The number of phosphates are indicated by the prefixes "bis-" (latin for twice) "tris-" (greek for three times) to indicate that these molecules contain the indicated number of phosphates but all placed individually at various positions. (contrast this with ATP which is a "triphosphate" with the phosphates linked to one another). There are no higher numbers than trisphosphates in phosphoinositides but there are in the soluble inositol phosphates, for which the numbers continue as "tetrakis-", "pentakis-" and "hexakis–" 'kis' being a greek prefix for –times. In the abbreviations it is recommended to italicise the "*P*" if it designates a phosphomonoester (see Michell et al. (2005) in the list below for more details on nomenclature recommendations).

Old literature used terms such as "DPI" and "TPI" for diphosphoinositide and triphosphoinositide, respectively. These correspond to mono- and bisphosphorylated PtdIns from a time when the exact configurations of the phosphates were not known.

Phosphoinositide kinases: Phosphoinositide kinases add a phosphate to a specific position onto the inositol ring of phosphoinositides using ATP. The kinases are named after the position they phosphorylate and hence we distinguish 3-, 4- and 5-kinases (no primes!!). There is an inherent inconsistency about the abbreviations used to designate these enzymes. For example, the term "PI 3-kinase" is used to refer to any of the 3-kinases, regardless of the substrates they phosphorylate. Since there are PI 3-kinases that can only phosphorylate PtdIns (and not further phosphorylated forms) (the Class III PI 3-kinases) they are also named PtdIns 3-kinases. However, the Class I PI 3-kinases that phosphorylate PtdIns(4,5)P_2 are rarely called PtdIns(4,5)P_2 3-kinases and in most articles unspecified "PI 3-kinase" refers to the Class I enzymes. In contrast, PI 4-kinases can only phosphorylate PtdIns (and not further phosphorylated forms) in which case it would be more correct to call them PtdIns 4-kinases. However, because of historical reasons, these inconsistencies are tolerated even if they defy logic based on current knowledge. The list of the various forms and classes of PI kinases are summarized in the respective chapters.

Phosphoinositide phosphatases: Phosphoinositide phosphatases remove one or more phosphates from PPIs. They can be specific to the position of the phosphate they remove and the substrate they can use. Some will dephosphorylate only PPIs while others can also use the water-soluble inositol phosphates as substrates. Phosphatases are usually named after the position of phosphate they attack such as 5-phosphatases or 3-phosphatases. Some PI phosphatases are not position specific, such as the monophosphatases (see Chapters 7 and 8 in Volume I for more details).

Phospholipase C: These enzymes (PLCs) hydrolyze PtdIns (or PPIs) by cleaving the phosphodiester group such that they leave diacylglycerol behind and release the

inositol headgroup, which carries the phosphate still attached at the 1-position (or other phosphates if the substrate is any of the PPIs). To discriminate from other PLCs that use other phospholipids as substrate (such as PC-PLC), PLCs that hydrolyze phosphoinositides are called PI-PLCs. This, however, also causes some confusion, since mammalian PI-PLCs are believed to hydrolyze primarily PtdIns(4,5)P_2 *in vivo* (although they can also hydrolyze PtdIns and PtdIns4*P* *in vitro*). However, there are bacterial PLC enzymes that will use either PtdIns or phosphatidylinositol glycan (GPI) linkages but cannot hydrolyze polyphosphoinositides. The literature that deals with the bacterial enzymes uses the term PI-PLC to emphasize that the bacterial enzymes are specific for PtdIns or GPI. So the term "PI-PLC" means two different enzyme groups depending on whether used in mammalian or prokaryotic studies. However, in most cases PLC without any designation refers to the mammalian phosphoinositide-specific PLCs.

Inositol 1,4,5-trisphosphate: Ins(1,4,5)P_3 is the water soluble molecule liberated after PLC-mediated hydrolysis of PtdIns(4,5)P_2. This molecule has a receptor located in the ER membrane that also is a Ca^{2+} channel and which is gated by Ins(1,4,5)P_3 binding. Ins(1,4,5)P_3 is a bona fide second messenger liberated upon stimulation of cell surface receptors coupled to PLC activation.

PH domain: PH domains (for pleckstrin homology domains) are protein modules of roughly 150 amino acid length that were first recognized in pleckstrin (Tyers et al. 1988). These were the first protein modules that were shown to bind PPIs. Many PH domains can recognize and bind phosphoinositides with variable specificities earning these domains the reputation of being PPI binding modules. Although several PH domains can, indeed, recognize PIs with high affinity and specificity, many PH domains show promiscuous PPI recognition and many do not bind PIs at all. Moreover, PH domains also recognize proteins and often bind proteins and lipids simultaneously (Lemmon 2004).

FYVE domain: This was the second protein module identified with specific PPI recognition, namely to recognize PtdIns3*P* (Burd and Emr 1998). Its name originated from the four molecules (three from baker's yeast) in which this module was first described (Fab1, YOTB, Vac1 and EEA1). FYVE domains use two Zn^{2+} ions to stabilize their structure and they are also called FYVE zinc fingers. They show structural similarities to the C1 domains that recognize diacylglycerol (Misra and Hurley 1999; Kutateladze et al. 1999).

PX domain: Phox-homology domains were also recognized as capable of binding PtdIns3*P*. They were initially found in sorting nexins (Ponting 1996) and NADPH oxidase subunits (Bravo et al. 2001; Ellson et al. 2001; Kanai et al. 2001), but they are present in a large variety of signaling molecules. PX domains can also bind other phospholipids, such as PtdOH and PtdIns(3,4)P_2, and they also interact with proteins (Vollert and Uetz 2004).

Phosphoinositide binding protein domains: In addition to the above defined protein modules, several other modular protein domains have been identified as phosphoinositide effectors (Lemmon 2008). Because of their increasing number they will not be listed here but can be found in the individual Chapters.

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