Advances in Enzyme Regulation 51 (2011) 84–90

Contents lists available at ScienceDirect

Advances in Enzyme Regulation

journal homepage: www.elsevier.com/locate/advenzreg

Inositol and its derivatives: Their evolution and functions

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Introduction

The last quarter of century has seen an extraordinarily diverse set of functions assigned to inositol (Ins) phospholipids and inositol polyphosphates. Most of the key advances have come from studies of animal and yeast cells. Buttressed by evidence from other eukaryotes, these studies have identified a ubiquitous suite of core eukaryotic functions for these molecules and also other functions that probably developed later in eukaryote evolution. Employment of PtdIns as an abundant membrane lipid and of PtdIns3*P* and PtdIns(3,5)P_2 as regulators of membrane traffic are amongst the ubiquitous functions. PtdIns(4,5)P_2 seems widely to be a target of phospholipase C action, but it is not clear either when and how during evolution this reaction came under receptor control or what events garnered PtdIns(4,5)P_2 its roles in other processes such as cytoskeletal regulation and ion channel modulation. And signalling through PtdIns(3,4,5)P_3 probably developed quite late in eukaryotic diversification.

So how, evolutionarily, did the current distribution of Ins derivatives and their numerous functions in diverse organisms develop? There is now widespread agreement that the initiating events that led ultimately to the modern eukaryote cell included a series of ancient symbiotic alliances between primeval prokaryotes. But it is still not certain which organisms were involved, and when and in what order the events that yielded the first cell that we would recognize as a eukaryote occurred. PtdIns is ubiquitous in eukaryotes, in which it is the precursor of all other Ins phospholipids. Extrapolating from various early observations I suggested, some time ago: “Assuming that the biosynthesis of PtdIns evolved only once, this must have happened in a prokaryote more than 1000 million years ago” (Michell, 1987).

At that time prokaryote taxonomy was undergoing a revolution of which I was unaware. This divided all of the diverse microorganisms that had previously been gathered under the heading ‘prokaryotes’ into the Eubacteria and the Archaea (Woese et al., 1978). It became clear that members of these two new groupings of microorganisms are genetically as dissimilar from each other as either is from eukaryotes. And then it was recognized that the machinery for some key nuclear and cytosolic functions in eukaryotes – such as DNA replication – is more similar to their equivalent in archaeons than in bacteria. Many, but not all, models of the origins of the eukaryotic cell now envisage it as having involved a merging of contributions from pre-existing bacteria and archaea (Baldauf, 2003; Poole and

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0065-2571/$ – see front matter
doi:10.1016/j.advenzreg.2010.10.002

Penny, 2007; Foster et al., 2009). Assuming this is correct – which can never be certain – the quote in the previous paragraph can be reformulated as a question: which of the eubacterial and archaeal progenitors of the emerging eukaryote brought Ins and Ins lipids with it?

Direct experimental information on Ins lipid chemistry and biochemistry in prokaryotes other than Actinobacteria remains pretty scant. However, there has been a recent deluge of genomic information from all types of organisms, and this allows deductions about Ins lipid usage in many unexplored organisms. When this evidence is considered as a whole, it permits a start on a speculative reconstruction of the evolutionary history of the use of Ins and Ins phospholipids by cells: this points to invention of Ins synthesis and utilization in membrane phospholipids by some early member of the Archaea. I will first discuss the growing information from this group of organisms, and then briefly move on to bacteria and consider eukaryotes. Detailed references for most of the information and arguments summarized here can be found in Michell (2007, 2008).

Whether *myo*inositol might be a molecule that existed even before the emergence of life is a question on which Agranoff (2009) has mused. Ins does not seem to have been reported amongst the molecules that have been produced by putative prebiotic synthesis experiments, but some unidentified inositol(s) have been tentatively identified in carbonaceous chondrites (Cooper et al., 2001) – these are meteorites that have long been known to harbour organic molecules that seem to be of prebiotic and extraterrestrial origin. Benner et al. (2010) offer a detailed discussion of chemical routes by which diverse cosmochemical polyols might have been formed.

Archaeal synthesis and use of Ins

Two of the most striking early discoveries, from analysis of the phospholipids of extreme halophilic 'bacteria' such as *Halobacterium cutirubrum*, were: a) that the hydrophobic components of their membrane phospholipids and glycolipids are polyisoprene ethers of glycerol; and b) that the stereochemical configuration of their core diradylglycerol is the mirror image of that in eukaryotes and bacteria (Kates et al., 1967): *sn*-2,3-diphytanylglycerol (or other *sn*-2,3-diradylglycerols in which the radyl groups were related polyisoprenoid chains), rather than the *sn*-1,2-diacylglycerol (or dialkyl/dialkenyl variants) that is found in Eukarya and in most other 'bacteria'.

Partly as a result of this information, these and many other 'prokaryotic' organisms – especially some that lived in various 'extreme' environments (salty, hot, acidic, etc.) – were reclassified out of Bacteria and into the new kingdom Archaea (Woese et al., 1978). The first pointer to the definition of this fundamental new subdivision of Life was that the 18S ribosomal RNA sequences of putative archaeal organisms formed a grouping that is as divergent from standard bacteria (now Eubacteria) as from eukaryotes. That *sn*-2,3-di-O-phytanyl-glycerol-1-phosphate formed the basic core structure of their membrane phospholipids was then recognized as another cardinal feature of all Archaea: this phospholipid backbone was given the name archaetidyl (abbreviated Arc) to distinguish it from the phosphatidyl (Ptd) core of bacterial and eukaryote phospholipids.

Early archaeal studies – mainly in extreme halophiles and in methanogens such as *Methanobacterium thermoautotrophicum* – revealed that sugars and phosphoglycerol are common headgroups of archaeal membrane lipids. A lipid with an Ins*P* headgroup – putatively archaetidylinositol (ArcIns: Fig. 1), the archaeal homologue of phosphatidylinositol (PtdIns) – was found in *Sulpholobus acidocaldarius* as early as 1974 (Langworthy et al., 1974), even before recognition of the Bacteria/Archaea dichotomy and assignment of *Halobacterium* sp. and *Sulpholobus* sp. to the Archaea (Magrum et al., 1978; Kaine et al., 1983). Not until 1991 was ArcIns again reported as an archaeal phospholipid (Nishihara and Koga, 1991; Nishihara et al., 1992), and it was then shown that the Ins*P* headgroup of ArcIns has the same D-Ins-1-*P* configuration as the headgroup of the PtdIns of bacteria and eukaryotes. Using the common convention that D-*myo*-inositol derivatives may be abbreviated simply to InsX, this becomes Ins1*P*.

For archaea to make Ins lipids they need a source of Ins. Many archaea live in hostile and largely abiotic environments such as hot springs, so must make their own. All biological *myo*inositol seems to be made by a single type of enzyme (*myo*inositol-3-phosphate synthase, MIPS) (Stieglitz et al., 2005). This converts the ubiquitous central metabolite glucose-6-phosphate, via a 5-ketoglucose-6-phosphate intermediate, to Ins3*P* (which is synonymous with L-*myo*inositol-1-phosphate). At least in eukaryotes,

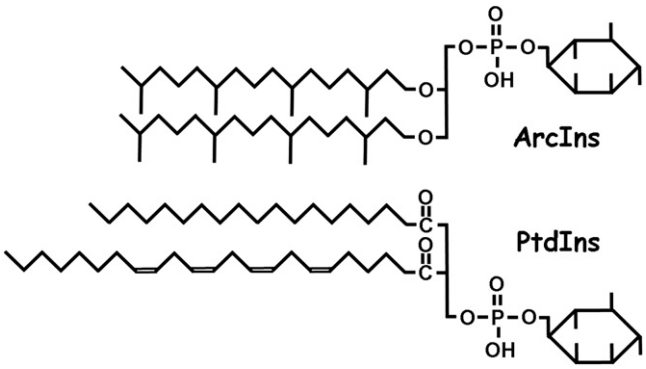

Fig. 1. Archaeal and eukaryal/bacterial phosphoinositides. Glycerophosphoinositides of archaea (exemplified by ArcIns) have glycerol backbones in which the Ins1*P* headgroup is attached to the *sn*-1 hydroxyl group of glycerol: polyisopranoid O-ethers are attached to the *sn*-2 and *sn*-3 carbons. The side-chains vary in different archaeons – they may include one or more cyclopentane or cyclohexane rings, double bonds or other modifications. PtdIns of eukaryotes and some bacteria has the same Ins1*P* headgroup, but it is attached to the *sn*-3 hydroxyl group of glycerol: in PtdIns molecules fatty acyl residues are attached to the *sn*-1 and *sn*-2 hydroxyls through carboxylic ester groups. PtdIns and other glycerophosphoinositides in mammalian tissues are often dominated by the depicted (*sn*-1-stearoyl,2-arachidonyl) pairing of fatty acids, but other organisms often employ different fatty acid pairings.

it appears that Ins3*P* is then dephosphorylated by inositol monophosphatase to yield the free Ins that is used for later reactions. This and a number of the metabolic reactions involved in the metabolism of Ins derivatives in the various classes of organisms are summarized in Fig. 2.

Biochemical and genomic exploration has shown that MIPS is found in most archaeons (the extreme halophiles are a notable exception), in a minority of bacteria (notably most or all actinobacteria and some hyperthermophiles) and in almost all eukaryotes (see Michell, 2008), though often not in all tissues.

MIPS-encoding genes are present in most organisms from the Euryarchaeota and Crenarchaeota, the two archaean phyla studied to date, and a database search also identifies MIPS genes in archaeons from two more recently characterised deeply branching phyla (Thaumarchaeota and Korarchaeota). This near-ubiquity make it likely that MIPS first emerged in an archaeon that predated the separation of these phyla, and that it has been retained by most extant Archaea. Archaeal Ins lipids do not form stable bilayers in high salt media – the phospholipids of extreme halophiles lack Ins lipids and are dominated by archaetidylglycerolmethylphosphate (ArcGro*P*Me) (Tenchov et al., 2006): maybe these archaeons lost an ancestral capability to make Ins and Ins phospholipids as they became adapted to increasingly salty environments (see Michell, 2007)?

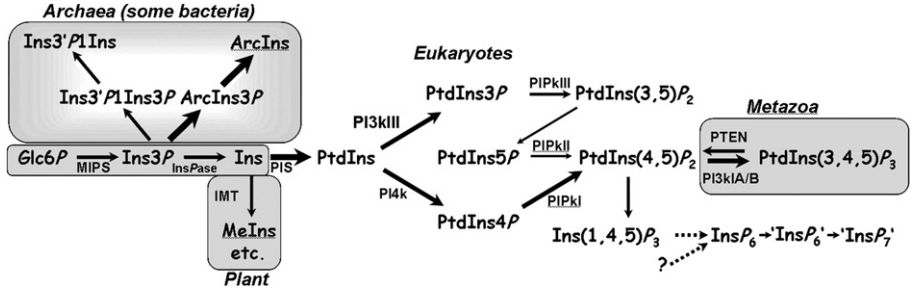

Fig. 2. Outline of metabolic pathways for inositol derivatives. The widths of arrows give some indication of the relative rates of the pathways. The boxes indicate in which restricted groups of organisms there is evidence for each pathway: the unlabelled box encloses the universal synthetic route to Ins. The question-mark acknowledges the existence of multiple, but not fully understood, routes to InsP_6. Abbreviations: **MIPS**, Ins3*P* synthase; **Ins*P*ase**, inositol monophosphatase; **PIS**, phosphatidylinositol synthase; **IMT**, inositol methyltransferase; **PI4k**, PtdIns 4-kinase; **PIPkI**, PtdIns4*P* 5-kinase; **PIPkII**, PtdIns5*P* 4-kinase; **PI3kIII**, PtdIns 3-kinase; **PIPkIII**, PI3*P* 5-kinase; **PI3kIA/B**, PtdIns(4,5)P_2 3-kinase Types A and B; **PTEN**, PtdIns(3,4,5)P3 3-phosphatase; **PIC**, phosphoinositidase C.

Archaeal Ins3′P1Ins3P synthesis

Archaea use Ins for at least two purposes: to make membrane phospholipids and – in some species – to make several 'compatible' or 'protective' solutes: di-inositol-1,3′-phosphate (Ins3′*P*1Ins); mono- and di-mannosides of Ins3′*P*1Ins; and/or a glycerophosphoinositol (Gro3*P*1Ins) (see Rodrigues et al., 2009). These typify the quite widespread use of Ins derivatives for such purposes in a variety of organisms. (e.g. Yancey, 2005). For example, springtails (eudaphic collembolans) – which are small invertebrates with permeable external cuticles that live in and on damp soil – respond to dehydration by synthesis of remarkably high concentration of free Ins (Bayley and Holmstrup, 1999). These both physically stabilize cell components and provide an osmotic drive when the supply of water to rehydrate them is limited.

Elucidation of the synthesis of Ins3′*P*1Ins, a 'compatible solute' made by some hyperthermophilic archaeons, introduced an unexpected new 'headgroup' donor in the form of CDP-Ins (termed Ins3*P*-CMP in the accompanying equations, to make clear its role as a donor of Ins3*P*): see Reactions 1 and 2. Ins3*P*-CMP is synthesized from CTP and Ins3*P* (Reaction 1), it donates Ins3*P* to the 1-hydroxyl of a second molecule of Ins3*P* (Reaction 2), making Ins3′*P*1Ins3*P*, and this is dephosphorylated (Reaction 3). This reaction sequence converts two molecules of newly synthesized Ins3*P* into a single molecule of Ins3′*P*1Ins (Borges et al., 2007; Rodionov et al., 2007).

$$\mathrm{Ins3}P + \mathrm{CTP} \rightarrow \mathrm{Ins3}P - \mathrm{CMP} + \mathrm{PP_i} \quad (1)$$

$$\mathrm{Ins3}P + \mathrm{Ins3}P - \mathrm{CMP} \rightarrow \mathrm{Ins3'}P\mathrm{1Ins3}P + \mathrm{CMP} \quad (2)$$

$$\mathrm{Ins3'}P\mathrm{1Ins3}P \rightarrow \mathrm{Ins3'}P\mathrm{1Ins} + \mathrm{P_i} \quad (3)$$

Archaetidylinositol biosynthesis

Many years ago, studies of PtdIns biosynthesis in eukaryotes led to acceptance of the idea that introduction of Ins into PtdIns occurs by linkage of the free 1-hydroxyl of Ins to a phosphatidyl residue that is donated by CDP-diacylglycerol (Agranoff et al., 1958; Paulus and Kennedy, 1960). It was therefore a surprise when it was discovered (Morii et al., 2009) that the biosynthesis of archaetidylinositol (ArcIns) in *Methanothermobacter thermoautotrophicus* follows a different pathway that is analogous to the biosynthesis of Ins3′*P*1Ins just described (Reactions 4 and 5, and Fig. 2). In the process the free 1-hydroxyl of Ins3*P* is linked to archaetidate (the archaeal homologue of phosphatidate) in a reaction similar to that involved in PtdIns biosynthesis – except that the archaetidate is donated to Ins3*P* rather than Ins. Prior to this, there were no reports outside the eukaryotes of any Ins lipid that has a monoester phosphate on the Ins ring.

$$\mathrm{CMP} - \mathrm{Arc} + \mathrm{Ins3}P \rightarrow \mathrm{ArcIns3}P + \mathrm{CMP} \quad (4)$$

$$\mathrm{ArcIns3}P \rightarrow \mathrm{ArcIns} + \mathrm{P_i} \quad (5)$$

ArcIns3*P*, this novel lipid intermediate in ArcIns synthesis, is structurally analogous to eukaryal PtdIns3*P*, but it is synthesized by a quite different route (see Fig. 2). In eukaryotes, PtdIns3*P* is essential both for central membrane-sorting events in endosomal trafficking and for effective cytokinesis, and its interaction with parts of the membrane-sorting ESCRT-III complex is important to the latter process (Sagona et al., 2010; Nezis et al, 2010). Very recent evidence indicates that cell division in some archaea also involves proteins homologous to parts of the eukaryotic ESCRT-III apparatus (Samson and Bell, 2009; Makarova et al., 2010), so might ArcIns3*P* yet prove to have a role in such processes?

Inositol in bacteria

Ins lipids were discovered in a mycobacterium (Anderson and Roberts, 1930), but the majority of bacteria lack the ability to synthesize Ins and have no Ins in their membrane phospholipids.

Some time ago a comparison of the gene sequences of the MIPSs of Archaea and of those bacterial clades that were then known to make Ins derivatives led to the conclusion that the sequences of bacterial MIPSs, at least in Actinobacteria and in the thermophiles *Aquifex* and *Thermotoga*, were unexpectedly similar to those of archaeal MIPSs. This was interpreted as meaning that these bacteria or their ancestors probably obtained their MIPSs by multiple lateral gene transfers from various Archaea (Bachhawat and Mande, 2000; Nesbø et al., 2001). Gene sequences of putative MIPSs have since been reported from the genomes of many more Eubacteria, and it will be interesting to examine whether their sequences suggest that they were also recruited at some time in the past by transfer of archaeal genes.

Moreover, some hyperthermophilic eubacteria, including *Aquifex* and *Thermotoga*, have an Archaea-like ability to make Ins3′*P*1Ins when stressed, it seems by the same pathway as in Archaea. Where did this pathway arise originally, in Archaea or in Eubacteria – and was its appearance in both kingdoms again a result of gene transfers? Rodrigues et al. (2007) discussed this question but came to no clear conclusion.

Some bacteria, notably most or all Actinobacteria, use PtdIns as the core of a number of membrane and cell wall constituents, including several PtdIns mannosides and complex lipomannans. Ins is also a component of mycothiol, present in most actinobacteria as an essential and unusual cellular redox regulator – mycothiol synthesis is one possible target for new antitubercular medications (Newton et al., 2008).

Another similarity between archaea and mycobacteria was revealed by the recent discovery that when the putative PtdIns synthases of several *Mycobacterium* species are introduced into *E. coli* (which neither contains nor can make Ins) they are very inefficient at synthesizing PtdIns by transferring a phosphatidyl residue to the 1-hydroxyl of free Ins – i.e. by the pathway that was expected and previously reported (Jackson et al., 2000). Instead, these enzymes rapidly catalyse the transfer of a phosphatidyl residue from CDP-diacylglycerol (shown as CMP-Ptd to emphasise its role as a Ptd donor) to the 1-hydroxyl of Ins3*P* in a reaction analogous to that by which archaea make ArcIns3*P* (Reaction 6) (Morii et al., 2010). Just before this report, another group independently found PtdIns3*P* in a mycobacterium (Morita et al., 2010), complementing the slightly earlier discovery of ArcIns3*P* in archaea (see above).

$$\text{Ins3}P + \text{CMP} - \text{Ptd} \rightarrow \text{Ptd1Ins3}P + \text{CMP} \tag{6}$$

$$\text{PtdIns3}P \rightarrow \text{PtdIns} + \text{P}_\text{i} \tag{7}$$

These discoveries of phosphoinositides carrying a 3-phosphate group on the Ins ring both in archaea and in mycobacteria were the first to show the presence in organisms other than eukaryotes of a phosphoinositide with a phosphorylated Ins headgroup – and they established a new type of biosynthetic route that seems most likely to have originated in early Archaea. These observations pose several obvious and immediate questions: for example, might this type of biosynthetic route occur and/or have any role in eukaryotes; and do ArcIns3*P* and PtdIns3*P* – the only polyphosphoinositides so far seen in Archaea or Eubacteria – have any roles in these organisms other than as intermediates in ArcIns and PtdIns synthesis?

All eukaryotes use inositol lipids

All eukaryote cells employ Ins in their membrane phosphoinositides, and usually for other processes such as the synthesis of diverse Ins polyphosphates. Again information on their distribution and usage comes from a combination of direct biochemical evidence on a few species and genomic inferences about the distribution of various enzyme activities and of protein domains with binding specificities for particular phosphoinositides and/or Ins polyphosphates.

The text and Table 1 of Michell (2008) both summarise the status in various eukaryote groupings of the enzymes catalysing many of the reactions summarized in Fig. 2 and comment on the evolution of the uses of polyphosphoinositides by eukaryotic cells. A detailed discussion of the evolutionary origins of these distributions will not therefore be offered here. Instead, some key points, summarized in Fig. 3,

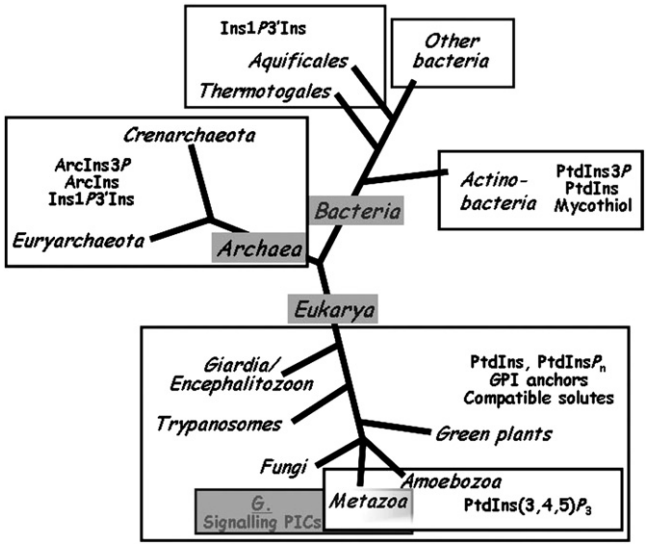

Fig. 3. Development of the diverse usage of inositol derivatives through evolution. The underlying tree, emphasising organisms from which there is information on utilisztion of inositols and/or a near-complete genome, is based on recent attempts at reconstructing the Tree of Life, especially the emerging close relationship between Metazoa, Amoebozoa and Fungi (see Michell, 2008 for details and references). Each box emphasises the most characteristic aspects of the utilization of inositols in each group of organisms. Details of other uses of inositol by those phylogenetic groups are given in Michell (2007) and in Table 1 of Michell (2008).

can be noted. First, PtdIns3*P*, PtdIns(3,5)P_2 and PtdIns(4,5)P_2 all seem likely to be made by all eukaryotes – in all cells? There might be a very few extreme exceptions (for example, microporidian intracellular pathogens that have very reduced genomes) but whether these obtain these lipids from their hosts is not known. Signalling through PtdIns(3,4,5)P_3 seems to have been a late-comer during eukaryote diversifications. It appears to be confined to a later-evolved group of eukaryotes that includes amoebozoans, choanoflagellates and metazoans – but not fungi. Assuming that recent interpretations of eukaryote diversification are basically correct, it seems likely that PtdIns$(3,4,5)_3$ and the machinery needed for its core functions were present in the common ancestor of all fungi, but were lost before the evolutionary radiation that gave rise to today's fungi (see Michell, 2008).

Summary

Ins and Ins phospholipids are present in and are made by most Archaea and all eukaryotes. Relatively few bacteria possess Ins phospholipids: and only one major grouping, the Actinobacteria, is known to have evolved multiple functions for Ins derivatives. The Ins phospholipids of all organisms, whether they have diradylglycerol or ceramide backbones, seem to use the same Ins1*P* headgroup stereochemistry, so they are probably made by evolutionarily conserved pathways.

It seems likely that an early member of the Archaea made the first phospholipid with an Ins1*P* headgroup – maybe three billion years ago – and that a much later archaeal descendent was the ancestral contributor that brought these molecules into the common ancestor of all eukaryotes – maybe two billion years ago (Michell, 2007, 2008). It will only be possible to infer the likely details of these processes when we have learned much more about the Ins lipid biochemistry of modern archaeons.

All eukaryotes make substantial amounts of PtdIns, both as a 'bulk' membrane phospholipid and as the precursor of seven phosphorylated derivatives of PtdIns (the polyphosphoinositides; PPIn) and of the 'GPI anchors' of cell surface ectoproteins. PtdIns(4,5)P_2 – with its many functions – and its precursor PtdIns4*P* are found in all in eukaryotes. So are PtdIns3*P* and PtdIns(3,5)P_2, which have ubiquitous roles in the regulation of membrane trafficking events. However, synthesis of and signalling by PtdIns(3,4,5)P_3 appears to be confined to a later-evolved group of eukaryotes.

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