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Review

Enrichment of phosphatidylinositols with specific acyl chains ☆

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ABSTRACT

There are six major species of phospholipids in eukaryotes, each of which plays unique structural and functional roles. One species, phosphatidylinositol (PI) only contributes about 2–10% of the total phospholipid pool. However, they are critical factors in the regulation of several fundamental processes such as in membrane dynamics and signal transduction pathways. Although numerous acyl species exist, PI species are enriched with one specific acyl chain composition at both *sn−1* and *sn−2* positions. Recent work has identified several enzymes that act on lipids to lead to the formation or interconversion of PI species that exhibit acyl chain specificity. These enzymes contribute to this lipid's enrichment with specific acyl chains. The nature of the acyl chains on signaling lipids has been shown to contribute to their specificity. Here we review some of the critical functions of PI and the multiple pathways in which PI can be produced and metabolized. We also discuss a common motif that may confer arachidonoyl specificity to several of the enzymes involved. This article is part of a Special Issue entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

Contents

Abbreviations: 2-AG, 2-arachidonoylglycerol; CDS, CDP-diacylglycerol synthase; CDP-DAG, CDP-diacylglycerol; DAG, diacylglycerol; DGK, diacylglycerol kinase; ER, endoplasmic reticulum; IP_3, inositol triphosphate; LPA, lysophosphatidic acid; LPIAT1, lysophosphatidylinositol acyltransferase 1; PA, phosphatidic acid; PI, phosphatidylinositol; $PI(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; PI4P5K, phosphatidylinositol-4-phosphate 5-kinase; PIP_ns, phosphorylated forms of PI; PIS, PI synthase; PKC, protein kinase C; PLC, phospholipase C; PM, plasma membrane; PUFA, polyunsaturated fatty acids; SAG, 1-stearoyl-2-arachidonoyl glycerol

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1. Introduction

The major focus regarding the lipid composition of biological membranes and the roles of lipids in signal transduction has been on the nature of the lipid headgroup. However, it is well established that the acyl chain composition of lipids also has an important biological role. This is at first surprising since acyl chains are only hydrocarbons and do not contain a variety of polar groups that can result in specific interactions. An example of a specific role of an acyl chain is the finding that one specific acyl chain, the arachidonoyl (20:4) chain (Table 1 shows some acyl chain structures) attached to phosphatidylcholine oscillates during the cell cycle and delays cell cycle progression as a consequence of inhibiting the binding of Akt [1]. There are several mechanisms by which acyl chains can modulate function. One mechanism is by changing the physical properties of the membrane, with no specific requirements for a particular chemical structure. One example of this is tafazzin, an acyl transferase that enriches cardiolipin with linoleoyl (18:2) chains, yet exhibits no substrate specificity for particular acyl chains [2]. In contrast to this, there are very specific structural requirements of certain enzymes for particular lipids, such as the specificity of certain lipoxygenases for arachidonic acid [3].

Another indication that acyl chains play a functional role is the observation that they are very unevenly distributed among lipids of different classes, *i.e.* among lipids containing different headgroups. Even within the same organism, the acyl chain composition of specific lipids is different in different organs. Furthermore, changes in the acyl chain composition of a lipid can affect its function and even lead to disease states. The factors determining the specific incorporation of particular acyl chains in certain lipids and the consequences of the loss of this specificity are only recently attracting more attention. One lipid class that is highly enriched in specific acyl chains is phosphatidylinositol (PI).

1.1. Properties of phosphatidylinositols

Phosphatidylinositol (PI) is composed of a glycerol backbone, with an inositol ring and a phosphate at the *sn−3* position and two acyl chains esterified at the *sn−1* and *sn−2* positions [4]. The inositol ring can be phosphorylated at multiple positions, which can yield seven unique species known as phosphoinositides (PIP_ns) (Fig. 1) [5]. PIP_ns are spatially and temporally maintained in distinct sub-cellular compartments through the concerted actions of PI-kinases and phosphatases. For example, phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$) is primarily enriched in the plasma membrane (PM), whereas phosphatidylinositol-4-phosphate (PI4P) is high in the Golgi [6,7].

Table 1
Examples of polyunsaturated fatty acids.

Common name	Lipid name	Chemical name
Omega-3 fatty acids		
Alpha-linolenic acid (ALA)	18:3 (n−3)	*All-cis*-9,12,15-octadecatrienoic acid
Eicosatrienoic acid (ETE)	20:3 (n−3)	*All-cis*-11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 (n−3)	*All-cis*-8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA, timnodonic acid)	20:5 (n−3)	*All-cis*-5,8,11,14,17-eicosapentaenoic acid
Docosapentaenoic acid (DPA, clupanodonic acid)	22:5 (n−3)	*All-cis*-7,10,13,16,19-docosapentaenoic acid
Docosahexaenoic acid (DHA, cervonic acid)	22:6 (n−3)	*All-cis*-4,7,10,13,16,19-docosahexaenoic acid
Omega-6 fatty acids		
Linoleic acid	18:2 (n−6)	*All-cis*-9,12-octadecadienoic acid
Gamma-linolenic acid (GLA)	18:3 (n−6)	*All-cis*-6,9,12-octadecatrienoic acid
Dihomo-gamma-linolenic acid (DGLA)	20:3 (n−6)	*All-cis*-8,11,14-eicosatrienoic acid
Arachidonic acid (AA)	20:4 (n−6)	*All-cis*-5,8,11,14-eicosatetraenoic acid
Docosapentaenoic acid (osbond acid)	22:5 (n−6)	*All-cis*-4,7,10,13,16-docosapentaenoic acid

PIP_n species control several different cellular processes such as the regulation of ion channels, actin-cytoskeleton dynamics, vesicular transport, endocytosis, exocytosis and signal transduction pathways [8–10]. The interactions between PIP_ns and their downstream targets are numerous and complex, so only an overview of their interactions will be discussed. Simply, downstream targets of PIP_ns are recruited and/or activated at specific sub-cellular compartments through phosphoinositide binding motifs. These interactions are primarily mediated through a combination of electrostatic and hydrophobic interactions [11]. The role of the headgroup structure in these interactions is currently better understood, however evidence is accumulating to indicate that the acyl chain composition also has an important role. Currently, ten phosphoinositide binding motifs have been characterized, each showing specificity for different PI species [12]. For example, although the adaptor proteins AP1 and AP2 bind similar cargo proteins, AP1 binds PI4P and localizes in the Golgi. AP2 on the other hand, binds $PI(4,5)P_2$ and is enriched in the PM [13,14].

1.2. Phosphatidylinositol biosynthesis

The *de-novo* biosynthesis of PI occurs exclusively in the endoplasmic reticulum (ER) and begins with the precursors, glycerol-3-phosphate or dihydroxyacetonephosphate (Fig. 2) [15]. These molecules undergo two sets of acylations through the actions of acyltransferases; the first acylation forms lysophosphatidic acid (LPA), whereas the second acylation step produces phosphatidic acid (PA) [16]. PA can also be formed through the actions of diacylglycerol kinase (DGK) on diacylglycerol

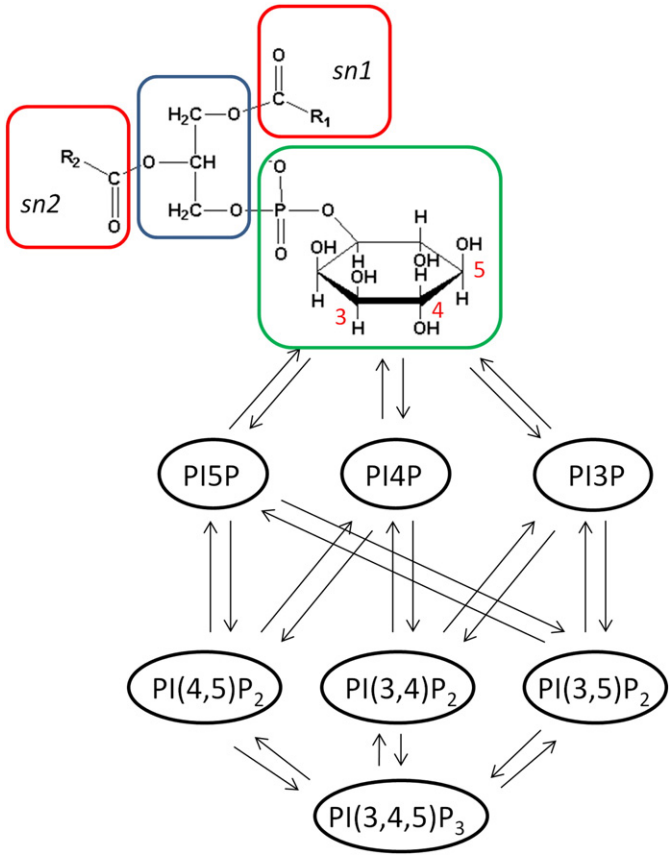

Fig. 1. The structure and production of phosphatidylinositol. Phosphatidylinositol is composed of a glycerol backbone (blue), two acyl chains at the *sn−1* and *sn−2* positions (red) and an inositol headgroup (green). The hydroxyl groups can be phosphorylated at positions 3, 4 and 5, which can yield up to seven unique phosphoinositide species. The production of these species is tightly regulated through the actions of PI kinases and phosphatases. PIP_n species can also be interconverted, as indicated by the arrows.