A tail of new lipids

Gerald R V Hammond & Tamas Balla

The inositol lipids play many essential roles in eukaryotic physiology, although the action has usually focused on the special properties of their headgroup. Now, a study by Clark *et al* (2014) re-focuses attention on the hydrophobic lipid tails, showing that these too exhibit unique biochemical properties—and are also likely to play a fundamental role in the biology of the lipid.

See also: J Clark *et al* (October 2014)

The expansive biology of inositol lipids is largely driven by reversible phosphorylation of their headgroups (Fig 1), which are then recognized by hundreds of cellular proteins (Balla, 2013). The remarkable diversity of these partner proteins explains the truly impressive array of physiological functions of these lipids. Since the binding proteins select a specific subset of phosphorylation states of the lipid headgroup, the field of inositol lipid biology has by-and-large been driven by efforts to measure the amount and cellular localization of these phosphorylated lipid isomers.

It was to this end that Clark *et al* were employing their newly devised mass spectrometry technique (Clark *et al*, 2011) to study the social amoeba *Dictyostelium discoideum*. This technique involves stabilization of the phosphorylated inositol headgroup, and scanning for ions that shed this now integral mass unit, allowing quantitative detection of the relative mass of each class of inositol lipid. The improved sensitivity and throughput make this technique a real step forward over prior isotope labelling or enzymatic methods, but with an added bonus: since it is the lipid backbone that is ionized and detected, the precise mass is measured and therefore the fatty acid composition can be deduced (Clark *et al*, 2011).

Eukaryotic lipids can select from a vast array of fatty tails, although the necessity of this variety is poorly understood. The Stephens/Hawkins laboratory had previously reported (Clark *et al*, 2011) that the fatty acid composition of inositol lipids from mammalian tissue was mostly stearyl/arachidonyl (Fig 1), as had been noted by many other studies (D'Souza & Epand, 2013). Indeed, mutant mice deficient in the capacity to synthesize arachidonyl-containing inositol lipids showed large decreases in the quantities of some (but not all) of these lipids (Anderson *et al*, 2013), proving a definitive requirement for the fatty acid, as opposed to mere circumstantial enrichment. But what is the significance of this finding? Why arachidonic acid? Does this fatty acid confer some specific property on the lipids?

These questions have so far proven largely intractable, but the current work

provides some much needed clues. Clark *et al* discovered that *Dictyostelium* also have a unique inositol lipid tail composition amongst the phospholipids. The big surprise is that rather than being occupied by a fatty acid, position 1 of the glycerol backbone is linked to a fatty alcohol (Fig 1). The resulting plasmanyl lipid is not unique; these lipids are found in all *Dictyostelium* phospholipids, not just those containing inositol (Clark *et al*, 2014). What is unique is the selective enrichment of plasmanyl lipid amongst the inositol lipids—accounting for over 95%, reminiscent of the stearyl/arachidonyl enrichment in mammalian inositol lipids. Therefore, although the biochemical nature of the lipid tails is dramatically different amongst these evolutionary distant branches, the theme of distinct hydrophobic chain profiles in inositol lipids is conserved.

Figure 1. The structure of mammalian phosphatidylinositol and the newly described amoeba plasmanyl inositol.

What is the biological consequence of this unique profile? The core eukaryotic functions of inositol lipids are conserved between *Dictyostelium* and animal cells. For example, PIP₃ in *Dictyostelium* is largely concerned with regulating the actin cytoskeleton, being nearly essential for macropinocytosis (Hoeller *et al*, 2013) and having a controversial role in chemotaxis (Hoeller & Kay, 2007); so conferring different functions on the lipids between these lineages seems unlikely. One proposal for the stearyl/arachidonyl enrichment in mammalian cells is that perhaps it enables specific interaction with other membrane lipid(s) or protein(s) that assist function or localization. Global differences in bulk membrane properties between the distant animal and amoeba lineages might then confer different physical-chemical requirements for the lipid fatty tails, and hence their different profiles.

A second intriguing possibility is put forward by Clark *et al* that the fatty tail profile might be a means of defining a metabolic pool of lipid intermediates. Stearyl/arachidonyl (mammals) or plasmanyl (Amoeba) lipids would be preferentially used for inositol lipid metabolism and thus

maintained in a separate metabolic flux from the other phospholipids. This may then enable distinct homeostatic mechanisms to control inositol lipids levels, which may be necessary given the stringent demands of their protein partners in regulating diverse physiological processes. This mechanism would also account for the deficit in inositol lipid synthesis observed when arachidonate selection is impaired (Anderson *et al*, 2013), and for the enrichment of plasmanyl lipids in the inositol lipid precursor, phosphatidic acid, in *Dictyostelium* (Clark *et al*, 2014).

For the moment, which (if any) of these theories actually explains the selection of distinct fatty tails in inositol lipid synthesis is speculative. Whatever the explanation, this study reveals yet more compelling evidence that rather than being a “business end” headgroup with a generic fatty tail, lipids are synthesized with carefully defined hydrophilic and hydrophobic moieties. We are only beginning to scratch the surface of the bilayer for what significance these structural features have, but we expect they will have profound and probably unexpected functions.

References

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