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Review

Nuclear inositide signalling—expansion, structures and clarification

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Abstract

The extent and content of this review issue highlights how our understanding of lipid signalling in the nucleus has grown, both in what we actually know, and the breadth of signalling pathways that we now have to consider. Here, a few key issues with regard to nuclear inositide signalling are briefly addressed.

Keywords: Inositol; Nucleus; Phosphatidylinositol 4,5-bisphosphate; Inositol hexakisphosphate; Inositol lipids; Nuclear envelope

1. Introduction

It is not yet 20 years since the concept of a distinct nuclear inositol lipid signalling system emerged [1], and during most of those years the world paid little attention to it. But the content of the February 2005 Gordon Research Conference in Nuclear Signaling (held in Buellton, CA, USA), which is in part reflected by the contents of this special issue, illustrates how we are increasingly re-thinking how much lipid signalling is going on inside the nucleus—more nuclear events involve the participation of lipids or their metabolic products, and more lipid pathways which we thought were only cytosolic are now emerging as also extant inside the nucleus. In fact, the wider concept of nuclear signalling removes the nuclear envelope as a major barrier to signal transduction, and embraces a flow of signals into, out of, and within both cytoplasm and nucleus. I will not make any attempt to summarise these major advances, but just briefly address a few key questions about inositol phosphates and lipids in the nucleus, as an update to an earlier discussion on these issues [2].

2. Physicochemistry

This refers to the key, but presently still unsolved problem—what is the physicochemical form of lipids within the nucleus? Because a significant part of the inositol lipids involved in nuclear signalling survives extraction of the nucleus with detergents (e.g., [1–3]), it has been an attractive idea that they are not in a lipid bilayer at all, which begs the question, so what are they in? After addition of detergent then the headgroups of the inositol lipids remaining must be bound to proteins—there are plenty to choose from [4]. Moreover, they may well have been bound to these same proteins in vivo, but the nub of the issue is, where do they put their hydrophobic tails? Perhaps, the most attractive possibility is that raised by the pioneering experiments of Hunt et al. [5], who showed that the nuclear environment contains a significant amount (they suggested up to 10% of the nuclear matrix) of dipalmitoyl phosphatidylcholine. The parallel with lung surfactant leads to the enticing thought that a kind of semi-crystalline lipid phase exists in some parts of the nucleus; could this be the environment to satisfy the hyrophobic requirements of the diacylglycerol moieties of the inositol lipids?

Alternatively, inositol lipids may be in a bilayer in the intact nucleus. If the latter possibility is true, then the paper of Echevarria et al. [6] provides an enticing insight. These authors show convincing evidence that invaginations of the nuclear envelope (itself an extension of the e.r. system), which had earlier been proposed from electron microscope studies by Fricker et al. [7], are detectable in live intact nuclei, and can generate Ins(1,4,5)P_3-mediated Ca^{2+} signals and cause PKC translocation to the nuclear envelope. If this

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is a true reflection of the state of affairs, then these lipids could be argued not to be intranuclear at all.

However, there is evidence against such an argument in the elegant quantitative studies of PtdIns(4,5)P_2 distribution in the nucleus from Osborne et al. [8] and Watt et al. [9], using respectively anti-PtdIns(4,5)P_2 antibodies, or a PtdIns(4,5)P_2-specific PH domain probe. Both groups showed extensive evidence for PtdIns(4,5)P_2 within the nucleus, but virtually none in the nuclear envelope (or the e.r.), so if invagination of the nuclear envelope is contributing the PtdIns(4,5)P_2, then these invaginations must be highly enriched in it. It is not inconceivable that PtdIns(4,5)P_2-binding proteins (which are genuinely intranuclear) could concentrate bilayer PtdIns(4,5)P_2, such that it appears to be (and functionally behaves as) intranuclear.

Most studies that have looked at PtdIns(4,5)P_2 localisation in the nucleus concur with the majority of both PtdIns(4,5)P_2 [8,9] and the enzyme that makes it, Type I PtdIns4*P* 5-kinase [10], being localised to nuclear 'speckles'. These are dynamic nuclear structures of undefined, possibly multiple functions (see [11] for review, and note that Osborne et al. [8] did present evidence linking PtdIns(4,5)P_2 with m-RNA splicing). If PtdIns(4,5)P_2 and its synthesis is indeed intimately associated with these speckles, it is interesting to note a recent connection drawn between the regulation of splicing and the PtdIns(3,4,5)P_3-Akt pathway [12]; the assumption in this study was that the Akt entered the nucleus already activated, but our new perspective on nuclear lipid signalling surely opens the likelihood that the PtdIns(3,4,5)P_3 was generated within the nucleus.

Another relevant observation in this context is that after detergent extraction of liver nuclei, the small amount of phosphatidylinositol (PtdIns) that is left is still capable of acting as a substrate for the PtdIns kinase present—indeed, it appears to serve as a 'privileged' substrate because with 95% of the PtdIns removed by detergent, at least 50% of the 'substrate PtdIns' remains [13]. Evidence from the same study [13], and another on murine erythroleukemia cells [14], implied the existence of multiple, metabolically distinct pools of other lipids within nuclei with similar 'privileged' access to enzymes. One could argue that overall this kind of phenomenon is not immediately consistent with the concept that these lipids are an artefactual remnant—that is, that they were in a classic lipid bilayer until the addition of the detergent, and then they stuck randomly to lipid-binding proteins instead of being extracted along with the majority of the lipids. Rather, these data suggest that the spatial architecture has not been radically altered by the removal of most of the lipids by detergents, and that something more like a direct substitution of lipid phase (nuclear envelope invaginations, or dipalmitoyl phosphatidylcholine) by detergent molecules has occurred.

Finally, in this context it may be useful to bring up the interesting concepts raised by McLaughlin and Murray [15] with regard to PtdIns(4,5)P_2 sequestering/binding and regulation by proteins. Their suggestion is that some PtdIns(4,5)P_2-binding proteins (in particular they suggest MARCKS and GAP43) act as 'sinks' of PtdIns(4,5)P_2, which the cell can call upon when PtdIns(4,5)P_2 is needed, this process of PtdIns(4,5)P_2 'release' probably being regulated by phosphorylation of the PtdIns(4,5)P_2-binding protein. This PtdIns(4,5)P_2 could still be contained within a lipid bilayer (in that context, the plasma membrane), so this idea is surely adaptable to the nucleus, and thus it could encompass the concepts of either intranuclear membrane invaginations [6,7], or a lipid phase of dipalmitoyl phosphatidylcholine [5]. Could this be a model for PtdIns(4,5)P_2 (and other inositol lipids) in the nucleus? And if so, what are the nuclear equivalents (if not themselves) of MARCKS and GAP43, and do nuclear 'speckles' contain high levels of them?

3. Enzymes

An exciting amount of progress has been made in the last couple of years in our understanding of the enzymology of nuclear lipid metabolism and how it is regulated. Phosphoinositide-phospholipase C (PI-PLC) β_1 is still the most well studied of these (see Cocco's and Martelli's reviews), though a recent quantitative analysis [16] of PI-PLC isoforms in the nuclei of regenerating rat liver emphasised the different contributions of other isoforms to separate phases of PI-PLC activation. Thus, tyrosine phosphorylation of PI-PLCγ was responsible for the increase in PI-PLC activity 20 h after partial hepatectomy, whereas the peak at 6 h could be attributed to the well known serine-phosphorylation (presumably by ERKs [17]) of PI-PLCβ_1; note that it was the PI-PLCβ_1b splice variant which was principally responsible for the latter increase [16]. This particular splice variant was also implicated by the same group in the alterations in PI-PLC activity during the cell cycle in synchronised HL-60 cells [18].

Crljen et al. [16] also confirmed the presence of the PI-PLCδ_1 isoform in rat liver nuclei (see review by Yagisawa for more on this isoform), but it is interesting that they found no change in nuclear PI-PLCδ_1 at any point of the liver regeneration process, despite the fact that this process is accompanied by extensive (and co-ordinated) cell proliferation. Yet, a recent paper by Stallings et al. [19] shows a cell-cycle-dependent control of nuclear localisation of PI-PLCδ_1 in NIH-3T3 fibroblasts. We are learning more and more about the various PI-PLCs that localise to the nucleus, but it is clear that we still have a lot to learn about what each isoform contributes. Note that the study of Strallings et al. study [19] also throws some interesting light on how PI-PLCδ_1 is retained in the nucleus—mutation of its PtdIns(4,5)P_2-binding PH domain decreased its nuclear localisation, which suggests a fascinating interrelationship between an enzyme and its substrate, whereby the location (and thus the activity in that location) of an enzyme is regulated in part by the presence of the substrate that it is removing.

4. Inositol phosphates

I include a short discussion of these too, as although they are not lipids, and are covered more extensively by York (see review in this issue), they remain a focus of personal interest [2,20,21]. The number of potential intranuclear functions for InsP_6 and pyrophosphorylated inositol phosphates have grown