EDITORIAL

Lipids as Central Mediators of Cellular Signalling

Historically, lipids were viewed as passive components of cellular membranes, providing structure and fluidity to allow regulated separation of various cellular components, as well as a platform for membrane protein insertion and localisation. It is now clear, however, that many lipids play a much more active role in cellular regulation as potent signalling molecules in their own right, often as intracellular second messengers, but in some cases acting extracellularly. As a consequence of the realisation that lipids play a significant role in cell signalling, there is considerable current research interest in both the means by which the levels of signalling lipids are regulated, and the molecular mechanisms which mediate their cellular effects. This issue's Showcase on Research presents four reviews that highlight these aspects of some important signalling lipids.

In the first article, Christina Mitchell and colleagues discuss the role of inositol polyphosphate 5-phosphatases in the regulation of phosphoinositide signalling. These lipid phosphatases, of which ten isoforms have been described in humans, remove the phosphate from the 5-position of the inositol ring of polyphosphoinositides and inositol phosphates. Their activity not only directly regulates the cellular levels of their substrates and products, but also indirectly alters the levels of other phosphoinositides in the cell through removing or providing substrates for other lipid kinases and phosphatases. Since many of these lipids act as second messengers, the activity of the 5-phosphatases have an important role in cellular signalling.

Phosphatidic acid is another signalling lipid that can be formed through the phosphorylation of diacylglycerol by diacylglycerol kinases, by the action of lysophosphatidic acid acyltransferases on lysophosphatidic acid, or through the cleavage of phosphatidylcholine by phospholipase D. The second article by William Hughes discusses the signalling functions of phosphatidic acid, and in particular phosphatidic acid produced by the activity of phospholipase D. Signalling via this phospholipase D-derived phosphatidic acid has been associated with numerous cellular processes, including phospholipid metabolism, signal transduction and vesicular trafficking.

The last two articles focus on cell signalling by sphingolipids. The first of these articles by Joanna Woodcock describes the signalling role of two sphingolipids, ceramide and sphingosine, in programmed cell death (apoptosis). For many years ceramide has been implicated in inducing apoptosis, although the molecular mechanisms of the action of this lipid are only now being elucidated. Discovery of the role of sphingosine in apoptosis is more recent, and like ceramide, acts via multiple targets. One such target of sphingosine that appears prominent in its pro-apoptotic role are the sphingosine-dependent kinases that phosphorylate and inactivate the pro-survival adaptor molecule 14-3-3.

In the fourth article, Tamara Leclercq and I discuss the roles of the pleiotropic signalling lipid sphingosine 1-phosphate that acts as both a ligand for cell-surface receptors and as an intracellular second messenger. This article describes the central function of sphingosine kinases, and their activation and cellular localisation in the regulation of sphingosine 1-phosphate signalling, particularly in the context of the development of potential therapeutics to combat cancer and inflammation.

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Cover Illustration

Localisation of PtdIns(4,5)P_2 in pancreatic β-cells.

This image shows the localisation of phosphatidylinositol 4,5-bisphosphate (green) in pancreatic β-cells via expression of green fluorescent protein fused to a pleckstrin homology domain that specifically binds this signalling lipid. Actin is stained red and insulin granules stained blue.

Image supplied by William Hughes, Garvan Institute of Medical Research, Sydney.

Lipid Signalling

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In the next issue...

In August, Showcase on Research will be on **Marsupial Models in Biochemistry** – *Guest Editor: Samantha Richardson*