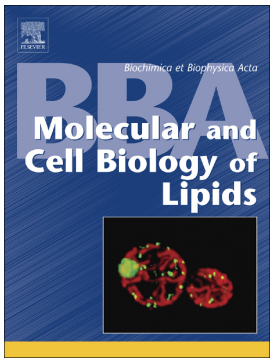
Special issue entitled Lipid transporters edited by Shamshad Cockcroft and Padinjat Raghu



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Editorial

Special issue entitled Lipid transporters edited by Shamshad Cockcroft and Padinjat Raghu.

In 2007, a Special issue of BBA Molecular and Cell Biology of Lipids was devoted to **Lipid transporters in Cell Biology** which was edited by Shamshad Cockcroft. At that time, the field of lipid transport was just beginning to be recognized as a new emerging topic as novel lipid binding proteins and their lipid ligands were being discovered. The structures of the different lipid binding pockets of lipid transport proteins (LTPs) were beginning to be structurally characterized demonstrating how specific lipids were accommodated in the hydrophobic pockets. Often, the lipid binding pocket accommodated two different lipids allowing for lipid exchange. Thus, the main concept was that LTPs were thought to transport lipids by a shuttling mechanism; the LTP extracts a lipid from a donor membrane, diffuses through the cytoplasm, and delivers the lipid to an acceptor membrane. Since the publication of the Special issue in 2007, the field has expanded in unexpected ways. Two major themes have emerged. First, the concept of lipid traffic taking place at membrane contact sites and secondly, identifying lipid transporters that use inositol lipids for the transport of lipids against their concentration gradients. Many LTPs working at membrane contact site are multi-domain proteins. In addition to the lipid binding domain, other domains bind to the opposing membranes to bring the two membranes together. Lipids such as phosphatidylserine and cholesterol are enriched at the plasma membrane and thus have to be moved 'uphill' from an area of low concentration to a high concentration. Here the use of phosphatidyl-4-phosphate to power this exchange has been a major conceptual advance. This theme is explored in a review by **Eammon Dickson**. In addition, new families of lipid transporters have been identified (chorein domain family) where these LTPs localize to two compartments simultaneously, forming a bridge to shuttle multiple lipids from a donor to an acceptor compartment.

Synthesis of phospholipids and cholesterol occurs primarily at the endoplasmic reticulum compartment with some contribution from the Golgi. Since different membrane compartments have distinctive lipid compositions contributing to their membrane characteristics and function, delivery of specific lipids by LTPs provides a mechanism for selective transfer, not accomplished by vesicular traffic. Moreover, some organelles such as mitochondria are not recipients of vesicular traffic. Whilst transfer of lipids can occur from their site of synthesis to other compartments based on concentration gradients, many lipids are transported against their concentration gradient. Thus, an important development in the field of lipid transport is the use of phosphoinositides in driving lipid transport.

The discovery of the chorein domain family of LTPs that can transport lipids in bulk is underscored by the identification of Vps13 (vacuolar protein sorting 13) and the autophagy-related protein 2 (Atg2). These proteins bind two membranes simultaneously and allow lipids to flow between the membranes in a hydrophobic channel formed by the LTP. The channel accommodates the lipid tails rather than the headgroup. The first two reviews by **Leonzino, Reinisch and De Camilli** on Vps13 and by **Noda** on Atg2 describe this mechanism of lipid transfer to provide for bulk lipid for membrane growth.

Cholesterol content in membranes is highly regulated and the plasma membrane is one of the major compartments where cholesterol is enriched. Its transport pathways within cells is an area of intense study and here **Hoglinger et al** describe methods on how to find cholesterol in cells. Many LTPs that can transport cholesterol have been identified including some members of the OSBP/ORP proteins and START family of proteins. The ORD and Start domain of these proteins can bind and transport cholesterol. Thus, the identification of a new family of proteins referred to as GRAMD1s/Asters/Lam

proteins in 2015 has added a new dimension to cholesterol traffic. **Saheki et al** describe this new family of cholesterol transporters.

Of all the cellular lipids, phosphoinositides are the most versatile. Phosphoinositides participate in lipid signaling via phospholipase C and Phosphoinositide kinases (PI3Ks), membrane traffic, cytoskeletal remodeling and as devices to recruit proteins to membranes. All phoshoinositides are derived by phosphorylation of the primary lipid, phosphatidylinositol (PI). The family of proteins that can bind and transport PI belongs to two unrelated families, the PITP family and the SEC14 family. **Raghu et al** describe the multi-domain family of PITPs which can function at membrane contact sites whilst **Cockcroft et al** describe the function of PITPs which are present as single domains and thus do not have other targeting domains for membrane recruitment. In contrast to the PITPs which have a limited number of family members, the SEC14 family is a very large family. **Griac et al** describe the functions of this family in yeast, where the founding member, Sec14p was first identified. Interestingly, the different members of this family all bind and transfer PI but their counter ligand ranges from phosphatidylcholine to sterols, squalene, PS and even heme.

Lipid transfer proteins that participate in sphingolipid/glycolipid transport are described by **Mattjus et al.** Ceramide transport protein (CERT) and glycolipid transfer protein (GLTP) family are described including the more recently identified member, CPTP, which transfer ceramide phosphate. Van Ooij et al provides a comprehensive analysis of LTPs present in the **plasmodium** parasite. Here members of Sec14 family, Start family, GLTP are all present but most LTPs remain poorly characterized. Most lipid transfer proteins contains highly structured domains as well as regions of intrinsic disorder. **Antonny et al** describe the various roles of these intrinsically disordered regions.

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Atg2 and Atg9: Intermmebrane and interleaflet lipid transporters driving autophagy
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GRAMD1-mediated accessible cholesterol sensing and transport
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Sec14 family of lipid transfer proteins in yeasts
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Raghu Padinjat is a Professor at the National Centre for Biological Sciences-Tata Institute of Fundamental Research (NCBS-TIFR), Bengaluru, India. He graduated with a degree in clinical medicine from St. John's Medical College, Bengaluru and then obtained a Ph.D from NCBS-TIFR. During this period his principal research interest was the regulation of TRP channel activation during phospholipase C signalling. Following postdoctoral work with Roger Hardie at the University of Cambridge, UK during which he participated in the discovery of TRP channel activation by lipid second messengers, he served as a David Phillips Fellow and then group leader at the Babraham Institute, Cambridge, UK. Since 2010 he has been a faculty member of NCBS-TIFR. Raghu Padinjat's group uses tractable genetic models such as Drosophila to understand the regulation of cellular function by lipid messengers during phospholipase C signalling. Most recently his work has also included the analysis of phospholipase C signalling in the context of human diseases.

Shamshad Cockcroft is a Professor of Cell Physiology in the Department of Neuroscience, Physiology and Pharmacology at University College London, UK. She did her undergraduate studies at the University of Manchester and a PhD at the University of Birmingham in the UK where she worked on cell-surface receptor-regulated phosphatidylinositol signaling with Professor Bob Michell. She moved to University College London in 1977 for postdoctoral research with Professor Bastien Gomperts where she developed a long-lasting interest in the field of lipid signaling and membrane traffic. Her postdoctoral work explored the relationship between exocytosis from mast cells and neutrophils and phosphatidylinositol signaling. She received a Fellowship from the Lister Institute (1985-1991) where her focus shifted to regulation of phospholipases C and D by G-proteins. Since the last two decades, her research has focused on lipid transfer proteins, specifically on the synthesis and transport of phosphatidylinositol during phospholipase C activation by cell surface receptors. The lipid transport field remains her major interest particularly with the emerging concepts of dynamic lipid transport at membrane contact sites.