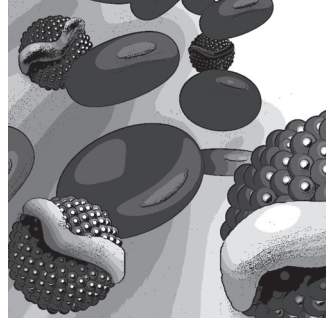

Lipid–Protein Interactions in Membranes: implications for health and disease

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It should come as no surprise that membrane lipids can profoundly affect the functions of membrane proteins. In turn, lipid–protein interactions play a major role in normal cell functioning, and hence in human health and disease. This meeting on 'Lipid–Protein Interactions in Membranes' brought together researchers from around the world to a serene oasis within the bustling metropolis of Hyderabad, India. Major aspects of this emerging field where lipids and proteins intersect were covered, with a particular focus on membrane receptors, ion channels and transporters, as well as technical challenges and advances. Here, we summarize the presentations, highlighting their clinical implications.

India's science scene is booming, with new research institutes being set up all over the country and attracting excellent researchers back to the subcontinent. Nowhere was this more evident than at the 'Lipid–Protein Interactions in Membranes' meeting, held at the Centre for Cellular and Molecular Biology (CCMB) in Hyderabad (India). This was the first Biophysical Society Thematic Meeting to be held in India and was hosted and chaired by Amitabha Chattopadhyay (CCMB), and co-chaired by Jean-Marie Ruysschaert (Free University of Bruxelles, Brussels, Belgium). The venue at the CCMB and the adjoining Indian Institute of Chemical Technology provided a serene tropical oasis within the boisterous bustling metropolis. The Indian Institute of Chemical Technology auditorium, replete with plush blue seats, is housed in an attractive building inaugurated in 1954 by India's first Prime Minister, Jawaharlal Nehru, who originally studied science at Cambridge University (UK). In his opening address, Samir Brahmachari (Director General of the Council of Scientific and Industrial Research, New Delhi, India), himself a biophysicist, spoke of Nehru as a champion of Indian science. Nehru once spoke of India as "a bundle of contradictions held together by strong but invisible threads" [1]. Much the same could be said about lipid–protein interactions.

It was fitting that Anthony Watts (Oxford University, UK) kicked off the scientific proceedings by speaking of the 'Protein–Lipid Interactions in Membranes' meeting that he attended in 1981, where the nature, and even the very existence, of lipid–protein interactions were still hotly disputed [2]. He also reviewed his work and that of others in relation to lipids influencing protein function, citing the classic example of the tight binding of the mitochondrial phospholipid, cardiolipin, to cytochrome C oxidase [3]. In many respects, this is the epitome of lipid–protein interactions, since cardiolipin is observed in the x-ray crystal structure of the protein and is known to be functionally and physiologically relevant. Anthony Watts then went on to introduce G-protein coupled receptors (GPCRs), discussing the role of cholesterol on the activity and stability of one of these, NTSR1 [4].

GPCRs were a recurring theme throughout the meeting, which was especially timely in light of the 2012 Nobel Prize in Chemistry being awarded to Robert Lefkowitz (Duke University, NC, USA) and Brian Kobilka (Stanford University School of Medicine, CA, USA) for their studies of this large important family of receptors. Comprising 1000 family members, these receptors help us to respond to the world around us, sensing light, flavors and smells, as well as fear (adrenalin) and other emotions (dopamine and serotonin). They are

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also of intense interest to the pharmaceutical industry, being targets for approximately half of all medications. Several GPCRs were discussed, including receptors for angiotensin for regulating blood pressure (Sadashiva Karnik, Cleveland Clinic, OH, USA), opioids for pain treatment (Laurence Salomé, CNRS, Paris, France) and the mood-determining neurotransmitter, serotonin (Durba Sengupta, National Chemical Laboratory, Pune, India; Evgeni Ponimaskin, Hannover Medical School, Hannover, Germany). Durba's talk highlighted a computational study demonstrating that membrane cholesterol binds preferentially to certain sites on the serotonin$_{1A}$ receptor. In speaking about the intimate interaction between cholesterol and the serotonin$_{1A}$ receptor, Amit Chattopadhyay demonstrated that statin treatment depressed the activity of this GPCR, which may help explain the symptoms of anxiety and depression sometimes noted in patients taking these commonly prescribed cholesterol-lowering drugs [5].

Lipid interactions with ion channels and transporters was another featured topic of the meeting with presentations on lipids regulating inwardly rectifying potassium channels (Irena Levitan, University of Illinois, IL, USA), mechanosensitive ion channels (Boris Martinac, Victor Chang Cardiac Research Institute, Sydney, Australia; Georg Pabst, Austrian Academy of Sciences, Vienna, Austria), a ligand-gated ion channel, the nicotinic acetylcholine receptor (John Baenziger, University of Ottawa, Canada), as well as various transporters (Caroline Koshy, Max Planck Institute of Biophysics, Frankfurt, Germany; Hassane Mchaourab, Vanderbilt University, TN, USA), including the multidrug resistance transporter, MRP1 (Jean-Marie Ruysschaert, Free University of Bruxelles).

There were implications for cancer research, with membrane lipid interactions being described for two proteins commonly aberrant in many cancers, the tyrosine kinase EGF receptor (Andrew Clayton, Swinburne University, Melbourne, Australia) and the lipid phosphatase PTEN (Matthias Lösche, Carnegie-Mellon University, PA, USA). Alzheimer's disease was the disease of interest for three presentations on membrane interactions between Aβ peptides (Frances Separovic, University of Melbourne, Australia; Ari Gafni, University of Michigan, MI, USA) and in amyloid-like fibril formation (Manuel Prieto, Technical University of Lisbon, Portugal). Erwin London (Stony Brook University, NY, USA), one of the pioneers of the lipid raft concept [6], discussed his work with *Borrelia burgdorferi*, a bacteria transmitted by ticks causing Lyme disease in humans. Bacteria of course are unable to synthesize cholesterol, and nor can ticks, so *B. burgdorferi* derive their cholesterol from their host and convert it into an unusual glycolipid [7]. Another microbiologically relevant presentation was delivered by Mibel Aguilar (Monash University, Melbourne, Australia) who is studying how frog peptides can punch holes into bacteria [8], demonstrating their potential as promising new antibiotics that could one day take on the superbugs.

A better understanding of lipid–protein interactions requires better ways to study them. Several methodological advances were presented, including taking the black magic out of reconstituting membrane proteins in liposomes through employing a more rational strategy (Sandro Keller, University of Kaiserslauten, Germany), the development of new membrane probes (George Barisas, Colorado State University, CO, USA; Rachel Kraut, Nanyang Technological University, Singapore), the use of synthetic peptides to model behavior of transmembrane domains (Roger Koeppe II, University of Arkansas, AR, USA) and advances in high-speed single-molecule tracking to observe glycosylphosphatidylinositol protein dimers as they tango in the plasma membrane (Akihiro Kusumi, Kyoto University, Japan).

Daniel Wüstner (University of Southern Denmark, Odense, Denmark) spoke about tracking cholesterol trafficking within cells defective in the cholesterol-binding protein, NPC2, which is mutated in a subset of cases of the Niemann–Pick type C lysosomal storage disease. This entailed the development of new imaging software to track both the sterol and the protein. Frederick Maxfield (Weill Cornell Medical College, NY, USA) presented on another cholesterol-binding protein, STARD4. This small, cytosolic protein helps mediate cholesterol transport between organelles, including the plasma membrane and endoplasmic reticulum. Fred Maxfield also presented work on how lysosomal synapses in macrophages can provide an extracellular hydrolytic and acidic compartment that can partially digest aggregated lipoproteins [9]. This work offers a novel angle on how cholesterol may accumulate in atherosclerotic lesions, for which existing hypotheses (e.g., oxidized lipoproteins) have been hard pressed to satisfactorily explain.

Bill Dowhan (University of Texas, Houston Medical School, TX, USA) spoke about the role of phospholipids in determining membrane protein topology, using an elegant *Escherichia coli* model system in which lactose permease undergoes a dramatic conformational change, almost a somersault, in response to altered cell levels of phosphatidylethanolamine [10]. The converse situation can also occur in which membrane lipids are remodeled by proteins, like those containing the BAR domain (Gregory Voth, University of Chicago, IL, USA).

Also discussed was the significance of lipid–protein interactions in fundamental cell biological phenomena, such as in cytokinesis (Toshihide Kobayashi, RIKEN, Saitama, Japan), membrane fission by dynamin (Thomas Pucadyil, Indian Institute of Science Education and Research, Pune, India) and sperm capacitation (Musti Swami, University of Hyderabad, India).

A major issue in the field and a common theme of the meeting was the tussle between a protein-centric view of membrane proteins directly binding lipids and a more lipid-centric view whereby bulk physicochemical properties of the membrane alter a protein's function. This issue was raised by Cedric Govaerts (Free University of Bruxelles) and examples fitting either of these two views cropped up throughout the meeting. Andrew Brown (University of New South Wales, Sydney, Australia) showed that these possibilities are not mutually exclusive. He illustrated this by employing the enantiomer (mirror image) of cholesterol in studies investigating cholesterol sensing by Scap in cholesterol homeostasis [11].

Just as lipids and proteins were interacting in the auditorium, so too were the delegates in the meal breaks over beer and biryani – our GPCRs were working overtime. Existing collaborations were strengthened and new ones forged. In closing, the host, Amit Chattopadhyay, described some of the intense activity behind the scenes precipitated by the forces of nature. Hurricane Sandy dashed the travel plans of some of the invited American speakers, while the journeys of others became heroic feats of endurance, with delegates then being greeted on arrival in Hyderabad by the fringe of Cyclone Nilam wreaking havoc across southeastern India. The meeting, however, successfully weathered these storms, sailing smoothly through. And for that we have to thank Amit at the helm, as well as his trusty crew, for their wonderful hospitality, hard work and adroit problem-solving abilities.

Disclaimer

The authors' remit for this conference wrap-up was to particularly focus on those presentations that relate most directly to clinical lipidology and so they apologize for not being able to do more justice to each talk. Also due to space limitations, they have not been able to discuss the many excellent posters on display.

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