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Editorial

Invisible Rafts at Work

Back in the early days of lipidology the phase behavior of membrane lipids was characterized in great detail, but only in the 1980s was its relevance for mammalian cell biology revealed. McConnell and colleagues found that membrane lipids can form coexisting fluid phases (1), and Tillack and coworkers demonstrated that some glycosphingolipids on the surface of erythrocytes occur in small clusters (2,3). It was then proposed that the sorting of such glycosphingolipid aggregates into the apical transport pathway in the Golgi of epithelial cells forms the molecular basis for maintaining their enrichment on the apical surface (4), and this proposal was extended to include a role for glycosphingolipid domains in sorting proteins (5) and to describe how the anterograde sorting of sphingolipid/cholesterol domains generates the different lipid compositions of plasma membrane and ER (6). The identification of the relevant lipids and the subsequent implication of lipid-based domains in signaling at the plasma membrane (7) challenged biophysicists to directly visualize the existence of what had then been termed 'lipid rafts' in the membranes of living cells. A long and frustrating quest suggested they were an illusion (8), but now the solution appears to lie in fusion.

In the present issue, three teams of eminent physicists reach the common conclusion that invisible nm scale aggregates of sphingolipids, cholesterol and proteins coalesce into large-scale stabilized rafts under certain conditions. Stabilized rafts can occur when raft proteins are immobilized by a membrane skeleton (caveolae) or by receptor oligomerization during signaling, while stabilization is also required during the formation of the tubulovesicular carriers of the antero- and retrograde transport pathways. Kusumi and colleagues (9) start from defining a raft as a molecular complex of at least three molecules and build their case on the basis of a careful methodological consideration of the literature and on the data they obtained at the unrivaled time-resolution of 25 μs. Mayor & Rao (10) emphasize that membranes are not systems at equilibrium and start from their studies on GPI-anchored proteins to argue that cells regulate raft formation in space and time. Finally, Devaux & Morris (11) point out that the published studies on model membranes have neglected the important fact that the two leaflets of eukaryotic plasma membranes have very different compositions. If sphingolipid/cholesterol rafts in the outer leaflet were superimposed onto structures of a similar nature (but with different composition) in the cytosolic leaflet, this coupling would be short-lived. Although the other authors would agree, there is no consensus on whether such connections must be protein-mediated, which illustrates that even some basic issues remain to be resolved; for example, the nature of the relevant protein–lipid interactions.

The biophysical views are complemented by three papers on raft function. Helms & Zurzolo (12) try to reconcile conflicting data on raft-mediated sorting of proteins by including in the raft model the concept that various proteins will have different affinities for the raft lipids, whereby the affinity can be increased by oligomerization. Chamberlain and colleagues (13) discuss a role for lipid rafts as plasma membrane platforms for docking and fusion in regulated exocytosis. The role of lipid rafts in signaling is exemplified in the paper by Harder & Engelhardt (14), who present their view on how the coalescence of lipid rafts upon receptor activation results in the protein–protein interactions leading to the (relatively) stable immunological synapse of T lymphocytes.

The above papers signify the impressive progress in the elucidation of the physics of lipid rafts, and clearly delineate their important functions in cell physiology. Still, this should not hide the fact that many investigators in raft cell biology use the insolubility of raft components in cold detergent as the method of choice, and that these results are now generally overinterpreted to be direct reflections of molecular events in the membrane. To unravel how cells apply the beautiful principles of physics in using their broad range of lipids to manipulate proteins, we now need new methodology and, above all, a critical mind.

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