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Hypothesis of unit rafts as organizers of the meso-scale domain structure and function in the plasma membrane

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Single-molecule imaging and tracking techniques that are applicable to living cells are revolutionizing our understanding of the plasma membrane dynamics, structure, and signal transduction functions. The plasma membrane is considered the quasi-2D NON-ideal fluid that is associated with the actin-based membrane-skeleton meshwork, and its functions are likely made possible by the mechanisms based on such a unique dynamic structure, which I call membrane mechanisms. My group is largely responsible for advancing high-speed single molecule tracking with simultaneous multicolor recording. Based on the observations made by this approach, we propose that the cooperative action of the hierarchical three-tiered mesoscale (2–300 nm) domains—actin-membrane-skeleton induced compartments (40–300 nm), raft domains (2–20 nm), and dynamic protein complex domains (3–10 nm)—is critical for membrane function and distinguishes the plasma membrane from a classical Singer-Nicolson-type model.

In this presentation, I will talk about how domains of tiers 2 and 3 are coupled, with a special attention paid to the dynamic organization of raft-associated glycosylphosphatidylinositol-anchored proteins (GPI-APs) in the plasma membrane and their stimulation-induced changes. In resting cells, virtually all of the GPI-APs are mobile and continually form transient ($\sim$200 ms) homodimers (termed homodimer rafts) through ectodomain protein interactions, stabilized by the presence of the GPI-anchoring chain and cholesterol. Heterodimers do not form, suggesting a fundamental role for the specific ectodomain protein interaction. Under higher physiological expression conditions, homodimers coalesce to form hetero- and homo-GPI-AP oligomer rafts through raft-based lipid interactions. This indicates that through evolution of GPI-anchored proteins, the physical property to form homodimers rafts have been maintained, suggesting the importance of homodimers in the function of GPI-anchored proteins.

Upon ligation, the homodimers rafts of a GPI-AP, CD59, for example, formed stable oligomer rafts containing up to four CD59 molecules, which triggered intracellular Ca^{2+} responses that were dependent on GPI anchorage and cholesterol. This result strongly suggest a key role played by transient homodimer rafts. Transient homodimer rafts are most likely one of the basic units for the organization and function of raft domains containing GPI-APs.

Surprisingly, in steady state cells, similar findings were made for glycosphingolipids.

The presence of these unit rafts emphasizes the individuality rather than generality of raft compositions, except for the ubiquitous contributions of cholesterol to the formation of the unit rafts and greater raft domains consisting of unit rafts.