Biology of Lipid Rafts: Introduction to the Thematic Review Series

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Abstract Lipid rafts are organized plasma membrane microdomains, which provide a distinct level of regulation of cellular metabolism and response to extracellular stimuli, affecting a diverse range of physiologic and pathologic processes. This Thematic Review Series focuses on Biology of Lipid Rafts rather than on their composition or structure. The aim is to provide an overview of ideas on how lipid rafts are involved in regulation of different pathways and how they interact with other layers of metabolic regulation. Articles in the series will review the involvement of lipid rafts in regulation of hematopoiesis, production of extracellular vesicles, host interaction with infection, and the development and progression of cancer, neuroinflammation, and neurodegeneration, as well as the current outlook on therapeutic targeting of lipid rafts.—Sviridov, D., and Y. I. Miller. **Biology of Lipid Rafts: Introduction to the Thematic Review Series. *J. Lipid Res.* 2020.** 61: **598–600.**

Metaphorically, lipid rafts are islands of order in a sea of chaos. In a simplified way, lipid rafts are solid regions of plasma membrane embedded into (or floating in) predominantly fluid membrane. They are small and often short-lived; they are heterogeneous in just about any parameter, and yet, they are distinct. A vague definition, instability and heterogeneity made it difficult to evaluate, let alone to isolate and characterize lipid rafts, which resulted in a great deal of controversy. Do they really exist? Can you see them? Are they cellular organelles or a cell biology concept? Do they represent a novel level of regulation of cellular metabolism or reflect a mystical conceptualization of the unknown? A solid paradigm to some, nonsense to others.

And yet, biologically there is a great "need" for lipid rafts to exist. Sensing soluble signals is predominantly achieved through a complex network of receptors transmitting external signals across the membrane into an intracellular chain of amplification and translation. Most receptors are complexes working through rapid interaction between the subunits and cofactors to switch the signal on and off; a good example is Toll-like receptors (1). All participants in this interaction need to be in one compartment, close to each other. However, anything placed into a fluid, which most of the plasma membrane is, drifts apart, necessitating existence of mechanisms that would keep parts of the receptor in close proximity to each other, ready to interact when a ligand becomes available. One solution is to embed subunits into a part of the plasma membrane that is not fluid and can hold moving parts close—lipid rafts. These considerations apply not only to cofactors, but also to inhibitors; positioning a sensor in lipid rafts ensures their close proximity to an inhibitor, release from rafts renders a sensor active. Examples include the glucose transporter GLUT2, which exists in inactive form in rafts but becomes active when released to cytosol (2), or eNOS inactivated by interaction with caveolin in caveolae (3). With both activation and inhibition, rafts can be of a variety with rapid turnover, ensuring rapid response, like planar rafts, or of a more stable variety ensuring long-lasting stable response, like caveolae.

Another type of communication between cells and the outside world is the secretion and uptake of whole molecules and particles. Small molecules often require a simple shuttle, which works in a fluid membrane. Bigger molecules and particles require sophisticated exo- and endocytosis machineries, which are made of many parts that need to be held together, or separate, when required (4, 5). Also, consistent transport across plasma membrane involves making a pore in the membrane—making and maintaining holes in a fluid is difficult; existence of a floating platform makes this easier. Many other examples could be cited, suggesting that physicochemical heterogeneity of the plasma membrane and existence of the solid bits is a foundation of many physiological pathways.

Lipid rafts are an important and under-appreciated level of physiologic regulation; many pathways described above are enhanced or reduced depending on the availability of rafts. Lipid raft availability is tightly regulated through changes in lipid metabolism, receptor activation, and cytoskeleton (6), but the exact mechanisms of how

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lipid raft regulation is integrated with other levels of metabolic regulation is poorly understood. It is easy to envisage how deficiency of rafts, such as caveolae, can restrict a vital pathway (7). Less intuitive is a situation when an excess of rafts leads to a pathway being enhanced beyond control, and yet, this is a common occurrence; inflammation, where excessive lipid rafts result in excessive and poorly controlled inflammation, being a good example.

"Nature, in her indifference, makes no distinction between good and evil" (8, ch. XXVII, vrs. 263), and many pathological processes rely on lipid rafts, too. Numerous infections that involve interaction between pathogens and host cells utilize host rafts as a "point of contact". High concentration of receptors in lipid rafts helps guide and bind pathogens, endocytosis machinery takes an obligate intracellular parasite inside, and lipid rafts provide a platform for pathogen self-assembly as well as an exit gate (9). Misfolding of amyloidogenic proteins is a key element of neurodegeneration. The two key requirements for nucleation to occur and the chain reaction of misfolding to spread across the brain are the presence of an initial copy of a misfolded protein and a high local concentration of a "normal" amyloidogenic protein. Most amyloidogenic proteins concentrate and are sometimes processed in lipid rafts, initiating the rollover of neurodegeneration (10). Raft mitigation strategy using β- cyclodextrins and apolipoprotein A-I binding protein (AIBP) were successfully tested for restricting inflammation, neuropathic pain, atherosclerosis, and HIV infection (11-14), but a delicate balance must be preserved in order not to affect physiological pathways relying on lipid rafts.

Lipid rafts are not limited to the membranes of animal cells. HIV membrane has lipid content and properties similar to those of the host cell rafts (15), a "stolen" lipid raft. Bacteria have their own lipid rafts, called functional membrane microdomains (FMMs), and lipid rafts were described in protozoa, fungi and plants (16, 17). Overall, available data point to lipid rafts as a distinct layer of metabolic regulation affecting a diverse range of metabolic processes in a wide range of cells in organisms from different taxa. This layer is not only of key importance for the specific physiologic and pathologic situations, but also mechanistically explains a connection between previously unexplained associations, such as between cardiovascular disease and diabetes and neurodegeneration (18, 19).

Lipid rafts were extensively studied over the years. The focus of most studies, however, was on the structure and properties of lipid rafts, targeting the question of what they are. This is very important; one needs to understand what they are dealing with before trying to find what it does. A variety of models, from lipid films to giant plasma membrane vesicles and a range of methods, from physical chemistry to super-resolution microscopy, were used to gain a great deal of understanding of the structural organization of rafts, the role of their lipid and protein constituents, and their turnover and interaction with the rest of the membrane; a number of excellent reviews were published on these issues (6, 20, 21). Much less is said about a biology of lipid rafts and their functions and most of the information is split between the silos of specialized fields.

This Thematic Review Series focuses on the biology of lipid rafts rather than their structure. We intentionally do not offer in our introduction one definition of lipid rafts for the whole series. Each article will likely give a slightly different definition, emphasizing structural components and characteristics of lipid rafts important for specific biologic processes. The aim is to provide an overview of ideas on how lipid rafts are involved in the regulation of different pathways, both physiologic and pathologic, and how they interact with other layers of metabolic regulation. The series will review the involvement of lipid rafts in regulation of hematopoiesis, production of extracellular vesicles, host interaction with infection, and the development and progression of cancer, neuroinflammation, and neurodegeneration. The series will close with the current outlook on therapeutic targeting of lipid rafts.

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