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Lipid Domains

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PREFACE

How cell membranes are organized is a question that has fascinated researchers since the fluid mosaic model of membranes was put forward by Singer and Nicolson (Nicolson, 2014; Singer & Nicolson, 1972). In their original description of the mosaic nature of membranes, Singer and Nicolson predicted that proteins and lipids should be randomly distributed within membranes over distances from a few tenths of a micron or greater, but that short-range order could exist (Singer & Nicolson, 1972). In recent years, interest in membrane organization has become even more intense following the proposal by Kai Simons and colleagues that cell membranes contain submicron domains consisting of both proteins and lipids known as lipid rafts (Simons & Ikonen, 1997). The history of the lipid raft field has been a contentious one (Edidin, 2003; Hancock, 2006; Jacobson, Mouritsen, & Anderson, 2007; Kenworthy, 2008; Kraft, 2013; LaRocca et al., 2013; Lichtenberg, Goni, & Heerklotz, 2005; Lingwood & Simons, 2010; London, 2005; Munro, 2003; Owen, Williamson, Magenau, & Gaus, 2012; Pike, 2006; Simons & Gerl, 2010), and the purpose of this volume is not to take sides in the arguments for and against the lipid raft model. Rather, it is to highlight the breadth of methodologies and vast body of knowledge about biological membranes that have emerged in the search for lipid rafts.

In the literature, lipid rafts have often been equated with liquid-ordered domains (Ahmed, Brown, & London, 1997; Brown & London, 1998), and in vitro reconstitution systems have played an essential role in exploring the properties of membranes capable of forming coexisting liquid-ordered and liquid-disordered domains. One of the most widely studied model systems utilizes giant unilamellar vesicles (GUVs) consisting of ternary lipid mixtures (Veatch & Keller, 2002, 2003). These systems have been reviewed elsewhere (Morales-Penningston et al., 2010; Veatch, 2007; Veatch & Keller, 2005; Wesolowska, Michalak, Maniewska, & Hendrich, 2009) and will not be discussed here. Instead, we begin with a discussion of supported bilayer systems in the study of raft domains in Chapter 1 by Lukas Tamm and colleagues. This chapter highlights several approaches currently used to generate planar membranes, including both symmetric and asymmetric bilayers, and discusses how these have been used to investigate the partitioning of proteins and peptides between liquid-ordered and liquid-disordered domains. Next, the merits of giant plasma membrane-derived vesicles (GPMVs) as a model system for exploring raft domains are summarized by Ilya Levental and colleagues in Chapter 2. Derived from the plasma membrane of living cells, GPMVs contain a complex mixture of lipids as well as a high concentration of membrane proteins, but lack cytoskeletal underpinnings. They thus offer an

intermediate level of complexity between reconstituted systems such as supported bilayers or GUVs and live cells.

Compared to model systems, raft-like domains in living cells remain much more challenging to detect. In recent years, super-resolution microscopy has opened up the possibility of visualizing lipid or protein clusters too small to be resolved using conventional approaches (Owen & Gaus, 2013; Owen, Magenau, Williamson, & Gaus, 2012). In Chapter 3, Samuel Hess and colleagues provide an update on how fluorescence photoactivation localization microscopy and other super-resolution techniques are being used to identify and characterize membrane domains not only at the cell surface, but also in intracellular compartments such as mitochondria. The use of high-resolution microscopy techniques to study domains is explored further in Chapter 4 by Dylan Owen and colleagues. Here, the focus is on signaling nanoclusters.

Lipid rafts are but one example of the types of domains that have been proposed to laterally organize cell membranes. The presence of domains that constrain the diffusion of proteins and lipids within the plasma membrane has long been inferred from approaches such as single molecule tracking and fluorescence recovery after photobleaching (Edidin, 1992; Jacobson, Sheets, & Simson, 1995; Sako & Kusumi, 1994). Interactions of proteins and lipids with such domains can cause them to undergo anomalous diffusion, where the mean-squared displacement of the diffusing molecules is not linear in time. In Chapter 5, Diego Krapf outlines mechanisms that contribute to anomalous diffusion in the plasma membrane. This comprehensive review starts off with a description of theoretical models to describe anomalous diffusion before summarizing examples of how a variety of membrane domains, including clathrin-coated pits and cytoskeletal corrals, impact the lateral diffusion of proteins and lipids at the cell surface.

Given that many classes of membrane domains rely on both protein–lipid and lipid–lipid interactions, it is not surprising that the exact lipid composition of membranes can heavily influence both the structure and function of domains. In Chapter 6, Saame Raza Shaikh describes the role of dietary fatty acids in modulating the structure and function of lipid rafts, with a special emphasis on the impact of polyunsaturated fatty acids. The works summarized here offers an interesting perspective on how dietary modulation of membrane lipids, through its effects on membrane domain organization, may directly impact human health.

The proposed functions of lipid rafts in mammalian cells have been extensively investigated, but only recently has the possibility that such domains play important roles in other classes of organisms been explored. Through the joint efforts of several authors including Erwin London and Amir Farnoud, our state of knowledge on the role of rafts in both pathogenic bacteria and yeast is reviewed in Chapter 7. In contrast, Chapter 8 revisits one of the earliest proposed functions of lipid rafts: the regulation of the trafficking of GPI-anchored proteins in polarized epithelial cells. As outlined by Simona Paladino, Chiara Zurzolo and colleagues, current models for how these proteins are handled by cells not only includes a potential role for rafts, but also for protein-driven oligomerization events and sorting steps at multiple intracellular compartments.

About the same time that the lipid raft model was being developed, another interesting class of membrane domains came to the forefront following the discovery of the protein caveolin-1 as a major structural protein of caveolae (Rothberg et al., 1992). Residing on the plasma membrane of many different cell types, these flask-shaped invaginations have been implicated in a wide range of cellular processes, including membrane trafficking and cell signaling (Parton & del Pozo, 2013). However, despite intense study, many questions about caveolae remain unanswered, including how the packing of caveolin-1 within membranes contributes to membrane bending and caveolar assembly. As described in Chapter 9, recent biophysical studies have now begun to shed light on this issue. Here, Kerney Jebrell Glover and colleagues describe how findings from his lab, as well as others in the field, are revealing the structure, topology, and oligomerization status of this integral membrane protein.

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