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Review

Interaction of membrane/lipid rafts with the cytoskeleton: Impact on signaling and function☆

Membrane/lipid rafts, mediators of cytoskeletal arrangement and cell signaling

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ABSTRACT

The plasma membrane in eukaryotic cells contains microdomains that are enriched in certain glycosphingolipids, gangliosides, and sterols (such as cholesterol) to form membrane/lipid rafts (MLR). These regions exist as caveolae, morphologically observable flask-like invaginations, or as a less easily detectable planar form. MLR are scaffolds for many molecular entities, including signaling receptors and ion channels that communicate extracellular stimuli to the intracellular milieu. Much evidence indicates that this organization and/or the clustering of MLR into more active signaling platforms depends upon interactions with and dynamic rearrangement of the cytoskeleton. Several cytoskeletal components and binding partners, as well as enzymes that regulate the cytoskeleton, localize to MLR and help regulate lateral diffusion of membrane proteins and lipids in response to extracellular events (e.g., receptor activation, shear stress, electrical conductance, and nutrient demand). MLR regulate cellular polarity, adherence to the extracellular matrix, signaling events (including ones that affect growth and migration), and are sites of cellular entry of certain pathogens, toxins and nanoparticles. The dynamic interaction between MLR and the underlying cytoskeleton thus regulates many facets of the function of eukaryotic cells and their adaptation to changing environments. Here, we review general features of MLR and caveolae and their role in several aspects of cellular function, including polarity of endothelial and epithelial cells, cell migration, mechanotransduction, lymphocyte activation, neuronal growth and signaling, and a variety of disease settings. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters.

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Abbreviations: AC, adenylyl cyclases; AD, Alzheimer's disease; AJ, adherent junctions; AMPAR, alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor; APC, antigen presenting cell; APP, amyloid precursor protein; Aβ, amyloid beta peptide; CAM, cellular adhesion molecules; cAMP, cyclic adenosine 3′,5′ monophosphate; Cav, caveolin; CBD, caveolin binding domain; CRAC, cholesterol recognition/interaction amino acid consensus; CSD, caveolin scaffolding domain; cSMAC, central supramolecular activation cluster; CTX, cholera toxin; EC, endothelial cell; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase (NOS3); FAK, focal adhesion kinase; Flot, flotillin; GD, ganglioside disialic acid; GJ, gap junctions; GM, ganglioside monosialic acid; GPCR, G-protein-coupled receptor; GPI, glycosylphosphatidylinositol; ICAM/VCAM, inter/vascular CAM; JAM, junctional adhesion molecules; mGluR, metabotropic glutamate receptor; MLR, membrane/lipid rafts; MT, microtubules; NMDAR, *N*-methyl-*D*-aspartate receptor; pMHC, peripheral major histocompatibility complex; PrP, prion protein; PTRF, polymerase I and transcript release factor; RTK, receptor tyrosine kinases; TCR, T cell receptor; TEM, tetraspanin-enriched microdomains; TJ, tight junctions; Trk, tropomyosin receptor kinase; TRPC1, transient receptor potential cation channel; TSPN, tetraspanin; VGCC, voltage-gated Ca^{2+} channels

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1. Introduction

The plasma membrane is a dynamic entity. It is both a barrier that separates the extracellular and intracellular environments and a structure composed of proteins and lipids that controls and is controlled by many biological processes. Hydrophobic moieties of lipids self-associate while their hydrophilic regions interact with the aqueous environment (in both the extracellular and intracellular milieus) to create the physical basis of the plasma membrane bilayer [1,2]. This amphipathicity of lipids is essential for separating internal cellular structures from the external environment. Eukaryotic plasma membranes are composed of glycerophospholipids, sphingolipids, and sterols (in particular, cholesterol). The head group of the glycerophospholipids varies, as can the length and degree of saturation of the associated fatty acyl chains. Sphingolipids also vary in their ceramide backbones and the >500 different carbohydrate structures in the head groups. The introduction of cholesterol to the plasma membrane appears to have occurred later in evolution than that of certain other membrane lipids; its presence coincides with the increase in environmental oxygen concentration that occurred ~2.5 billion years ago [3]. The presence of sphingolipids and sterols increases the complexity of eukaryotic membranes and distinguishes them from the membranes of prokaryotes. Cholesterol increases the thickness and stiffness of lipid bilayers [4] and allows for protein sorting [5]. The hydrophobic effect of the amphipathic molecules on lipid shapes (i.e., inverted cones, cylindrical, or conical) forms lamellar, micellar, or cubic supramolecular structures. Certain lipids of eukaryotic cells are not cylindrical and therefore not predicted to support the formation of a membrane (lamellar) bilayer; however, the inclusion of proteins in membranes results in macromolecular assemblies and bilayer asymmetries that help promote the formation of the lamellar membrane bilayer.

Forty years ago Singer and Nicolson described the plasma membrane (PM) as having a 'fluid mosaic' environment that randomly partitions proteins and lipids so as to achieve the lowest free energy [6]. Substantial subsequent evidence has revealed that this partitioning of proteins is not homogenous and random but instead consists of clusters of structural proteins (e.g., integrins and intracellular scaffolds), enzymes, signaling receptors, transporters and channels within lipid domains; some of these lipid domains are enriched in cholesterol and certain saturated acyl lipids and are termed lipid or membrane rafts [7–11]. These membrane domains and their unique protein and lipid content are critical for many cellular functions. Along with clathrin-coated pits, membrane/lipid rafts (MLR) are structurally and functionally distinct, important regions of the PM [10].

There are two major types of MLR: those that contain the cholesterol binding protein caveolin (Cav) and those that do not. Cav-containing MLR form morphologically distinct entities, caveolae ("little caves"), flask-like invaginations of the PM (detectable at the resolution of electron microscopy) while MLR that lack Cav are flat and not identifiable by electron microscopy. However, some cells, such as neurons and lymphocytes, that express Cav and contain lipid rafts do not have morphologically identifiable invaginated structures [12]. It remains unclear why such cells express Cav but do not form caveolae.

Interactions between MLR and cytoskeletal components can contribute to the regulation of MLR assembly/clustering and cytoskeletal dynamics [13,14]. Although the association between cytoskeletal components and MLR/caveolae had been previously described [15,16], recent evidence has extended the notion that cytoskeletal components (e.g., actin, tubulin, vinculin, filamin, and tau) [17,18] can localize to MLR and be platforms for cytoskeletal tethering and for communication to the extracellular matrix (ECM) via integrins, cadherins, occludins, and other cellular adhesion molecules (CAMs). Moreover, MLR can cluster and this clustering may depend upon cholesterol and actin tethering to the membrane [19]. Kusumi and colleagues proposed a 'picket-fence' model, whereby actin filaments anchored to MLR regulate lateral diffusion of membrane proteins and lipids [20,21]. This transient anchoring of transmembrane proteins with actin filaments was hypothesized to resemble a row of 'pickets' that regulate (slow) diffusion of adjacent proteins and lipids. Based on their additional work, Kusumi and colleagues have proposed that the transient 'clustering' or coalescing of homodimer rafts forms hetero- and homo-GPI-anchored protein oligomeric rafts, within the inner leaflet, through raft-based lipid interactions that generate functional raft domains [22,23]. Gowrishankar et al. have demonstrated that this nanomicrodomain clustering depends upon cholesterol, sphingolipids and an active cortical actin meshwork [24]. These actin meshwork "snippets" are composed of 250 nm actin filaments cross-linked by myosin motors that facilitate lateral movement of GPI-anchored proteins in an energy-dependent manner. The combination of lateral membrane movement and transmembrane interaction among integrins, membrane bilayer lipids, and membrane proteins within MLR, along with interaction of the actin/myosin cytoskeleton and cytoskeletal tethering partners, can contribute to cellular migration, mechanotransduction, cell growth, endothelial and epithelial barrier formation, and immune cell activation—physiologically important responses and ones that can be altered in disease settings.

MLR thus serve as regulators of numerous cellular events, including: 1) cellular polarity and organization of trafficking and sorting mechanisms, 2) formation of platforms for ECM adhesion and intracellular cytoskeletal tethering to the PM (intracellular–extracellular skeletal linkage, in particular via integrins, and lateral membrane clustering), and 3) transduction of signaling cascades across the PM ("outside–in" signaling), which in turn can rearrange cytoskeletal architecture and alter cell growth, migration, and other functions and 4) entry of viruses, bacteria, toxins and nanoparticles. The remainder of this review focuses on MLR–cytoskeletal interactions that influence signaling receptors and channels within the PM and emphasizes articles published in the past 5 years (Table 1).

1.1. Methods for the isolation and enrichment of raft domains

A subset of MLR, termed caveolae were first observed microscopically by Palade and Yamada [25,26], however the concept of lipid domains was formalized by Karnovsky et al. [27]. These domains were subsequently termed glycolipid-enriched membranes by Parton and colleagues [28] and then known as *detergent-resistant membranes* (originally coined by Baird and colleagues [29] based on their insolubility to detergents, in

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