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Review

Lipid Rafts & Co.: An integrated model of membrane organization in T cell activation

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Abstract

The model of membrane compartmentalization by self-organizing functional lipid microdomains, named lipid rafts, has been a fruitful concept resulting in great progress in understanding T cell signal transduction. However, due to recent results it has become clear that lipid rafts describe only one out of several membrane organizing principles crucial for T cell activation besides fences and pickets and protein–protein interactions that take part in the formation of the immunological synapse as a highly organized structure at the T cell contact site to the antigen-presenting cell. This review describes the concepts of lipid rafts and other membrane organizing principles to evolve a novel integrated model on the functional role of microdomains in immunological synapse formation and T cell activation. Further research has to elucidate the relative contribution and interrelation of different modes of membrane organization in productive T cell activation.

Keywords: Membrane microdomains; Immunological synapse; Single molecule tracking; T cell signaling

Contents

Abbreviations: APC, antigen-presenting cell; ERM, ezrin/radixin/moesin; F-actin, filamentous actin; FRAP, fluorescence recovery after photobleaching; FRET, fluorescence resonance energy transfer; GFP, green fluorescence protein; GPI, glycosylinositolphosphatidyl; ICAM, intercellular adhesion molecule; l_d, liquid-disordered; l_o, liquid-ordered; LAT, linker for activation of T cells; LFA-1, leukokocyte functional antigen-1; MHC, major histocompatability complex; PAG, phosphoprotein associated with glycosphingolipid-enriched microdomains; PIP_2, phosphatidylinositol 4,5-biphosphate; PUFA, polyunsaturated fatty acid; (c-/p-)SMAC, (central/peripheral) supramolecular activation cluster; TCR, T cell receptor; Tm, melting temperature.

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1. Introduction

T cell recognition of antigen that is presented in context of a major histocompatability complex (MHC) is the central theme of the adaptive immune response. Understanding the transduction of signals provided by ligation of the T cell receptor (TCR) and subsequent T cell activation is of high priority for immunologists and cell biologists. It is understood that spatial organization and compartmentalization of the membrane and its signaling machinery is a prerequisite for signal transduction. The lipid raft model has evolved to describe a compartmentalization of the cell membrane that is based on phase separation of membrane lipids due to their physical properties and the specific targeting of proteins into the resulting lipid microdomains. A plethora of publications deals with the functional role of lipid rafts in several cellular functions including signaling by TCR, B cell receptors, IgE receptors, neurotrophic factors, growth factors, chemokines, interleukins, and insulin, as well as lipid and protein trafficking [1,2]. Thus, it may be surprising that despite considerable efforts of many researches no consensus on the nature and even the existence of lipid rafts has been found by now, mainly due to limitations in assessing the nature of lipid fluid phases in living cells. Consequently, lipid rafts have been named ''slippery platforms'' and ''unidentified floating objects'' to satirically highlight the serious question whether rafts are just ''illusive'' [3,4].

In this review, the lipid raft model, relevant open questions, and problems with this concept are discussed in the context of T cell activation. A modified understanding of lipid rafts and up-to-date knowledge of membrane organization in general are integrated into a current model of membrane compartmentalization that is crucial for initiation of T cell signaling. In addition, the formation of an immunological synapse between antigen-presenting cells and T cells has emerged to be of vital importance for T cell activation. In this review we evolve an integrated up-to-date model for the membrane-associated mechanisms of T cell activation.

2. The lipid raft model

2.1. Phase separation in biological membranes

Cellular membranes contain glycerophospholipids, consisting of a glycerol backbone to which two fatty acids are linked via ester bonds. In addition, eukaryotic membranes, particularly the plasma membrane, contain sphingolipids (sphingomyelin and glycosphingolipids) and sterols, in vertebrates mainly cholesterol. The structures of these lipids determine the physical properties of the lipid bilayer. Whereas glycerophospholipids usually contain one unsaturated acyl residue at the sn2 position, sphingolipids comprise a long-chain (16–26 carbons) sphingoid base with an amide-linked usually saturated acyl chain. The ceramide backbone facilitates hydrogen bonds preferably with cholesterol [5]. Sterols are rigid structures comprising four carbon rings.

The relative abundance of these lipids within the plasma membrane varies between different cell types. Whereas glycerophospholipids usually predominate the plasma membrane lipid composition, sphingomyelin and cholesterol are present at 10–20 mol% and 30–40 mol%, respectively. Glycosphingolipids usually represent a low proportion of membrane lipids with some exceptions such as cells in barrier epithelia [6,7].