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Lipid rafts and T-lymphocyte function: Implications for autoimmunity

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Abstract

Experimental evidence indicates that the mammalian cell membrane is compartmentalized. A structural feature that supports membrane segmentation implicates assemblies of selected lipids broadly referred to as lipid rafts. In T-lymphocytes, lipid rafts are implicated in signalling from the T-cell antigen receptor (TCR) and in localization and function of proteins residing proximal to the receptor. This review summarizes the current literature that deals with lipid raft involvement in T-cell activation and places particular emphasis in recent studies investigating lipid rafts in autoimmunity. The potential of lipid rafts as targets for the development of a new class of immune-modulating compounds is discussed.

Keywords

Lipid raft; T-cell receptor; Autoimmunity

1. Introduction

The original lipid raft hypothesis proposes the existence of assemblies of specific lipids that compartmentalise the plasma membrane into functionally distinct areas [1-4]. Studies with model membranes have shown that sphingolipids aggregate to form microdomains which are stabilized by addition of cholesterol. These self-assembled domains are in liquid ordered phase and are resistant to solubilisation with non-ionic detergents [5,6]. Likewise, mammalian cells extracted with similar detergents produce a detergent resistant membrane (DRM) fraction. DRMs are enriched in sphingomyelin, glycosphingolipids and cholesterol, however, it is debatable as to whether they reliably correspond to lipid raft domains as they exist in living cells [7,8]. Microscopy and the ability to observe differential membrane condensation using specific fluorescent probes provide additional methods which have significantly improved detection of specialized areas in the plasma membrane either before or after cell stimulation [9,10].

The latest results suggest that lipid rafts in non-stimulated cells are dynamic and of a size too small to detect with conventional microscopy. Various studies have suggested a size as small as 20 nm and up to 200 nm [11-14]. Despite their small size, molecules that are thought to partition into rafts show restricted lateral mobility, while proteins that are

excluded diffuse freely [15,16]. Upon receptor stimulation, however, small lipid rafts may coalesce into bigger structures or become more rigid possibly by associating to the cytoskeleton [17]. Stimulation-induced protein–protein interactions are important as they most likely promote microdomain aggregation [18–20]. However, the prototypical raft model which proposes that self assembly of certain lipids creates platforms capable of regulating protein topology and function, is intensely debated [21–23]. Thus, far the evidence for their existence is suggestive rather than direct. The publication, in some instances, of opposing results and skepticism regarding the validity of certain methods used to describe lipid rafts (summarized in [22]) have tempered initial enthusiasm. Nevertheless, as more refined technologies are developed and new data are incorporated into existing ones, the intricacies of the lipid raft model will evolve accordingly. Any alternative theory that is put forward, however, will have to explain the large volume of data that show the critical role of protein acylation, and of cholesterol and glycosphingolipid manipulation on cell function.

Biological functions attributed to lipid rafts include endocytosis, pinocytosis, sorting and transport of proteins, and signal transduction [1,24]. The presence of many key signalling proteins and receptors including Src-family kinases, GTP-binding proteins and glycosylphosphatidyl-inositol (GPI)-linked receptors into lipid rafts and the potential of these domains to support protein–protein interactions at the plasma membrane has attracted many researchers into studying their involvement in signal transduction across many biological disciplines [1,25–27]. It is important to note here that for many proteins thought to localize to lipid rafts, this assignment has often been made because of their copurification with DRMs. Also, following fractionation, many of these proteins are detected in both DRM and detergent-soluble fractions (see discussion below for T-cell lipid rafts). In the text that follows we only concentrate on lipid raft function in TCR signalling and activation.

2. Structure and signalling by the T-cell antigen receptor

The TCR identifies antigenic peptides presented in the context of cognate Major Histocompatibility Complex (MHC) proteins expressed on the surface of antigen presenting cells (APCs). The part of the receptor that recognizes the large variety of antigens is a highly polymorphic heterodimer of α and β chains. For a subset of T-cells with limited tissue distribution this dimer is composed of the related γ and δ chains. The polymorphic dimer closely associates with a cluster of signal transducing, non-polymorphic proteins named the CD3 complex [28]. The polypeptides that comprise the CD3 complex are γ , δ , ϵ and ζ in a stoichiometry of 2ϵ , one of each γ and δ and a ζ homodimer. All CD3 chains contain a signal transducing motif called ITAM (immunoreceptor tyrosine-based activation motif) [29,30]. The γ , δ and ϵ chains contain one ITAM while ζ has 3. Therefore, a single TCR is equipped with 10 ITAMs altogether. The large number of ITAMs is needed to augment the strength of the signal generated by the receptor even if only a very small number of stimulatory antigen/MHC complexes are presented by the APC [31]. Direct evidence for this premise comes from a recent study. By generating animals with TCRs that contained variable number of functional ITAMs, it was shown that reduced number (7 or less) of functional ITAMs resulted in breakdown of central tolerance and development of autoimmune disease. This was due to incomplete deletion of autoreactive T-cells during development, a process that requires intact TCR signaling [32].

Signal transduction by the TCR is initiated by the phosphorylation of the tyrosine residues (Y) within the ITAMs primarily by the Src-family tyrosine kinase Lck [33–35] (Fig. 1). The 2 phospho-Y in each ITAM recruit from the cytosol the ZAP-70 tyrosine kinase which is phosphorylated and activated by Lck [36]. Activated ZAP-70 propagates transmission of the signal by phosphorylating the adapter molecule linker for activation of T-cells (LAT) [37].

LAT is phosphorylated on multiple Y residues, which then form docking sites for other adapter proteins like SLP-76, Grb-2 and Gads, and enzymes such as PI3K and PLC γ 1 [37]. Thus, the central role of LAT in TCR signalling is its capacity when phosphorylated, to form complexes at the plasma membrane from which a number of signalling cascades originate. Lack of LAT expression uncouples TCR proximal tyrosine phosphorylation from these down-stream signalling cascades [38].

Like all the members of the Src-family kinases, Lck is regulated by the phosphorylation/dephosphorylation cycle of a C-terminal Y (Y-505). This Y when phosphorylated by the C-terminal kinase (Csk) associates with the Src homology 2 (SH2) domain of the molecule inducing a 'closed' conformation, which has low catalytic activity. Y-505 is dephosphorylated by the receptor-type tyrosine phosphatase CD45 [39]. Dephosphorylation converts Lck into an 'open' form [40]. At this stage autophosphorylation of another Y within the kinase domain (Y-394) renders the enzyme fully active [39]. Therefore, the primary role of CD45 is to prevent deactivation of Lck. Studies of CD45-null mice and cell lines which show hyperphosphorylation of Y-505 and impaired TCR signalling confirm the positive role of CD45 in T-cells [41,42]. Paradoxically, CD45 can also play a negative role by dephosphorylating Y-394 [43,44]. A recent report addressing this dichotomy has shown that while low levels of CD45 expression are sufficient for Y-505 dephosphorylation, high wild type levels of expression were necessary for Y-394 dephosphorylation and suppression of unwanted signalling [45].

Upon its stimulation the TCR changes topology forming signal transducing microclusters. Formation of TCR-rich microclusters, which also contain activated Lck and ZAP-70, is the earliest event measured following TCR stimulation [46,47] (Fig. 1). Pharmacological disruption of actin polymerization inhibited microcluster formation. Interestingly, TCR microclusters were observed in the presence of a Src-family kinase inhibitor indicating that their formation precedes Lck activation [46]. It will be important to dissect how the TCR induces actin polymerization independent of Lck activity. The TCR microclusters subsequently gather in an area in the membrane which is commonly referred to as central supramolecular activation cluster (cSMAC) [47,48]. This area is part of the immunological synapse formed between a T-cell and the APC [49]. Coreceptors and signalling molecules also concentrate in the cSMAC, while large glycosylated molecules such as CD45 and CD43 are excluded [50-52]. It is thought that the TCR molecules accumulating into the cSMAC do not transduce signals but are rather destined for endocytosis. However, newly formed TCR microclusters in the periphery maintain signal transmission by recruiting ZAP-70 and SLP-76 [47,53]. Staining of cells with cholera toxin B subunit (CTB), which binds to raft associated glycosphingolipid GM1, has shown that lipid rafts accumulate at the IS during T-cell activation [20,54,55]. Furthermore, the use of membrane intercalating fluorescent dyes such as Laurdan and di-4-ANEPPDHQ has provided evidence for increased condensation of the membrane at the site of TCR activation [19,56]. However, other reports argue against the preferential accumulation of lipid rafts to the IS [57,58].

3. Lipid rafts in TCR signalling and activation

Appropriate spatio-temporal localization of proteins is a key factor determining signalling activity. Dual acylation is required for Lck to transmit signals by the TCR [59] and LAT palmitoylation is important for its function [60]. Since acylation of proteins frequently determines their localization to cholesterol-sensitive lipid raft domains, these results have been interpreted as evidence that lipid rafts play a critical role in TCR signalling by means of the proteins they accrue. This premise was strengthened by experiments showing that extraction of cholesterol with chelating agents or treatment of cells with statins destabilize lipid rafts and modulate signalling [61-64].

The mechanistic model of how lipid rafts could regulate TCR signalling proposes that signalling starts when the TCR comes into close proximity with Lck- and LAT-containing lipid rafts (the size of which is yet to be defined). However, initiation of signalling should be controlled by receptor engagement. Such regulation could take place at two levels. First, at the formation of actin-dependent microclusters as mentioned earlier [46,47], and second at the upregulation of the enzymatic activity of a pool of Lck that is in the vicinity of the TCR. Regarding the first level of regulation, Lck-containing lipid rafts should become part of the TCR-rich microclusters, whose initial formation does not require Src-family kinase activity [46] (Fig. 1). Although this has not been shown directly, a recent report provides some evidence that shows clustering of membrane rafts is dependent on actin cytoskeleton and that the actin cytoskeleton and cholesterol levels determine the status of Lck activation [65,66]. Furthermore, single particle tracking technology revealed that the actin cytoskeleton slows down the lateral diffusion of acylated Lck in the plasma membrane and thus facilitates accumulation of the kinase to areas of stimulated TCR clusters [67].

During the second step of control, the activity of the pool of Lck that gathers to the TCR-microclusters may need to be transiently increased. This is because Lck was found to be hyperphosphorylated on Y-505 and to have reduced catalytic activity in DRMs [68,69]. Csk was present in these preparations and most likely is responsible for Lck inactivation in these domains [70]. Inactivation of Lck in lipid rafts might be required to preserve homeostatic control and to avoid inappropriate signalling in the absence of antigenic challenge [27]. Two proteins that bind to Csk were identified in T-cell DRMs. These are the Csk-binding protein (Cbp) [71], also known as PAG [72], and the Lck-interacting molecule (LIME) [73,74], which are palmitoylated adapter molecules and substrates for Src-family tyrosine kinases. Cbp is constitutively phosphorylated in DRMs [75,76]. Significantly, stimulation of the TCR induced its dephosphorylation and release of Csk [70,72]. These observations led to the hypothesis that Cbp could be the protein anchor that recruits Csk to the plasma membrane to inactivate Lck. However, the generation of mutant mice deficient in Cbp expression has shown that T-cell development and function remain normal in the absence of Cbp [77], although this adapter may have an important role as a tumor-suppressor protein [78]. Similarly, LIME knock-out animals show no overt signs of abnormal T-cell development and function [79]. Therefore, the search for the plasma membrane Csk-anchor in T-cells is still ongoing, although generation of Cbp/LIME double knock-out animals may show that these two adapters have a redundant function in T-cells (Fig. 2).

Transient activation of Lck in microdomains that move adjacent to TCR-microclusters could be initiated by CD45-mediated dephosphorylation of Y-505 (Fig. 1). Although CD45 is not an integral part of lipid rafts [9,50], upon TCR triggering, a small fraction may affix to lipid raft domains [80,81]. This pool of CD45 although small, could be sufficient for Y-505 dephosphorylation [45]. Such movement of CD45 to lipid rafts could be mediated by binding to raft associated molecules including CD26 or influenced by actin polymerization [82].

Following the initial steps of TCR stimulation many signalling proteins translocate to DRMs and colocalise with lipid rafts as shown by CTB staining [20,65,83-87]. Furthermore increased condensation of the plasma membrane at the site of TCR activation [19,56] and on the other hand decreased TCR signaling in cells loaded with a cholesterol derivative that inhibits membrane condensation [88], point towards a role for lipid raft membranes in TCR signalling. However, the exact size of these microdomains and their detailed mechanism of action remain undefined.

4. Lipid rafts in autoimmunity: potential drug targets?

An important question arising from the work summarized above is whether the status/function of lipid rafts is altered in autoimmune diseases. Elevated cholesterol and GM1 have been noted in activated T-cells [89,90] and in cells from older donors [91,92]. Interestingly, peripheral blood T-cells from patients with the autoimmune disease systemic lupus erythematosus (SLE), contain higher levels of GM1 and cholesterol [93]. These levels gradually revert to normal when the cells are 'rested' in vitro. This may indicate that T-cells in these patients are continuously activated by autoantigens. A pending question is whether higher levels of cholesterol and GM1, and possibly of other lipids, signify only a higher metabolic rate or whether they induce changes in membrane density and segmentation. If the latter is true then changes in protein mobility and function may occur potentially impacting on signalling homeostasis. Defects in various signalling cascades and in expression of key molecules have been noted in SLE T-cells [94-96]. For example, T-cells from patients with active disease expressed less Lck owing to increased consumption of the protein [94]. This is reminiscent of what was seen after sustained activation of normal T-cells [83]. In addition, we have observed higher levels of CD45 in lipid rafts in autoimmune lymphocytes and stimulation of cells with anti-CD3/CD28-coated beads revealed faster kinetics of CD45 reorientation in relation to the cell:bead contact area [93,97]. It will be interesting to investigate the topology and kinetics of CD45 in autoimmune T-cells in relation to TCR microclusters. These results suggest that the size of a pool of CD45 within or in close proximity to lipid rafts could be important for converting Lck into an active form to support signalling by the TCR (Fig. 3).

There is evidence for a role for lipid rafts in other autoimmune diseases as well. For example, CD4^{lo}CD40⁺ is an autoreactive T-cell subpopulation recently identified to be expanded in autoimmunity [98]. Survival and expansion of these cells is dependent on the distribution of the CD40 receptor and its associated signalling complex into lipid rafts [99]. In neuroinflammatory diseases including multiple sclerosis (MS), there is breach of the blood-brain barrier by inflammatory leukocytes [100]. Transmigration of inflammatory cells into the central nervous system requires expression of adhesion molecules. Proteomic analysis of lipid raft microdomains from human blood-brain barrier endothelium identified CD166 the expression of which was elevated during neuroinflammation [101]. CD166 was found to have an important role in the transmigration of leukocytes from blood to the CNS [101].

Recent studies where levels of raft-forming lipids were altered by pharmacological or other means have shown that there is a correlation between their level of expression and regulation of the immune system. For example, it has been shown recently that sialidases, a group of plasma-membrane-associated enzymes, play a role in modulating microdomain-associated glycosphingolipid content and influencing activation in T-lymphocytes [102,103]. Interestingly, inhibitors of sialidase, such as oseltamivir (Tamiflu), down-regulated GM1 expression on the surface of T-cells and reduced cytokine production in activated T-cells [104].

Interestingly, B-cell depleting anti-CD20 antibodies, such as rituximab, which are used for the treatment of rheumatoid arthritis (RA), were shown to induce translocation of CD20 to the lipid raft fraction [105]. This event was crucial for induction of cell apoptosis and was prevented by cholesterol extraction and disruption of lipid rafts [106]. Therefore, certain biologic agents used in the clinic may require intact lipid rafts to exert their therapeutic function.

The development of statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase), which are blockers of cholesterol biosynthesis, have provided an additional tool to address how reduction of cholesterol affects subcellular targeting of proteins and signalling. The use of statins in various autoimmune conditions has started to provide some interesting results [107,108]. In experimental autoimmune encephalomyelitis (EAE), an animal model of MS, statin treatment reduced pathogenesis by interfering with leukocyte recruitment, T-cell activation and cell adhesion (reviewed in [109]). Furthermore, statin treatment was found to reduce *N*-methyl-D-aspartate (NMDA)-induced neuronal damage most likely because it reduced NMDA receptor movement to lipid rafts [110]. Also, statins reduce human blood–brain barrier permeability and downregulate transmigration of leukocytes [111]. Therefore, statins may prove to be beneficial in the early stages of MS. It is unclear however, how statins affect the immune system. In addition to reducing cholesterol, they interfere with post-translation modification and membrane targeting of signalling proteins such as several small GTP-binding proteins [112]. These proteins become isoprenylated, a process that depends on the action of HMG-CoA reductase and mevalonate production, and is required for lipid raft targeting. Another action of statins could be their ability to modify lipid raft structure and function. Ex vivo treatment of T-lymphocytes from SLE patients with atorvastatin reduced colocalisation of Lck and CD45 resulting in less active Lck and reduced production of the pathogenic cytokines IL10 and IL6 upon stimulation [63]. In an animal model of acute colitis, simvastatin reduced the severity of the disease and downmodulated the activity of the NF- κ B pathway in stimulated intestinal epithelial cells [113]. Furthermore, production of pathogenic chemokines from intestinal epithelial cells was dependent on cholesterol suggesting possible involvement of lipid rafts in this process [114]. Therefore, statins mediate their effects on the immune system via multiple mechanisms. In certain cases their effect may be mediated by inducing alterations in lipid rafts and/or inhibiting targeting of key signalling molecules to these domains. Nevertheless, additional roles for cholesterol and its metabolites are becoming apparent. A recent report makes some progress in unraveling how cholesterol levels affect T-cell proliferation. Activation of T-cells induced cholesterol synthesis and suppression of its transport, which is mediated by the LXR (liver X receptor) pathway [115], suggesting that a specific pool of cellular cholesterol is important for T-cell proliferation, although its location is unclear.

Polyunsaturated fatty acids (PUFAs) are shown to intercalate and remodel lipid raft domains [116]. Treatment of T-lymphocytes with PUFAs resulted in the delocalisation of raft-anchored signalling proteins such as LAT [117]. LAT delocalisation was accompanied by its reduced tyrosine phosphorylation and IL2 production following TCR stimulation [118]. PUFAs were also shown to interfere with the formation of the IS [119]. In addition, cell treatment with dietary fish oils altered the structure and size of membrane domains [120] and reduced signalling by the TCR [121,122]. In an experimental model of colitis, PUFA administration prevented inflammation-induced exit of tight junction proteins from lipid rafts and diminished disruption of tight junctions in the intestinal mucosa [123]. Collectively, these results lay the case for closer investigation of PUFAs and dietary fish oils as lipid raft modifiers and as beneficial agents in autoimmunity and inflammation.

5. Perspectives

Suggestive evidence argues for the involvement of lipid rafts in autoimmunity. Some existing agents used in the clinic, such as anti-CD20 antibodies and statins, may exert their therapeutic effect, at least in part, via lipid rafts. In our view, there is sufficient evidence suggesting that lipid rafts are valid targets for the development of new pharmaceuticals capable of modifying their function in autoimmunity. These can be agents that are either general lipid raft modulators acting on all cells or specific for a raft-associated protein with a

restricted pattern of expression. More specific agents will also serve as tools to better elucidate the role of lipid raft domains in the development and pathophysiology of autoimmune diseases.

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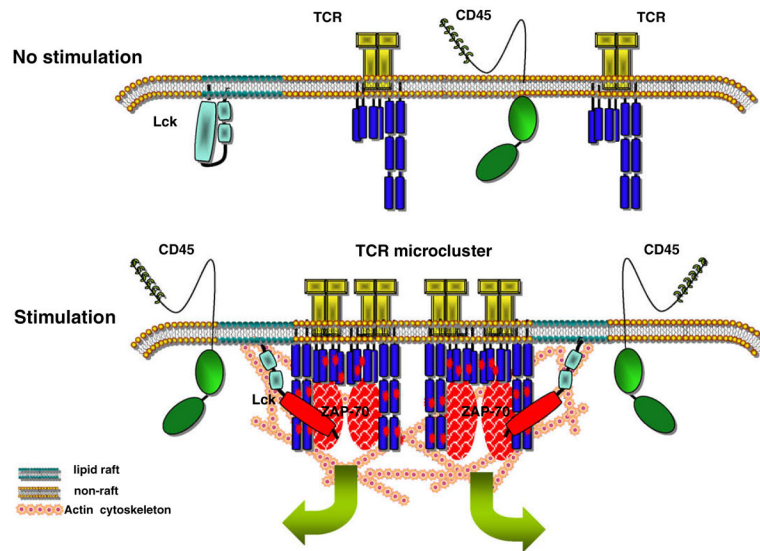


Fig. 1.

A model that correlates changes in the plasma membrane with TCR stimulation. In non-stimulated T-cells, the TCR is in monomeric form and its interaction with lipid rafts is transitory and unable to initiate signalling. Upon antigenic challenge, the reorganization of actin cytoskeleton results in formation of TCR microclusters and reduces the mobility of lipid rafts thus creating an environment conducive to long-lasting interactions. Concomitantly, the activity of Lck in lipid rafts increases owing to the action of a pool of CD45 molecules that moves to close proximity. These changes favour phosphorylation of ITAMs and initiation of signalling.

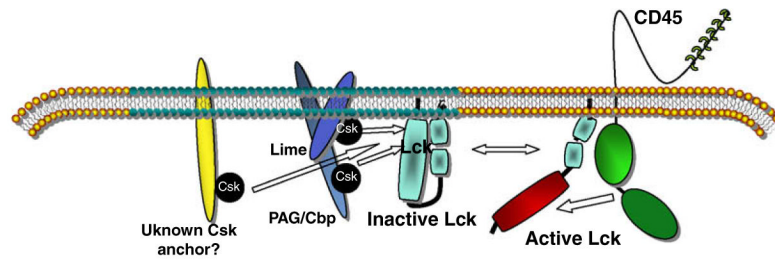


Fig. 2.

A schematic model for the regulation of Lck activity in T-cells. The activity of Lck in lipid rafts is low owing to the recruitment of Csk by PAG/Cbp, LIME and possibly an additional, as yet unknown, adaptor to these domains. Movement of Lck out of lipid rafts or transient association of lipid rafts with CD45 could result in Y-505 dephosphorylation and increase in Lck activity.

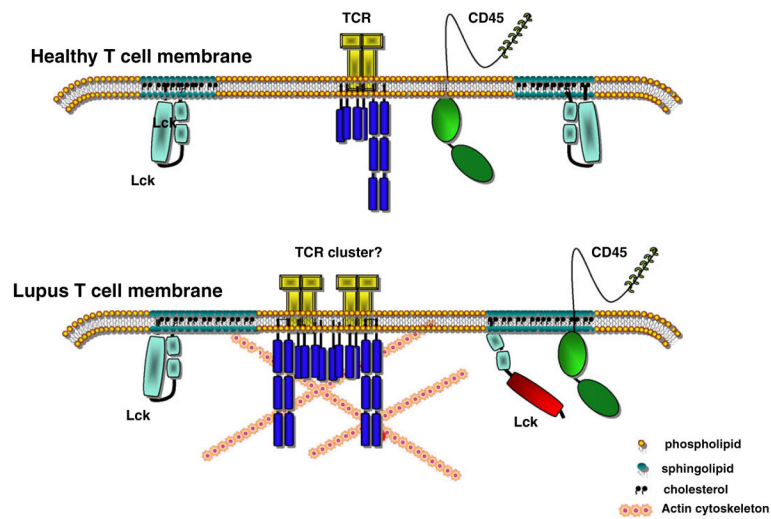


Fig. 3. Changes in the membrane of lupus T-cells may associate with their autoimmune phenotype. The higher cholesterol and GM1 content of lupus T-cell membrane may result in larger and/or less mobile lipid rafts. This in combination with the increased association of CD45 with lipid rafts, higher Lck activity, and changes in the actin cytoskeleton seen in these cells could reduce the threshold for activation.