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Editorial

Emergence of New Roles of Lipid Rafts in Neurological Disorders

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EDITORIAL

The traditional model of the plasma membrane as a homogeneous fluid lipid bilayer has been extended in recent years, as it has become clear that the plasma membrane consists of thousands of different lipids and is a much more complex structure than previously thought. Ceramide, cholesterol, and phophatidic acid are major membrane lipids, and most of them are modified with glucose to generate glucosylceramide (GlcCer), cholesterylglucoside (ChlClc) and phosphatidylglucoside, respectively. These glycosylated lipids are enriched in lipid rafts or membrane microdomains and play important roles in a variety of cellular processes. Many researchers now recognize the importance of the functions through membrane lipid rafts which contain a variety of signaling and transport proteins. In addition, these structures became also known to be involved in the disease processes such as Alzheimer's disease, Parkinson's disease, Prion disease, and atherosclerosis. In the present communication, I will describe a current understanding of how lipid rafts are involved in various neurological disorders and future direction of the research concerning about lipid rafts and human neurological disorders.

The size of membrane lipid rafts is variable (10-200 nm), heterogenous in their contents of sterol, glycosphingolipids (GSLs), sphingomyelin (SM) and highly dynamic in different cell types. Furthermore, we now know that their lipids contents can be modified by daily diet, particularly by dietary fatty acids. Polyunsaturated fatty acids (PUFA) have low affinity to cholesterol, a major sterol of lipid rafts, and therefore are speculated that they cause phase separation from rafts and displacement of raft proteins [1]. Thus, GSLs in membrane lipid rafts are regarded as potential targets for inhibition of tumor growth by n-3 PUFA [2]. In addition to these lipids, various important signaling molecules relating to neurotransmitters are the resident proteins in lipid rafts. Various neurotransmitter signaling systems, especially receptor function, are modified by lipid rafts. These include AMPA receptors, g -aminobutyric acid (GABA) receptors, N-methyl-D-aspartate (NMDA) receptor, nicotinic acetylcholine (nACh) receptors as well as G-protein coupled receptors such as muscarinic acetylcholine receptor (mAChR) [3]. These wide varieties of receptors are therefore sensitive to the alterations of lipid rafts functions.

Recent techniques allowing us direct visualization have characterized them in a wide range of cell types. For example, SM and cholesterol can be visualized with lysenin, a SM-binding toxin, which binds to SM in membrane lipid rafts and the fluorescent esters of poly (ethylene glycol) cholesteryl ether (PEG-Chol) that label cholesterol-rich domain [4].

Although the above-mentioned characteristics have been not extensively examined in various neurological disorders yet, some recent works revealed how lipid rafts are related to the development of human disorders such as AD, PD, and Guillain-Barré syndrome (GBS). I will make a brief comment of the possible link between lipid rafts and the respective disorder.

AD (Alzheimer's disease) is characterized by aggregation of the Aβ (amyloid β-peptide) and subsequent plaque formation, leading to the progressive neuronal death in the central nervous system (CNS). Symptoms of AD include progressive memory disturbances (dementia) and changes in behaviour. Cleavage of the APP (amyloid precursor protein) by the sequential enzyme actions of β- and γ-secretase yields Aβ and the AICD (APP intracellular domain). The accumulation of Aβ has been observed to be related to lipid rafts [5]. Previous work already disclosed that β- and γ-secretase were both localized to lipid rafts [6]. Therefore, disruption of lipid rafts by pharmacological removal of cholesterol from lipid rafts is reported to have some beneficial actions on Aβ formation. Another line of evidence has recently emerged. Mutations in *presenilin 1* (*PS1*) gene, an essential component of g-secretase activity complex are associated with familial AD. These mutations cause the preferential deposition of pathogenic Aβ. Intriguingly, GlcT-1, an enzyme for the production of GlcCer, expression is reduced in mutant *PS1*-transfected neuronal cells without any effect on its mRNA expression [7]. Correspondingly, the amount of GlcCer and gangliosides which is synthesized from GlcCer, is significantly reduced in these cells. Reduction of GlcCer and neuroprotective gangliosides in these cells may affect the functions of lipid rafts and therefore make these cells vulnerable to cellular stress. In fact, Trk, high affinity nerve growth factor (NGF) receptor which is resident in lipid

rafts, became insensitive to its ligand, NGF in these mutant PS1 expressing cells [8]. These cells are more sensitive to oxidative stress than those of their parental cells [8].

In Parkinson's disease (PD), neurons in the substantia nigra brain region producing dopamine, a hormone involved in the control of movement, are destroyed, which leads to a decrease in dopamine production and subsequent uncontrolled muscle contraction and movement [9]. α-Synuclein, a protein of unknown function which is present in both healthy and PD brains, has been accumulated in intracellular Lewy bodies in neurons of patients with PD [10]. Another study by Fortin et al. specifically investigated the interaction of α-synuclein with lipid rafts using binding assays of the protein with isolated DRMs from HeLa cells. These experiments showed that α-synuclein co-localizes with CD55, a raft-associated protein, and appears attached to the plasma membrane regions using immunofluorescence staining and gradient fractionation [11]. In a similar study [12], α-synuclein interaction with raft-like membrane structures was not impaired after proteolytic disruption of raft proteins, which implies that it binds to raft lipids, rather than to raft proteins. These previous studies just opened the door for better understanding of molecular pathogenesis of this disorder and more detailed investigations of the roles of lipid rafts in this disorder should be explored in the future.

Accumulating evidences have suggested that patients with GBS exhibit anti-gangliosides antibodies in their sera and cerebrospinal fluid (CSF) [13]. Although many authors so far claimed that these anti-gangliosides antibodies are pathognomonic for this disorder, the detailed molecular mechanisms how these antibodies cause this syndrome remained to be elucidated. Our recent work, however, strongly suggested a possible link of anti-ganglioside antibody and its disruption of lipid rafts in neuronal cell culture system [14]. Anti-ganglioside GM1 antibodies can dislocate Trk, a lipid rafts-resident high affinity NGF receptor, into non-rafts fraction of the plasma membrane, and therefore result in the unresponsiveness to NGF, an essential neurotrophic factor for neuronal survival and differentiation [14]. This study indicates the importance of lipid rafts for the development of this disorder.

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