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Lipid rafts involvement in the pathogenesis of parkinson's disease

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1. ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative diseases affecting an increasing number of people worldwide with the aging society. Although the etiology of PD remains largely unknown, it is now clear that genetic factors contribute to the pathogenesis of the disease. Recently, several causative genes have been identified in mendelian forms of PD. Growing evidence indicates that their gene products play important roles in oxidative stress response, mitochondrial function, and the ubiquitin-proteasome system, which are also implicated in idiopathic PD, suggesting that these gene products share a common pathway to nigral degeneration in both familial and idiopathic PD. Interestingly, several lines of evidence show that the gene products associate with lipid rafts which are thought to be involved in important cellular functions such as membrane trafficking, signal transduction, and cytoskeletal organization. Lipid rafts are cholesterol- and sphingolipid-enriched microdomains on the cell membranes that provide a highly saturated and viscous physicochemical microenvironment to promote protein–lipid and protein–protein interactions. In this article, we will review studies focusing on PD in association with lipid rafts and discuss implication of lipid rafts in the pathogenesis of PD.

2. INTRODUCTION

Cell membranes are crucial to the life of the cell. The plasma membrane encloses the cell, defines its boundaries, and maintains the essential differences between the cytosol and the extracellular environment. Inside eukaryotic cells, the membranes of the endoplasmic reticulum, Golgi complex, mitochondria, and other membrane-enclosed organelles maintain the characteristic differences between the contents of each organelles and the cytosol. All biological membranes have a common general structure: lipid molecules are arranged as a continuous bilayer which provides the basic fluid structure of the membrane and serves as a relatively impermeable barrier to passage of most water-soluble molecules. Protein molecules that associate the lipid bilayer mediate nearly all of the

other functions of the membrane. Lipid molecules constitute about 50% of the mass of most animal cell membranes, nearly all of the remainder being protein. Because a lipid bilayer is a two-dimensional fluid, we might expect most types of lipid molecules in it to be randomly distributed in their own monolayer. With certain lipid mixtures, however, different lipids can come together transiently, creating a dynamic patchwork of different domains. The lipid bilayer provides the basic structure for all cell membranes and its structure is attributable exclusively to the special properties of the lipid molecules, which assemble spontaneously into bilayers even under simple artificial conditions (1). It is no exaggeration to say that research in cell membranes has developed based upon the lipid raft concept (2) over the past ten-odd years. According to the concept, there exist microdomains consisting of specific lipid constituents on cell membranes as if rafts floated on the ocean. Lipid rafts form liquid-ordered domains in the lipid bilayer and are dispersed in the bulk of a liquid-disordered domains that comprise the remainder of cell membranes, and are thought to function in cellular signaling by forming platforms for individual receptor signaling complexes (2). In addition to signal transduction, lipid rafts are also believed to play important roles in intracellular membrane trafficking, cytoskeletal organization, and viral infection (2-4).

Accumulating evidence has been suggesting that alterations in lipid rafts are implicated in the pathologic processes in various neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and prion diseases (5, 6). In this article, we summarize the lipid raft concept and discuss an importance of lipid rafts in neurodegeneration focusing on Parkinson's disease.

3. LIPID RAFTS

3.1. Lipid raft concept

Lipid rafts are highly enriched in cholesterol and sphingolipid, and are defined biochemically by their insolubility in Triton X-100 (TX-100) at 4°C and their buoyant density which permits their isolation by flotation through density gradients (7). The special features of lipid rafts are thought to be due to the tight packing of highly saturated fatty acid residues in raft lipids with cholesterol (2, 8). Furthermore, polyunsaturated lipids have also been suggested to be implicated in formation of stable lipid rafts (9, 10). Certain specialized regions of the plasma membrane, such as the caveolae involved in endocytosis, are enriched in sphingolipids and cholesterol, and it is thought that the specific proteins that assemble there help stabilize these lipid rafts. Because the hydrocarbon chains of sphingolipids are longer and straighter than those of other membrane lipids, raft domains are thicker than other parts of the lipid bilayer and better accommodate certain membrane proteins. Thus, the lateral segregation of proteins and of lipids into raft domains would, in principle, be a mutually stabilizing process. In this way, lipid rafts could help organize membrane proteins, concentrating them either for transport in membrane vesicles or for working together in protein assemblies, as when they convert extracellular signals into intracellular ones. However, there has been a long debate among scientists whether the lipid rafts really exist on the cell membranes, because of lack of methodology showing their existence on the cell membranes. Biochemically defined lipid rafts, i.e., detergent-resistant membranes (DRMs), are an artificial product with no assurance of their presence on real cell membranes, leading to the skepticism against the lipid raft concept.

3.2. Lipid rafts becoming a reality

In the previous concept, there exist "large" lipid rafts tightly packed with composition of cholesterol and sphingolipids of micrometers in diameter on cell membranes. These "preformed" rafts contain molecules including receptors required for signal transduction regardless of presence or absence of stimuli, making it more efficiently once the stimulus is brought on. Although the concept appeared reasonable for functionality of cell membranes, recent advances in technology such as single-molecule spectroscopy and microscopy techniques decipher the real rafts (11-20). Cell membranes display a tremendous complexity of lipids and proteins designed to perform the functions cells require. To coordinate these functions, the membrane is able to laterally segregate its constituents. Raft-associated molecules dispersed on cell membranes in the resting state cluster together to form the rafts on the stimuli and they can be stabilized to coalesce, forming platforms that function in membrane signaling and trafficking. Lipid rafts are fluctuating nanoscale assemblies of sphingolipid, cholesterol and proteins, short-lived with a timescale of tens to hundreds milliseconds. Cell membranes are actually organized based on dynamic liquid-liquid immiscibility and lipid rafts are thought to form on demand (Figure 1). The misleadingness into the presence of the large preformed lipid rafts appeared based on the

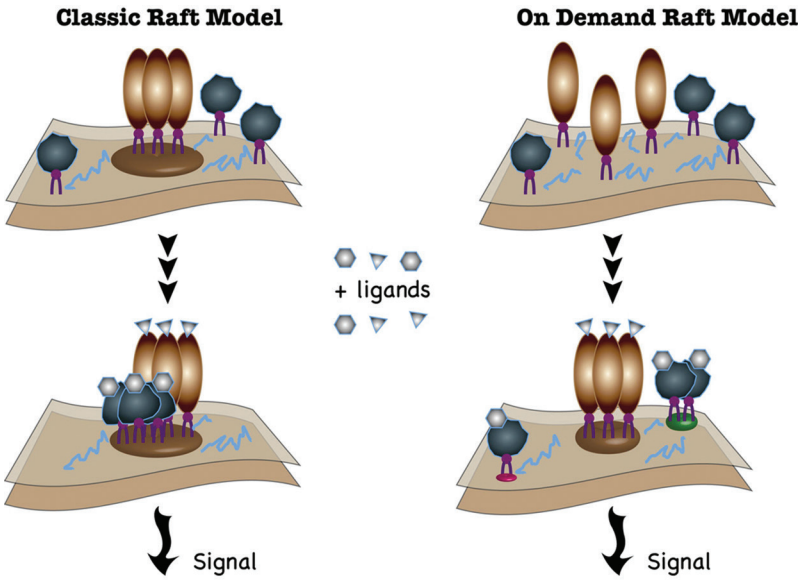

Figure 1. In the classic concept, lipid rafts ( ) are preformed with molecules including receptors required for signal transduction regardless of presence or absence of stimuli. Based upon recent advances in technology, raft-associated molecules dispersed on the cell membranes in resting state cluster together to form the rafts on the stimuli such as binding of ligands to receptors.

observations using immunocytochemistry in which antibodies as an external stimulus could assemble raft components artificially.

3.3. Biological roles of lipid rafts

Lipid rafts have been thought to be involved in a great variety of cellular functions and biological events. For instance, T cell receptors (TCRs) in the resting state may associate with raft lipids to form nanoscale assemblies that cluster into a raft platform (TCR microclusters) on activation of the T cell by the ligand on an antigen-presenting cell. The TCR then becomes phosphorylated by the Src family kinase lymphocyte cell-specific protein Tyr kinase, and recruits and activates the Tyr kinase 70 kDa ζ-associated protein (ZAP70), which initiates further downstream signaling (21, 22). The nervous system provides many examples of lipid raft-associated signaling proteins and lipid raft-dependent signal transduction (23). Lipid rafts in nervous system cells have been implicated in neurotrophic factor signaling (24-26), cell adhesion and migration (25, 27, 28), axon guidance and neurite outgrowth (29), synaptic transmission (25, 30), neuron-glia interactions (31, 32), and myelin genesis (33). Lipid rafts also appears to play roles in the membrane trafficking. In the endoplasmic reticulum (ER)-to-Golgi vesicular transport of yeast, it is required for ER exit of the vesicles that glycosylphosphatidylinositol (GPI)-anchors are remodeled with a saturated, long-chain fatty acid or a ceramide that confers detergent resistance (34, 35, 36). In membrane traffic departing from the Golgi complex, raft cargo proteins are delivered to the cell surface in a raft carrier. The protein and lipid-sorting process probably involves raft clustering to drive segregation in the membrane of the TGN (37). Lipid rafts also associate with the cytoskeleton and mediate cytoskeletal organization (38). Several cytoskeletal components as well as enzymes that regulate the cytoskeleton localize to lipid rafts and help regulate lateral diffusion of membrane proteins and lipids in response to extracellular events such as receptor activation. Lipid rafts regulate cellular polarity, adherence to the extracellular matrix and signaling events, and are sites of cellular entry of certain pathogens, toxins and nanoparticles. The dynamic interaction between lipid rafts and the cytoskeleton thus regulates many aspects of the function of cells and their adaptation to changing environments.

4. PARKINSON'S DISEASE AND LIPID RAFTS

4.1. Parkinson's disease

Parkinson's disease (PD) is one of the most common neurodegenerative diseases,

affecting more than 1-4% of people aged 65-85 years (39). The clinical features consist of motor dysfunction including rest tremor, rigidity, bradykinesia, postural instability as well as non-motor symptoms such as cognitive decline, sleep disturbances and dysautonomia. The pathological hallmarks of PD are marked loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), which causes dopamine deficiency in the striatum, and the presence of intracytoplasmic eosinophilic inclusions known as Lewy bodies in the remaining cells. Neurodegeneration and Lewy body formation are recognized not only in the SNc but also in locus coeruleus, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulb, parasympathetic as well as sympathetic post-ganglionic neurons, nucleus basalis of Meynert, amygdaloid nucleus and cerebral cortex. The widespread neurodegeneration is thought to be responsible for the motor and non-motor symptoms of PD (40). The discovery of levodopa, a precursor of dopamine, has dramatically elongated the life expectancy of PD, although it does not necessarily improve the quality of life. Levodopa, in fact, is a symptomatic drug and long-term treatment with levodopa is associated with adverse effects, such as motor fluctuations (wearing-off and on-off phenomenon) and dyskinesias. New therapies are therefore required to improve the long-term functional prognosis. To develop a new remedy for PD, it will be essential to elucidate the pathogenic mechanisms underlying the neurodegeneration.

Mitochondrial dysfunction and oxidative stress are critical components of most current theories of nigral degeneration in PD (41-44), however the mechanisms responsible for the cell death remain largely unknown. Recently, there has been increasing evidence that genetic factors play an important role in PD. Although most PD cases are sporadic (idiopathic PD), a small proportion of cases shows a Mendelian inheritance. Genetic mutations can be detected in ~3% of patients with parkinsonism (45). The identification of responsible genes for rare familial forms of PD has provided vital clues to understanding the molecular pathogenesis of the more common idiopathic PD.

4.1.1. Monogenic forms of PD

To date, at least 18 distinct genetic loci and 13 genes have been reported to be linked to PD, that is, PARK1 and PARK4/*α-synuclein*, PARK2/*parkin*, PARK5/*ubiquitin carboxyl-terminal hydrolase L1* (*UCHL1*), PARK6/*PTEN-induced putative kinase 1* (*PINK1*), PARK7/*DJ-1*, PARK8/*leucine-rich repeat kinase 2* (*LRRK2*), PARK9/*ATPase type 13A2* (*ATP13A2*), PARK11/*Grb10 interacting GYF protein 2* (*GIGYF2*), PARK13/*Htr serine peptidase 2* (*HTRA2/OMI*), PARK14/*phospholipase A2, group VI* (*PLA2G6*), PARK15/*F-box protein 7* (*FBXO7*), PARK17/*vacuolar protein sorting protein 35* (*VPS35*) and PARK18/*eukaryotic translation initiation factor 4 gamma 1* (*EIF4G1*) (Table 1). The phenotype of these familial forms of PD is consistent with that of idiopathic PD in terms of levodopa-responsive parkinsonism indicative of dopamine deficiency in the nigrostriatal pathway, whereas there seem to be some characteristic features dependent on the genes. Mutations in α-synuclein cause cognitive impairment and dysautonomia with Lewy body pathology. LRRK2 mutations may result in a clinical phenotype closely resembling idiopathic PD with pleomorphic neuropathology. Mutations in parkin, PINK1, or DJ-1 may lead to young-onset parkinsonism with a low risk for cognitive impairment with a pathology mainly restricted to the brainstem. Carrier of mutations in the other genes may rarely develop a disease resembling idiopathic PD (46, 47). Whether the mutations in these Mendelian forms of parkinsonism converge on the same cellular pathways such as mitochondrial dysfunction and oxidative stress remains to be elucidated, while understanding the mechanisms of each of these monogenic forms might decipher the pathogenesis of dopaminergic neurodegeneration in these diseases as well as in the idiopathic PD.

4.2. Lipid rafts in PD

4.2.1 α-Synuclein

α-Synuclein has been attracting a great deal of attention because of its implication in the pathogenesis of α-synucleinopathies including Lewy body disorder (LBD), i.e., PD, PD with dementia or dementia with Lewy bodies and multiple system atrophy as well as Alzheimer's disease (48-51). Point mutations in the α-synuclein gene cause rare forms of autosomal dominant familial LBD (52-54). In addition, increased dosage of the wild- type gene appears sufficient to produce LBD (55-58). α-Synuclein is also a major component of Lewy bodies (LBs) and Lewy neurites, abnormal filamentous aggregates that are neuropathological hallmarks of LBD (59, 60). Although a growing body of evidence suggests an important role of α-synuclein in the pathogenic process of the disorder, the precise mechanism by which α-synuclein influences

Table 1. Genetic risks of Parkinson's disease

Gene symbol	Gene Locus	Mode	Gene name	Age at onset	Lewy bodies
PARK1(SNCA), PARK4	4q22.1	AD	α-synuclein	Around 40	+
PARK27	6q26	AR	Parkin	<40	− (+ in some patients)
PARK3	2p13	AD	?	35-89	+
PARK5	4p13	AD	UCH-L1	<50	?
PARK6	1p36.12	AR	PINK1	Around 50	+ in heterozygotes
PARK7	1p36.23	AR	DJ-1	27-40	?
PARK8	12q12	AD	LRRK2	Around 65	+/-
PARK9	1p36.13	AR	ATP13A2	11-16	?
PARK10	1p32	SP	?	Late	?
PARK11	2q37.1	AD	GIGYF2	Late	?
PARK12	Xp21-q25	SP	?	Late	?
PARK13	2p13.1	SP	HtrA2/Omi	Late	?
PARK14	22q13.1	AR	PLA2G6	20-25	+
PARK15	22q12.3	AR	FBXO7	10-19	?
PARK16	1q32	SP	?	Late	?
PARK17	16q11.2	AD	VPS35	Late	-
PARK18	3q27.1	AD	EIF4G1	Late	+
GBA	1q22	SP	Glucocerebrosidase	52+-7	+

neural degeneration and indeed its normal function remain poorly understood. α-Synuclein consisting of a 140-amino acid (a.a.), an abundant and highly conserved neuronal protein in vertebrates, is enriched in presynaptic nerve terminals (61-64) and has been suggested to play a role in synaptic plasticity and neurotransmitter release (64-68). However, unlike most presynaptic protein, α-synuclein is not tightly associated with either the synaptic vesicle or the synaptic plasma membrane, because it behaves as soluble protein by differential centrifugation and gradient fractionation (63, 65, 69, 70). The mechanisms responsible for its synaptic localization are thus not preserved in standard biochemical studies. *In vitro* studies suggest that α-synuclein binds to artificial vesicles, especially those containing acidic phospholipids (71-73). α-Synuclein has also been shown to associate with axonal transport vesicles (74), lipid droplets (75), and yeast membranes (76). We have elucidated that α-synuclein associates specifically with lipid rafts and that the raft association is required for the synaptic localization of α-synuclein (77). The A30P but not A53T mutation linked to PD disrupts the interaction of α-synuclein with lipid rafts. The results thus suggest an important role for lipid rafts in the normal function of α-synuclein and raise the possibility that perturbing raft association may induce changes in α-synuclein that contribute to the pathogenesis of PD. To understand how α-synuclein interacts with lipid rafts, we have developed an *in vitro* binding assay to rafts purified from native membranes (78). Recapitulating the specificity observed *in vivo*, recombinant wild type but not PD-associated A30P mutant α-synuclein binds to lipid rafts isolated from cultured cells and purified synaptic vesicles. Proteolytic digestion of the rafts does not disrupt the binding of α-synuclein, indicating an interaction with lipid rather than protein components of these membranes. We have also found that α-synuclein binds directly to artificial membranes whose lipid composition mimics that of lipid rafts. The binding of α-synuclein to these raft-like liposomes requires acidic phospholipids, with a preference for phosphatidylserine (PS). Interestingly, a variety of synthetic PS with defined acyl chains do not support binding when used individually. Rather, the interaction with α-synuclein requires a combination of PS with oleic (18:1n-9) and polyunsaturated (either 20:4n-6 or 22:6n-3) fatty acyl chains, suggesting a role for phase separation

within the membrane. Furthermore, α-synuclein binds with higher affinity to artificial membranes with the PS head group on the polyunsaturated fatty acyl chain rather than on the oleoyl side chain, indicating a stringent combinatorial code for the interaction of α-synuclein with membranes.

4.2.2. LRRK2

LRRK2 protein is a 2527 a.a. polypeptide (~280 kDa), consisting of leucine-rich repeats (LRR), Ras of complex proteins (ROC) followed by the C-terminal of Roc, mitogen-activated protein kinase kinase kinase (MAPKKK) and WD40 domains (79). LRRK2 protein belongs to the ROCO protein family. Although the functions of ROCO protein family remain unknown, LRRK2 might play a role in cell division and development according to the information from Dictyostelium ROCO proteins (80). In the rodent brain, LRRK2 is widely distributed including the SNc, caudate putamen, and olfactory bulb (81-83). In the human brain, recent *in situ* hybridization and immunohistochemical analyses revealed that LRRK2 also localizes within various brain regions associated with PD pathology (84). Therefore, LRRK2 supposedly has important functions in broad areas of the brain as well as the nigro-striatal dopaminergic pathway. In cells, LRRK2 proteins are mainly found in the cytoplasm. However, LRRK2 proteins are also present in membranous organelles including ER, Golgi complex, early endosomes, lysosomes, synaptic vesicles, mitochondria and plasma membrane (81, 85-87). Moreover, other groups reported that LRRK2 regulates the maintenance of neurite process morphology in mammalian brains (88) and interacts with Rab5a, which facilitates membrane internalization at synaptosomes (89). In C. elegans, LRRK2 homolog (LRK-1) also localizes in the Golgi complex and regulates the axon-dendritic polarity of synaptic vesicles (90). To characterize membrane association of LRRK2, we used cultured cells including primary neurons from mouse brains and showed the localization of LRRK2 in the Golgi complex, plasma membrane and synaptic vesicles. The localization of LRRK2 to the membranes resists solubilization by ice-cold 1% Triton X-100 but not extraction with increasing salt concentrations, indicating that LRRK2 associates with lipid rafts through an electrostatic bond. We also investigated the effects of mutations found in PD patients on the biochemical properties of LRRK2. Intriguingly, the mutants behave in a manner similar to the wild type, with regard to association with membrane including lipid rafts (87). The results suggest that LRRK2 mutants cause PD by inhibiting the normal function of wild type or gain of function effects on lipid rafts. Recently, Li and colleagues reported that LRRK2R1441G BAC transgenic mouse exhibited age-dependent levodopa-responsive bradykinesia and loss of TH positive dendrites in SNc (91). In addition, most of LRRK2-interacting proteins are cytoskeleton and trafficking proteins such as moesin (92), alpha/beta-tubulin heterodimers (93), clathrin and vimentin (94). These observations suggest that LRRK2 plays key roles in membrane trafficking and axon guidance through lipid rafts.

4.2.3. Parkin

Parkin, a 465 a.a. polypeptide, is implicated in the ubiquitin-proteasome system (UPS) as an E3 ubiquitin ligase, and mutations in the *parkin* gene is reported to result in loss of ligase function (95, 96). The UPS is involved in two tasks. One is the accurate timely regulation of the level of short-lived proteins that plays a role in processes such as cell-cycle regulation, signal transduction, and metabolism. The other task is protein quality control. Polyubiquitination of the target proteins for degradation by proteasomes is catalyzed by three enzymes, E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 ubiquitin ligase. Parkin has been shown to catalyze the proteasomal degradation of target proteins by interacting with E2 and target proteins through its RING domain (95, 97, 98), and by binding the Rpn10 subunit of 26S proteasomes through its Ubl domain (99). The target proteins tagged with the polyubiquitin chain linked via lysine27 or 48 are recognized and degraded by the proteasome (100). On the other hand, parkin has recently been shown to catalyze lysine63-linked ubiquitination which is not recognized by the proteasome (101, 102). Lysine63-linked ubiquitination is involved in diverse cellular processes such as endocytosis(103-106) and protein sorting and trafficking (107-109). We have reported that parkin occurs in the Golgi complex in addition to the cytoplasm in human brain, although parkin has no transmembrane domain (110). In cultured cells and rat brain, parkin also associates with cellular vesicles as a peripheral membrane protein (111). The association of parkin with cellular vesicles might relate to that parkin plays a role in the membrane trafficking system through K63-linked ubiquitination. In our study to characterize the membrane association of parkin, treatment of the membranes at 4°C with high salt but not 1% TX-100 solubilizes parkin (111). Consistently, Fallon and colleagues have shown that parkin co-localizes with CASK,

mammalian homolog of *Caenorhabditis elegans* Lin-2, at synapses in cultured cortical neurons as well as in postsynaptic densities and lipid rafts in brain (112).

4.2.4. DJ-1

DJ-1 is a 189 a.a. protein that forms a dimer and belongs to the THiJ/Pfp1/DJ-1 family. Several pathogenic mutations causing recessive PD have been identified in the DJ-1 gene, including exonic deletion, truncations, and homozygous and heterozygous missense mutations (46). To date, the functions of DJ-1 remain unclear, however, several experiments suggest that DJ-1 is involved in multiple functions, such as redox-sensitive chaperone (113), mitochondria protection against oxidative stress (114) and fertility (115). Especially, the anti-oxidant functions of DJ-1 have been extensively reported in cultured cells (116), rodent (117), and drosophila models (118, 119). Intriguingly, DJ-1 null mice showed normal numbers of dopaminergic neurons in the substantia nigra, whereas they displayed hypoactivity in open field and were also sensitive to MPTP and oxidative stress (120). Electrophysiological studies revealed that DJ-1 null mice had marked reduction of evoked DA overflow in the striatum, which is due to increased re-uptake of DA (121). Immunoelectron microscopic analysis identified DJ-1 proteins in striatal axons and pre-synaptic terminals (122), indicating that DJ-1 might be associated with membrane trafficking at synaptic terminals, including vesicle recycling and exocytosis. We have recently reported that DJ-1 distributes to the cytosol and membranous structures in a punctate appearance in cultured cells and in primary neurons obtained from mouse brain (123). DJ-1 colocalizes with the Golgi complex proteins GM130 and the synaptic vesicle proteins such as synaptophysin and Rab3A. Förster resonance energy transfer analysis revealed that a small portion of DJ-1 interacts with synaptophysin in living cells. Although the wild-type DJ-1 protein directly associates with membranes with no interposition of protein, the pathogenic L166P mutation of DJ-1 exhibits less binding to synaptic vesicles. These results indicate that DJ-1 associates with membranous organelles including synaptic membranes to exhibit its normal function. Very recently, Kim and colleagues (124) have shown that DJ-1 associates with lipid rafts via palmitoylation of three cysteine residues (C46/53/106) and C-terminal region of the protein with an enhancement of the association on stimulus with lipopolysaccharide (LPS) in astrocytes. Based on the observations of LPS-TLR4 signaling in astrocyte, they also showed an involvement of DJ-1 in the endocytic pathway through its lipid raft association. Discrepancy between results from their experiments and ours where DJ-1 associates with cellular membranes independent of lipid rafts can be due to the differences in the cell types or the external stimuli.

4.2.5. Idiopathic PD

Whereas there is little data suggesting the involvement of lipid rafts in idiopathic PD, it is exciting that lipids including sphingolipids represent a significant component of Lewy bodies (125, 126) of which α-synuclein is also a major component (59, 60). Fabelo and colleagues have recently reported alterations in lipid composition of DRMs from autopsied brains of PD. They purified DRMs from human frontal cortex and analyzed their lipid composition, showing dramatic reductions in their contents of n-3 and n-6 long-chain polyunsaturated fatty acids, especially docosahexaenoic acid (DHA) (22:6n-3) and arachidonic acid (AA) (20:4n-6) in PD compared with those in controls. Also, saturated fatty acids (16:0 and 18:0) were significantly higher than in control brains. PS and phosphatidylinositol were increased in PD, whereas cerebrosides, sulfatides and plasmalogens levels were diminished (127). Given that the association of α-synuclein with raft-like liposomes requires a combination of PS with oleic (18:1n-9) and polyunsaturated (either 20:4n-6 or 22:6n-3) fatty acyl chains (78), the depletion of DHA and AA in DRMs from PD might unbind α-synuclein from the membranes, eventually altering the dynamics of aggregation/fibrillation state of α-synuclein (71), likely facilitating the Lewy body formation.

5. SUMMARY AND PERSPECTIVE

We hope that this review has convinced the reader of important roles for lipid rafts in the normal cellular functions and their involvement in the pathogenesis of PD. On the basis of a comprehensive review of data published, we would conclude that familial PD-linked proteins at least α-synuclein, LRRK2, parkin, and DJ-1 play roles in association with lipid rafts, with the caveat that DRMs are considered as lipid rafts in most of the studies. The alterations in lipid composition of DRMs from brains of idiopathic PD recapitulate an importance of lipid rafts in pathological process in PD. Taken together, it seems plausible that the proteins responsible for familial PD may contribute to homeostasis of lipid rafts (Figure 2). Further studies will need to investigate the implication of the PD-linked proteins

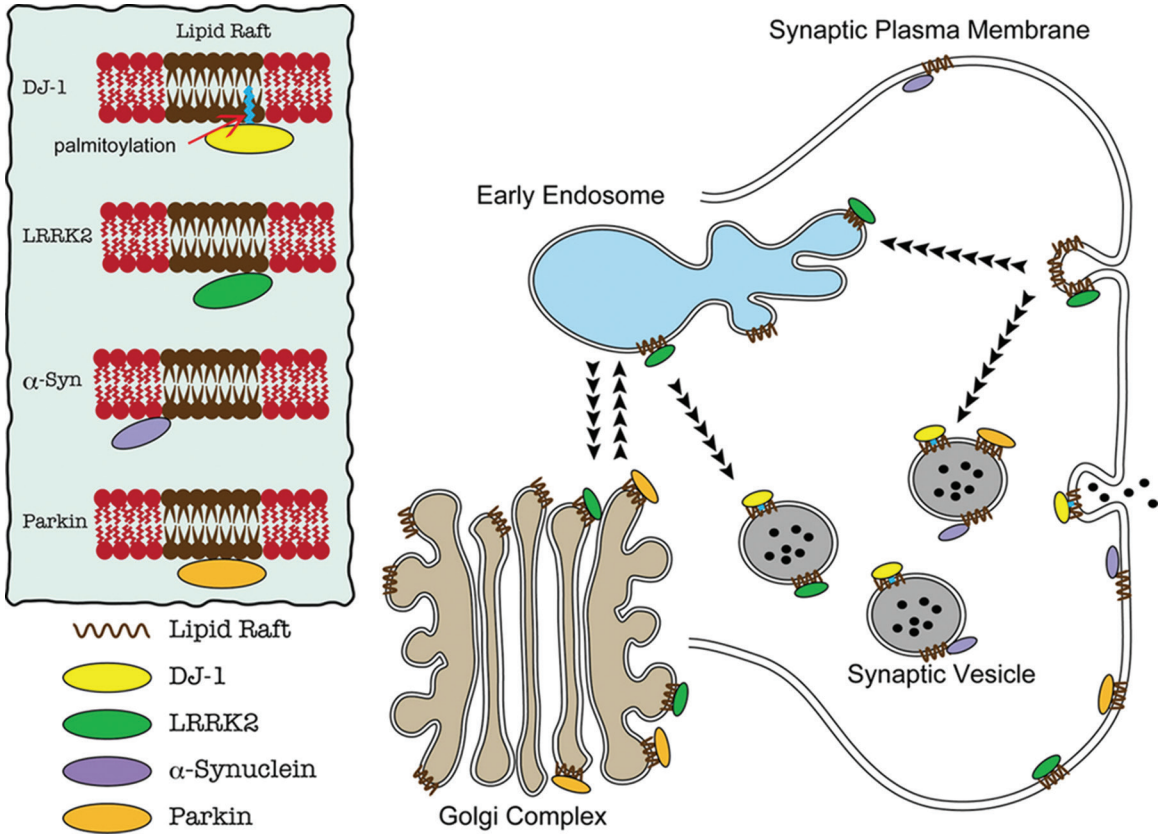

Figure 2. Proteins responsible for familial PD have been shown to associate with the cellular membranes of the organelles, such as the Golgi complex, endosomes, synaptic vesicles, and plasma membrane. On the basis of the observations that their membrane association resists being solubilized with ice-cold TX-100, lipid rafts are suggested to play a role for their subcellular localization (77, 87, 111, 112, 124).

in lipid rafts using living cells and to understand how lipid rafts are involved in the pathogenesis of PD.

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The authors declare no competing interests.

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