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Lipid rafts participate in aberrant degradative autophagic-lysosomal pathway of amyloid-beta peptide in Alzheimer's disease

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Abstract

Amyloid-beta peptide is the main component of amyloid plaques, which are found in Alzheimer's disease. The generation and deposition of amyloid-beta is one of the crucial factors for the onset and progression of Alzheimer's disease. Lipid rafts are glycolipid-rich liquid domains of the plasma membrane, where certain types of protein tend to aggregate and intercalate. Lipid rafts are involved in the generation of amyloid-beta oligomers and the formation of amyloid-beta peptides. In this paper, we review the mechanism by which lipid rafts disturb the aberrant degradative autophagic-lysosomal pathway of amyloid-beta, which plays an important role in the pathological process of Alzheimer's disease. Moreover, we describe this mechanism from the view of the Two-system Theory of fasciology and thus, suggest that lipid rafts may be a new target of Alzheimer's disease treatment.

Key Words: nerve regeneration; lipid rafts; amyloid precursor protein; autophagy; lysosome; Alzheimer's disease; Two-system Theory; amyloid beta peptide; autophagosome; National Financial Major Project of China; neural regeneration

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with aging. With the global trend of prolonging human life and the corresponding increase in the aged population, Alzheimer's disease has thus become one of the most important health and socioeconomic problems at present. By 2050, Alzheimer's disease is predicted to affect 1 in 85 people worldwide[1], causing great burden to society due to the lack of effective preventative measures against this disease, and a greater need of caregivers. Despite extensive research and significant progress made into the pathology of Alzheimer's disease, its cause is still not fully understood. The pathogenesis of Alzheimer's disease is complicated by numerous factors, such as genes[2-4], brain-derived neurotrophic factor[5], neuroinflammation[6], oxidative stress[7], hormones[8], gender[9], and systemic disorders[10-12]. Autopsies of Alzheimer's disease patients show brain atrophy, particularly in the entorhinal cortex and hippocampus, and microscopy reveals abnormal cells with neurofibrillary tangles in these regions[13]. However, these manifestations can also be found in elderly patients who are cognitively intact[13], thus causing a discrepancy in the brain anatomy associated with Alzheimer's disease. Individuals without dementia but exhibiting Alzheimer's disease neuropathology have been hypothesized to be in the preclinical stages of dementia, possibly experiencing mild cognitive impairment[14]. Therefore, the great difficulty in understanding Alzheimer's disease may be partially related to an unresolved understanding of the pathogenesis and neuropathology of this disease.

Despite this unresolved understanding, key diagnostic neuropathological features of the disease have been largely attributed to the presence of neurofibrillary tangles, senile plaques (SP), and loss of synapses[15]. These pathological phenomena may occur in different stages of Alzheimer's disease and may play a different role in its progression. The timing of synaptic loss and its association with amyloid-beta peptide and/or its oligomers, is controversial.

Different types of Alzheimer's disease (early/late-onset or familial) have been described[15]. Synaptic loss may not be the determinant factor of this disease. Neurofibrillary tangles occur intracellularly and consist of the accumulation of an abnormal form of protein, tau, which interrupts cell transport properties and results in weakened communication between cells in the brain. However, cognitive impairment

in animal models occurs earlier than the initial formation of fibrillary structures[16], suggesting that tau may not be the crucial pathological protein of this disease.

Amyloid-beta is the main component of SP, and is a 40- or 42-amino acid protein generated by the proteolytic cleavage of the transmembrane protein, amyloid precursor protein (APP), by beta- and gamma-secretases[17]. Amyloid senile proteins occur extracellularly. Amyloid-beta accumulates in the parenchyma of the Alzheimer's disease brain as diffuse plaques and dense neuritic or senile plaques. Amyloid-beta deposition results from an imbalance between its production and clearance. In cerebral amyloid angiopathy, these deposits accumulate in the vascular walls of arteries, veins and capillaries. Therefore, the blood-brain barrier can be compromised and thus, this impairment may influence the metabolism and clearance of amyloid-beta, thereby contributing to Alzheimer's disease pathogenesis[18].

Although controversial, amyloid precursor protein-mediated accumulation of amyloid-beta is an important phenomenon in the pathology of Alzheimer's disease. If the production and clearance of amyloid-beta is deregulated, the blood-brain barrier is thus compromised. Therefore, amyloid-beta degradation is required. Amyloid-beta clearance in Alzheimer's disease largely depends on the cells themselves. To the best of our knowledge, the ubiquitin-proteasome system and the autophagic-lysosomal system are the two proteolytic systems predominantly responsible for protein quality control in neurons, and play an important role in the pathogenesis of Alzheimer's disease[19]. However, whether an aberrant ubiquitin-proteasome system plays a causative or only a secondary role in Alzheimer's disease remains unclear. Protein aggregates and certain organelles that are tagged with ubiquitination can be selectively removed by autophagy[20]. Inhibiting autophagy by genetically knocking out the sequestration machinery causes ubiquitinated protein aggregates to appear in neurons. Furthermore, proteasomal subunits may be degraded by lysosomes[21]. Therefore, the autophagic-lysosomal pathway is recognized to play an important role in the clearance and turnover of cells.

Constitutive autophagy in neurons prevents the accumulation of ubiquitinated proteins. Generally, autophagy enhances cell survival in response to nutrient deprivation. However, dying cells often display accumulation of autophagosomes. Alternatively, sustained autophagy can lead to cell death. Although the impact factors are not fully understood, an appropriate level of autophagy is nevertheless crucial to neurons[22-23].

In contrast, lipid rafts are involved in the regulation of amyloid precursor protein proteolytic processing and amyloid-beta generation. Lipid rafts are the primary mediators of amyloid oxidative attack on plasma membranes[24]. Alterations of lipid rafts may result from complex deregulation of neuronal physiology[25]. Furthermore, lipid raft signaling disturbs autophagy in the Alzheimer's disease brain[26]. However, to the best of our knowledge, no report has provided an association between lipid rafts and autophagic-lysosomal pathway in the progression of Alzheimer's disease. In this paper, we discuss the importance of the autophagic-lysosomal pathway on amyloid-beta degradation, focusing on the role of lipid rafts in the pathology of the Alzheimer's disease brain. The associations of the autophagic-lysosomal pathway and lipid rafts with Alzheimer's disease are well reported, however the role of lipid rafts in the progression of Alzheimer's disease has been neglected. Therefore, we based our review on the Two-system Theory put forward by Yuan[27], which hypothesizes that the human body is under constant cleansing and renewing, thereby managing to achieve a dynamic balance. This theory may partially explain the clearance of pathological proteins and turnover of cells in the Alzheimer's disease brain, and also suggest a potential therapeutic target for drug development and clinical treatment of Alzheimer's disease.

The Two-system Theory and clearance mechanism in the human body

The Virtual Chinese Human Project has visualized that fascia connective tissues form a complete framework that spread throughout the human body[28-30]. This theory suggests that the living body can be viewed as two dynamic parts, the supporting-storing system and the functional system. The supporting-storing system consists of non-specific connective tissue of the human body, comprising undifferentiated cells. These cells can be regarded as stem cells (particularly of mesoderm origin) and may thus be pluripotent[31-33]. Therefore, the supporting-storing system can maintain the stability of the internal environment by cell proliferation and differentiation, cell repair and regeneration. In contrast, the functional system consists of various differentiated functional cells existing in different organs and tissues, which perform different biological activities. The functional cells are surrounded by the supporting-storing system. These cells undergo aging and death. However, before cell renewal during aging, the functional cells try to remain active to eliminate the growing burden of damaged, and potentially toxic, intracellular proteins and organelles. Therefore, cells experience a cycle of transitional steps that mutually interact with each other: proliferation→differentiation→maturation→aging→death→→collapse→engulfment→digestion→re-digestion→reuse→synthesis→recycle[27, 29]. All the steps prior to cell death involve cellular cleansing where autophagy plays an important role. Absence of the recycling process results in perturbed cell regeneration and repair[34-35].

Based on this dynamic view, important theoretic branches are evident, such as constant cell renewal from the supporting-storing system, clearance of unproductive organelles or metabolites, and recycling of human cells[28].

Constant renewal of functional cells can sustain their structural and functional stabilities to keep the body in a normal and healthy status, whereas constituents from dead cells can be reused by the body. Therefore, the renewal and clearance process maintains body homeostasis. However, the differentiation source is limited and the reuse process lacks specificity. Despite these limitations, functional cells themselves undergo autophagy, which is another mechanism

of self-clearance and thus, an important turnover mechanism to maintain cellular energy and activity. Therefore, self-clearance contributes to building a healthy niche for cell survival[23, 32, 34].

The recycling theory may help to explain the mechanism of some pathological factors as well as specific therapies. In light of the Two-system Theory, degenerative diseases can be attributed to either a shortage in regeneration or a dysfunction in clearance, both of which are closely related and mutually affected. The clearance failure may obstruct neurogenesis and neural regeneration, resulting in cases of severe diseases. Alzheimer's disease is a neurodegenerative disease caused by clearance failure, which hinders neural regeneration. Identifying the signals required to promote neurogenesis and neuronal survival is thus urgent for this disease. Unfortunately, the progress in identifying therapeutics that may improve neurogenesis for Alzheimer's disease patients is slow[36]. However, the clearance of pathological products may help to build a better niche for neurogenesis and neural regeneration in the Alzheimer's disease brain.

Possible clearance mechanisms in the Alzheimer's disease brain

Normal cell function and circulatory clearance

The adult human brain is a very active organ because it uses approximately 20% of the body's oxygen and about 20% of the body's energy. The relationship between neurovascular dysfunction and amyloid-beta accumulation contributes to neurodegenerative processes in the Alzheimer's disease brain[37]. Therefore, how brain cells function normally against mounting physiopathological impairments is largely determined by the efficiency at which it can eliminate the burden of damaged cellular components[19].

As mentioned above, clearance of amyloid-beta deposits is required in the Alzheimer's disease brain, and impaired cerebral vessels suffer from amyloid angiopathy, suggesting that circulative amyloid-beta may be a precursor of brain amyloid-beta[38]. Alternatively, systemic amyloid-beta may enter the brain passively *via* a leaky blood-brain barrier[39]. Therefore, clearance of amyloid-beta deposits may depend on cells in close proximity.

Microglia in Alzheimer's disease brain

Microglia are macrophage-like cells in the central nervous system (CNS). Activated microglia function to remove potentially deleterious debris and promote tissue repair in the brain[40]. In contrast, these cells also release potentially neurotoxic substances and are thus involved in neurodegenerative diseases[40], possibly exacerbating these conditions[41].

Proteasomal degradation and endocytic pathway

Proteasomal degradation has high selectivity, generally for only ubiquitinated substrates, which are primarily short-lived proteins. Lysosomes are often described as a "cellular garbage can", exhibiting more positive roles in cellular renovation[42]. Extracellular material and plasma membrane proteins can be delivered to lysosomes for degradation *via* the endocytic pathway[42].

Autophagy and the autophagic-lysosomal pathway in the Alzheimer's disease brain

Clearance of the last steps in cells is acknowledged to occur *via* the lysosomal pathway[15]. The lysosomal system is defined broadly as a family of communicating acidic compartments (pH 3.5–6.0), which contain varying levels of more than 80 lysosomal acid hydrolases. The cathepsins contained in the lysosomal acid hydrolases (acting across a broad range of acidic pH values) can degrade most proteins rapidly to their amino acid component. Substrates for degradation are delivered to lysosomes by two general routes, namely, heterophagy and autophagy, which carry extracellular and intracellular constituents, respectively. Both routes are relevant in amyloid precursor protein processing and to Alzheimer's disease pathogenesis[43-44].

Alzheimer's disease has been described as a neurodegenerative disease with particularly extensive autophagic-endosomal-lysosomal dysfunction. A magnitude of autophagic vacuoles accumulate within dystrophic neurites, which distinguishes Alzheimer's disease from other late-onset neurodegenerative diseases[19]. The autophagic-lysosomal compartments are the most prevalent organelles in dystrophic neurites of the Alzheimer's disease brain[45], thus possibly posing important implications for β-amyloidogenesis and neuronal survival in Alzheimer's disease[45]. The function of the lysosomal system is disrupted by factors that cause or increase the risk for Alzheimer's disease onset. For example, genetic factors that increase Alzheimer's disease onset, such as amyloid precursor protein (coding amyloid precursor protein), PSEN (coding presenilin), APOE (coding apolipoprotein E), CatD (coding cathepsin D polymorphisms), SORL 1 (coding Sortilin-related receptor), and CST3 (coding cystatin C polymorphisms), affect autophagic-lysosomal function as well as contributing to β-amyloidogenesis, and possibly lysosome-mediated neuronal cell death[46-48]. These proteins have their cellular location on the endosome, autophagosome, lysosome, cytoplasm or plasma membrane, indicating that the association of Alzheimer's disease with the lysosomal system has genetic evidence[44, 48].

Autophagy is a generic term for all pathways by which cytoplasmic materials are delivered to the lysosome in eukaryotic cells. It is a physiological, self-eating process involved in the degradation of cytoplasmic materials like damaged proteins and intracellular organelles[49]. Autophagy contributes to the regulation of proliferation, differentiation and cell death. It is a highly evolutionarily conserved degradation pathway necessary for maintaining cellular homeostasis and defense[42]. Moreover, autophagy is the sole pathway for organelle turnover in cells[49].

Three classes of autophagy are known: macroautophagy, microautophagy, and chaperone-mediated autophagy. Generally, autophagy is referred to as macroautophagy[42]. The intermediate organelle "autophagosome" is formed by an isolated membrane sequestering a small portion of the cytoplasm, which fuses with the lysosome to become an autolysosome and degrades the materials contained within it. Therefore, the autophagy process is mainly characterized by three steps: (1) dynamic rearrangement of membranes

(called autophagosome formation) that can engulf oligomeric protein complexes and organelles, as well as pathogens, (2) autophagosomes fusing with lysosomes, and (3) degradation of the contents[49]. Degradation of cytoplasmic materials is initiated when the autophagosome fuses with degradative compartments of the lysosomal system.

This autophagic-lysosomal degradation process is considered to be particularly important for the function of the CNS and neuronal survival because of the post-mitotic and non-dividing nature of neurons[50]. Neurons are dependent on autophagy for their survival. Blocking autophagosome formation by deletion of Atg5 or Atg7 genes leads to accumulation of ubiquitinated proteins and eventual neurodegeneration[22]. Overall, constitutive autophagy in neurons aims to prevent ubiquitinated proteins from accumulating. Therefore, self-clearance of neural cells is very important to the maintenance of normal function. In the healthy brain, clearance of the autophagic-lysosomal pathway is very efficient, and prevents build-up of proteins[49]. However, lysosomal function in the human brain declines with age[51]. Research over decades has implicated aberrant autophagy and lysosomal function as reliable markers and therapeutic targets for neurodegenerative diseases[19, 48, 50, 52-53]. Lysosomal degradative failure may allow for amyloid-beta and possibly tau protein to accumulate and further disrupt proteolysis or destabilize autophagic vacuoles or lysosomes. Therefore, compensatory activation of lysosomes follows protein accumulation events[54].

Furthermore, autophagy generally enhances cell survival in response to nutrient deprivation, however, dying cells often display accumulation of autophagosomes. Importantly, sustained autophagy can lead to cell death. Autophagy can be induced during nutritional deprivation, trophic factor withdrawal, and other circumstances of cell stress, to protect cells against apoptosis by degrading nonessential cell constituents for energy[55]. Overactive or dysfunctional autophagy may also promote neuronal cell death in disease states[56]. This suggests that the aberrant autophagic-lysosomal pathway may be further stressed by accumulated proteins in the Alzheimer's disease brain.

The lysosomal system, specifically the autophagic pathway, is the principal degradation mechanism to reduce the mounting burden of proteins (such as amyloid-beta and tau) accumulation, in the Alzheimer's disease brain. It is the only system in cells for degrading organelles and large protein accumulation or inclusions[19]. The activated autophagic-lysosomal pathway can partially protect neurons from the accumulation of cellular organelles and protein aggregates.

However, the main component of SP and main pathological protein in the Alzheimer's disease brain is amyloid-beta, which is located in the cells[13]. Therefore, how do these proteins cross the transmembrane to be degraded by the autophagic-lysosomal pathway?

The uptake mechanisms of amyloid-beta have been reported to involve glutamate and acetylcholine receptors, apolipoproteins and other amyloid-beta-binding proteins[25]. However, lipid raft-dependent endocytosis is the predominant mechanism for amyloid-beta uptake.

Lipid rafts

Plasma membranes are composed of a lipid bilayer, containing proteins that span this layer and/or interact with the lipids on either side of the two leaflets. Emerging studies[57-59] have introduced the lipid raft concept to explain the generation of the glycolipid-rich domains of the plasma membrane. The definition of a lipid raft was developed at the 2006 Keystone Symposium of Lipid Rafts and Cell Function: "Lipid rafts are small (10–200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes. Small rafts can sometimes be stabilized to form larger platforms through protein-protein and protein-lipid interactions."

One of the most important properties of lipid rafts is that they can include or exclude proteins within a certain range. The reason for some transmembrane proteins included into rafts is not fully understood. Within these membrane domains, certain types of protein tend to aggregate and intercalate into a lipid raft structure[60]. Other proteins are not so tightly bound, and their movement in and out of the rafts can be controlled by factors, such as ligand-binding or oligomerization[61-62]. Even a small change of partitioning into a lipid raft can initiate signaling cascades through amplification. Therefore, lipid rafts are considered to be crucial for the activation of many signal transduction pathways.

This area of research is still controversial because of the limitations in methodology and techniques for lipid rafts research. Nevertheless, lipid rafts are considered to be important signaling platforms whose structures are sensitive to membrane lipid composition[63-64]. Lipid rafts can associate with proteins directly or through binding with other cofactors or ligands. Lipid raft-associated proteins have key roles in protein entry and trafficking as well as signal transduction[63], and is also thought to be essential in neuronal signaling platforms[65]. An increasing amount of evidence derived from genetic, epidemiological and biochemical studies has focused on the role of cholesterol (a major component of lipid rafts) in some diseases, including Alzheimer's disease[66-67]. Raft domains may also provide an environment in which proteins involved in amyloid precursor protein processing cluster, thereby increasing amyloid-beta production. Therefore, lipid rafts may serve as a platform for secretases to differentiate amyloid precursor protein processing from other secretase-dependent cellular processes.

Because soluble amyloid-beta oligomers correlate better than plaque load with cognitive impairment and neuronal dysfunction, a principal toxic species of amyloid-beta may thus be involved in Alzheimer's disease[68]. Amyloid oligomers exogenously added to culture medium of fibroblasts bearing amyloid precursor protein V717I gene mutations readily insert into oxidative-damaged surfaces where membrane integrity was compromised[66, 69]. Therefore, membranes may be the initial triggers of the biochemical modifications culminating with neuronal death.

Neuronal lipid rafts are also required for the maintenance of dendritic spines and healthy synapses, which are vital for neural communication involved in learning and memory[65]. They represent a platform for protein-lipid and protein-pro-

tein interactions and for cellular signaling events in Alzheimer's disease[70-72]. Membrane destabilization as a natural consequence of primary defective lipid composition has been proposed to be important in brain cell death in Alzheimer's disease mediated[57]. This membrane damage has been found to occur selectively in neurodegenerative areas of the Alzheimer's disease brain, thus potentially accounting for localized lipid pathology[73]. Lipid rafts contain numerous membrane proteins, and their clustering is thought to provide a spatial and temporal platform for signaling and trafficking molecules[57, 63].

Interaction of lipid rafts with Alzheimer's disease-relevant proteins

Alterations of lipid rafts may result from complex deregulation of neuronal physiology. Numerous studies have reported the association of lipid rafts with neurodegenerative diseases, particularly Alzheimer's disease[25, 65, 71-72, 74-75].

Lipid rafts are involved in the regulation of amyloid precursor protein proteolytic processing and the generation of the amyloid-beta peptide. Key proteins involved in Alzheimer's disease (such amyloid-beta, intracellular NFTs of hyper-phosphorylated tau, and amyloid precursor protein) have been investigated for their possible raft localizations and association with physiopathological functions[70, 72]. Lipid rafts are involved in the modulation of amyloid precursor protein cleavage, and amyloid precursor protein and its associated cleavage enzymes that generate amyloid-beta are transmembrane proteins. Evidence shows that cholesterol plays a central role in regulating alpha- and beta-cleavage of amyloid precursor protein. Epidemiological evidence reveals that elevated cholesterol levels during mid-life may increase the risk of developing Alzheimer's disease[76]. Although amyloid precursor protein is not a raft protein (containing a single transmembrane domain)[67], a small proportion of amyloid precursor protein is localized in lipid rafts[77]. The regulation of raft localization of amyloid precursor protein has been suggested to involve an interaction between the C-terminus of amyloid precursor protein and flotillin-1 (marker of lipid rafts) in lipid rafts[78]. Flotillin-2 is suggested to act as a scaffolding protein, clustering amyloid precursor protein in lipid rafts[79]. A direct interaction of amyloid precursor protein with cholesterol has been identified[80]. Cholesterol has been reported to play a role in promoting amyloid precursor protein binding to its raft localization[80].

In addition to amyloid precursor protein processing, interactions between amyloid-beta and neuronal membranes have been suggested to play a pivotal role in the neuropathology of Alzheimer's disease[81]. amyloid-beta production is lipid raft-dependent[82], with its internalization occurring at lipid rafts[83]. Furthermore, amyloid-beta is highly concentrated in lipid rafts, which may also be an important site for the interaction between dimeric amyloid-beta, ApoE, and tau[84]. Cholesterol, gamma-secretase and amyloid-beta represent factors in a regulatory cycle for gamma-secretase signaling, amyloid precursor protein processing and amyloid-beta peptide, all of which down-regulate cholesterol and sphingolipid levels, and in turn, may regulate amyloid-beta production[85]. Gamma-secretase is also reported to reside in lipid rafts, which is also affected by cholesterol[86]. Lipid rafts may also promote interaction of amyloid precursor protein with the secretase β-site amyloid precursor protein cleaving enzyme-1, which is responsible for the generation of amyloid-beta[87]. Furthermore, lipid rafts are proposed to be a binding site for extracellular amyloid-beta and a niche for amyloid-beta aggregation[88-89].

Lipid rafts may function as platforms where neurotoxic oligomers of proteins are assembled, including the amyloid-beta peptides[24]. In Alzheimer's disease brains, binding of amyloid-beta to lipid rafts promotes its oligomerization and subsequently induce fibril formation[25]. Although amyloid-beta oligomers exist at nanomolar concentrations, they are nevertheless neurotoxic. Receptors that bind amyloid-beta oligomers have been found to reside primarily within lipid rafts[65, 90] (Figure 1).

Moreover, major lipid raft components, such as cholesterol, have been directly implicated in the pathogenesis of Alzheimer's disease[91-92]. Although targeting amyloidogenic processing in lipid rafts is a relatively unexplored area in Alzheimer's disease therapeutics, cholesterol has been considered as a major candidate for targeting amyloidogenic processing of amyloid precursor protein in lipid rafts[93]. Fabelo et al.[72] suggested that lipid rafts may be directly responsible for transmembrane cell signal transduction of amyloid-beta oligomer-mediated memory impairment and neurotoxicity, all of which characterize Alzheimer's disease.

Lipid rafts and the lysosomal system in the Alzheimer's disease brain

Lipid rafts are most abundant in plasma membrane, but are also found in the endocytic pathway. Lipid raft trafficking is

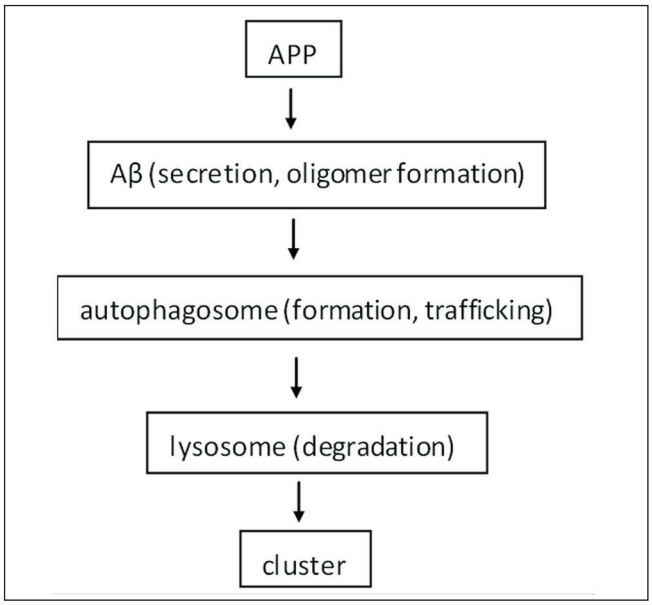

Figure 1 Processes of the autophagic-lysosomal pathway of Aβ in which lipid rafts play a role.
APP: Amyloid precursor protein; Aβ: amyloid-beta.

not terminated with surface delivery, but is continuously endocytosed from the plasma membrane[63]. Indeed, some lysosomes are fused into the cell membrane within lipid rafts platforms, which transmit and amplify signals. Lysosomes fuse with the plasma membrane for exocytosis and contribute to the formation of lipid rafts signaling platforms, thereby participating in transmembrane signaling[94].

Research has revealed that lipid rafts play a role in mediating Alzheimer's disease-relevant proteins to the lysosomal system. Lipid rafts are highly abundant on mature lysosomes[95]. Gamma-secretase subunits have been found in lysosomes and phagosomes, the plasma membrane, and mitochondria[96], which are essential components for the autophagic-lysosomal pathway. The regulatory cycle formed by gamma-secretase, amyloid-beta peptides, and cholesterol in amyloid precursor protein processing may be associated with the autophagic-lysosomal system.

The lysosomal membrane is a very diverse structure that receives membrane and protein contributions from a variety of subcellular sources and pathways. Lipid rafts can affect amyloid precursor protein processing *via* the induction of endocytosis of amyloid precursor protein[70]. Moreover, amyloid precursor protein is trafficked directly to lysosomes[97]. Flotillin-1 is accumulated in neuronal lysosomes in Alzheimer's disease[98].

Furthermore, high dietary low-density lipoprotein (LDL)-cholesterol and overexpressed ApoE (particularly ApoE 4 [ApoE4]) may elevate β-cleaved C-terminal fragment (β-CTF) levels. β-CTF is found in Alzheimer's disease, particularly in early-onset forms caused by certain mutations of amyloid precursor protein. ApoE is a plasma cholesterol transport molecule. ApoE4 has deleterious effects on the cerebral microvasculature, and vascular disease is an important component of Alzheimer's disease pathogenesis. Localization of amyloid-beta42 into lysosomes is neurotoxic, in particular in the presence of ApoE4. Metabolism of both ApoE and amyloid-beta42 are regulated by LDL receptor-related protein 1. In neuronal cells, overexpressing mini-receptor may increase the internalization of amyloid-beta42 and its accumulation[99]. Moreover, LDL receptor-related protein 1 mediates endocytosis and lysosomal trafficking of amyloid-beta42 in neuronal cells[99]. The endocytic activity of LDL receptor-related protein 1 may contribute to the appearance of plaques by increasing the internalization of amyloid-beta[25].

Therefore, lipid rafts may be extensively involved in amyloid precursor protein processing to the lysosomal system and therefore their signaling may play an important role.

Evidence that lipid raft signaling disturbs autophagy in the Alzheimer's disease brain

Lipid rafts consist of dynamic assemblies of cholesterol and lipids with saturated acyl chains, such as sphingolipids and glycosphingolipids. Lipids are located in the exoplasmic leaflet of the membrane bilayer, and cholesterol in the inner leaflet. Membrane lipid rafts are clustered to form relatively large macrodomains on activation of individual receptors by ligand binding. Autophagy begins with an isolated membrane (a phagophore), which is likely to be derived from the lipid bilayer contributed by the endoplasmic reticulum and/or the trans-Golgi and endosomes[100-101]. The phagophore expands to engulf intracellular cargo, such as protein aggregates, and then sequesters the cargo in a double-membrane autophagosome[102].

In some conserved catabolic processes, autophagosomes sequester cytoplasmic material and extraneous organelles within membranes derived from the secretory pathway, for delivery to lysosomes. Because the formation of the autophagosome relies on the reassembly of the membrane, and the pathological products in the membrane interact with lipid rafts, we thus speculate that autophagy can be triggered when the pathological product responds to the components of lipid raft activated domains[103]. However, sustained autophagy can lead to cell death. Overactive or dysfunctional autophagy may also promote neuronal cell death in disease states[104]. The elevated autophagic level, especially the accumulation of autophagic vacuoles, is an additional cause for neurodegenerative diseases[56]. Therefore, activation of the autophagic lysosomal pathway by lipid rafts may be fatal to neurons in the Alzheimer's disease brain. Furthermore, the lipid lysobisphosphatidic acid is a characteristic molecule of degradative organelle, and its membrane domains are believed to contribute to the selectivity in handling of lipid rafts of the lysosomal pathway[105]. Moreover, this lipid plays a role in protein trafficking[106].

Presenilin 1 (a peptide involved in the formation of amyloid fibrils in Alzheimer's disease) plays a role in the autophagic process and possibly in the maturation of autophagic vacuoles in Alzheimer's disease[107]. These findings are in line with endosomal/lysosomal abnormalities observed in the Alzheimer's disease brain[108-109]. Although the role of presenilin 1 in autophagy has been reported, it was found to not be dependent on gamma-secretase activity[110]. However, the role of presenilin 1 on amyloid precursor protein processing and in the autophagic-lysosomal pathway of amyloid cannot be ruled out. In contrast, presenilin 1 has been reported to modify lipid raft composition of neuronal membranes[111]. Protein-lipid signaling in the CNS is an important cause for neurological disorders, which may directly or indirectly act on autophagy.

Bacterial experiments reveal that pathogen internalization and stimulation of autophagy are cholesterol-sensitive[112]. Other findings from studies in endothelial cells show that autophagic cell death can be triggered by products of damaged plasma membranes, sphingolipids and ceramide. These results represent a mechanistic molecular cascade whereby advanced glycation end-products induce sphingomyelinase activity, accumulation of ceramide, clustering, and late internalization of lipid rafts[113]. Pathological proteins can be speculated to interact with lipid rafts, which can thus influence autophagosome formation and further disturb the autophagic-lysosomal degradation pathway. In the Alzheimer's disease brain, this pathway may be blocked, at least in part by lipid raft signaling, thereby exacerbating Alzheimer's disease.

Despite reports on the role of lipid rafts or the autophag-

ic-lysosomal pathway in the Alzheimer's disease brain[71, 114], we are the first to hypothesize their possible link with this disease. We hypothesize that lipid raft-dependent amyloid precursor protein processing influences formation of the autophagosome, thereby targeting the autophagic-lysosomal system and exacerbating Alzheimer's disease progression. Interestingly, a vicious cycle of these events may occur because the autophagic-lysosomal system is impaired in the Alzheimer's disease brain. Thus, the dysfunction in the clearance of pathological proteins in the Alzheimer's disease brain may obstruct neurogenesis and neuronal survival.

Perspectives and prospects

Amyloid-beta is generated from amyloid precursor protein, and is believed to be an important pathological protein in Alzheimer's disease. Lipid rafts are glycolipid-rich domains of the plasma membrane. Although amyloid precursor protein processing is associated with complex factors, lipid rafts may be an important processor for amyloid precursor protein, as well as amyloid-beta. Generally, the autophagic-lysosomal pathway is aberrant in Alzheimer's disease brain. However, lipid rafts that mediate amyloid precursor protein can disturb autophagy, thus blocking the autophagic-lysosomal pathway and aggravating the disease. Therefore, we speculate that in Alzheimer's disease, lipid rafts play an important role in blocking the autophagic-lysosomal pathway of amyloid precursor protein processing and amyloid-beta degradation, thereby exacerbating the progression of this disease. To our knowledge, no report has addressed this possible association. Furthermore, this review provided evidence, *via* the Two-system Theory, that the dynamic clearance of a pathological product may result from clearance fail or dysfunction that may subsequently affect neurogenesis and neuronal survival and thus, should be balanced to maintain the normal function of the brain[115].

Overall, therapeutic strategies should target these key signaling elements, such as the interaction of amyloid precursor protein and lipid rafts, the triggering of lipid rafts and autophagy, and the fusion of autophagosome and lysosome. In doing so, these strategies may facilitate the clearance of pathological proteins in the Alzheimer's disease brain and are thus potential ways of delaying or alleviating the progression of this disease. Statin therapy has been suggested for Alzheimer's disease treatment[116] because cholesterol is greatly involved in Alzheimer's disease progression. Statins may interact with enzymes that influence amyloid-beta production[67]. However, research has failed to draw a definitive conclusion on the ability of statins to modulate Alzheimer's disease progression[76, 117]. This discrepancy needs further study. Blockage in the autophagic pathway is recognized in neuronal ceroid lipofuscinosis and Danon disease[108]. Therefore, it is likely that these diseases share a similar treatment concept of the autophagic pathway modulation with lipid rafts, which would require further research.

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Conflicts of interest: *None declared.*

Peer review: *This study overviewed: (1) the role of lipid rafts in the formation and clearance of amyloid-beta peptide, (2) the characteristics of studies on Alzheimer's disease, (3) lysosome and autophagy, and (4) the interaction between the production and aggregation of amyloid-beta peptide and autophagy during the progression of Alzheimer's disease.*

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