A possible role of myristoylated alanine-rich C kinase substrate in endocytic pathway of Alzheimer's disease

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Abstract: It is believed that amyloid- β peptide (A β) plays a central role in the pathogenesis of Alzheimer's disease (AD). Thus, the process of amyloid precursor protein (APP) cleavage is a key event and has raised much attention in the field of AD research. It is proposed that APP, β - and γ -secretases are all located on the lipid raft, and the meeting of them is an indispensable step for A β generation. Endocytosis can lead to clustering of APP, β - and γ -secretases from separate smaller lipid rafts into a larger one. On the other hand, for myristoylated alanine-rich C kinase substrate (MARCKS), phosphorylation by protein kinase C (PKC) or interaction with Ca²⁺ can lead to its release from membrane into cytoplasm. This process induces the release of actins and phosphatidylinositol 4, 5-bisphosphate (PIP₂), which are important factors for endocytosis. Thus, the present review proposes that MARCKS may be implicated in A β generation, by modulating free PIP₂ level and actin movement, causing endocytosis.

Keywords: Alzheimer's disease; endocytosis; myristoylated alanine-rich C kinase substrate; lipid raft; phosphatidylinositol 4, 5-bisphosphate; actin cytoskeleton

1 Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a progressive process of decline in cognitive function. Histologically, it is characterized by the accumulation of extracellular senile plaques comprised of aggregated amyloid- β peptides (A β) and intraneuronal neurofibrillary tangles^[1,2]. The etiology of the disease still remains obscure. The early-onset AD or familial AD (FAD) accounts for approximately 5%–10% of all the AD cases worldwide. Mutations in the amyloid precursor protein (APP) and presenilin genes may lead to A β overproduction.

The late-onset AD, also called sporadic AD (SAD), accounts for 90%–95% of the remaining cases^[3,4,5]. The cause of SAD is complex. The apolipoprotein E (*ApoE*) ϵ 4 allele is a strong risk factor for SAD, increasing the likelihood of developing SAD^[6]. Other factors, including the low educational level, head injury, high-calorie diet, *etc.*, are also responsible for SAD onset^[7].

Lines of evidence have shown that lipid rafts^[8-10] and endocytic pathway^[11-13] are implicated in AD pathogenesis. Myristoylated alanine-rich C kinase substrate (MARCKS), an important membrane protein, can associate cell signal with actin cytoskeleton. The present review mainly outlined current understanding of the roles of lipid rafts and endocytosis pathway in AD pathogenesis, and the important roles of MARCKS in the 2 important processes were also highlighted.

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Article ID: 1673-7067(2010)04-0338-07

Received date: 2010-01-31; Accepted date: 2010-04-25

2 A β generation

Fibrillar A β deposit, which initiates a series of crucial pathological events that ultimately lead to neuronal loss and dementia, is broadly considered as a central step in the pathogenesis of AD^[14]. Recently, the smaller, soluble forms of A β have been indicated as the primary neurotoxic species^[15]. Due to the central role of A β production in the pathology of AD, the mechanism of A β generation from APP has been a focus in AD research. APP is a widely distributed transmembrane protein that resembles glycosylated cell-surface receptors^[16]. The A β peptide is derived from the sequential processing of APP at β - and γ -secretase sites. As is known, APP can be cleaved in 2 mutually exclusive proteolytic pathways. One is amyloidogenic pathway by β - and γ -secretases. β -Secretase cleaves APP to generate the 99-amino acid C-terminal fragment of APP (C99), which is further cleaved by γ -secretase to produce A β _{40/42}. The other is the nonamyloidogenic pathway catalyzed by α -secretase, which cleaves APP in the A β region, producing APP α and precluding A β production^[17,18]. In SAD, which is without APP gene mutation, the availability of APP to either α - or β -secretase determines A β peptide generation^[19]. So it is very important to find out the modulators of APP interaction with α - or β -secretase.

3 Lipid raft functions in AD

Lipid rafts are cholesterol- and sphingolipid-enriched microdomains within cell membranes^[8], and are closely related to the process of A β production. There is growing evidence that cholesterol is of particular importance in regulating α - and β -cleavage^[9]. Extensive research has demonstrated that reducing neuronal cholesterol levels could inhibit the amyloidogenic pathway, probably through removal of APP from lipid raft^[10]. Epidemiological studies also suggest that the prevalence of AD is strongly decreased in patients treated with 3-hydroxy-3-methylglutaryl-coenzyme (a statin drug), indicating the important role of lipid raft in AD^[10].

APP processing by both β - and γ -secretases depends on the lipid raft environment. In living cells, β -secretase seems to require intact rafts for activity, since β -secretase outside the rafts appears to be inactive. It is observed that the sites of γ -secretase activity are also associated with lipid rafts^[20].

In contrast, APP α production occurs in membrane regions with a low cholesterol content^[21]. Thus, it is hypothesized that APP is present in 2 cellular pools: one is associated with lipid rafts where A β is generated, and the other is outside the rafts where α -cleavage takes place^[22]. The availability of β - or α -secretase to APP may be determined by dynamic interactions of APP with lipid rafts.

4 Endocytic pathway in A β generation

Abnormal endocytic pathway is an early event of AD, and may contribute to abnormal A β generation. Endocytosis is the process that the plasma membrane invaginates into the cell, resulting in production of endosomes which would then enter the endo-lysosomal membrane system^[23]. In neurons, the endocytic pathway is responsible for extracellular nutrient take-up, membrane lipid recycle, and degradation of trafficking proteins and receptors, all of which provide appropriate microenvironments for the interaction of signaling proteins^[24]. The endocytic pathway can be divided into early and late endocytic pathways^[25]. The early endocytic pathway is implicated in internalization of molecules from the cell surface and the recycling of internalized materials back to the plasma membrane or outside of cells. The late endocytic pathway mainly degrades the accepted materials from the early pathway^[26]. The early endocytic pathway involves the plasma membrane (PM), very early endosome (VEE), early endosome (EE), sorting endosome (SE) and endocytic recycling compartment (ERC). VEEs initially dissociate from the PM and form their downstream EEs. Then EEs join in SE, in which the contents are subsequently sorted into downstream organelles at later stages of endocytosis. Sorted materials like A β can be either directly recycled back to the plasma membrane, transferred to the downstream endocytic recycling compartment, or delivered to late endosomes (LEs)^[27]. Endosomal trafficking is a cytoskeleton-dependent event, mainly supported by microfilaments and microtubules dynamics^[28].

As a widely distributed membrane protein, APP undergoes continued recycling and trafficking throughout its lifetime. A β production appears to dynamically involve endocytic recycling of APP from the cell surface. There has

been compelling evidence that enlargement of EE is an early event in SAD, and it occurs before substantial A β accumulation in brain and the presence of clinical symptoms^[11,12]. In addition, A β accumulation has also been found in abnormally enlarged endosomes^[14]. Prominent alterations of EE suggest that the neuronal endocytic pathway, particularly internalization, is overactivated, which represents a possible basis of accelerated amyloidogenesis in SAD^[5]. Although the specific contribution of APP endocytic processing to A β production has not yet been fully elucidated, it is believed that APP can be reinternalized to the clathrin-based endocytic pathway^[29,30]. Firstly, the internalized APP is shuttled into EE where it is cleaved by β -secretase to generate C99. C99 is then recycled back to the plasma membrane, and it meets γ -secretase in VEE. VEE executes its cleavage function on APP-C99 to generate A β .

5 Relationship between endocytic pathway and lipid raft in AD

The mechanisms underlying the trafficking and clustering of APP and β -secretase need to be identified. Partitioning of APP and β -secretase into rafts alone is not sufficient to induce β -cleavage. Normally, the β -cleavage also depends on endocytosis. It has been reported that β -cleavage occurs during endocytosis^[31]. Besides, lipid rafts, the dynamic structures of proteins and lipids that float freely in the bilayer cellular membranes, play an important role in linking endocytosis with amyloidogenic pathway. Lipid rafts are highly dispersed at the cell surface, containing only a few protein molecules. When activated, many small rafts could cluster together to form larger platforms in which functionally-related membrane proteins can interact^[32]. The likelihood of interaction between APP and β -secretase is low in individual raft, since APP and β -secretase are mainly localized in separate rafts. Clustering of lipid rafts can potentially regulate the access of APP to β -secretase. Therefore, endocytosis is essential for the clustering of APP- and β -secretase-containing rafts into the same raft platform, for consecutive β -cleavage. Thus, it is hypothesized that APP and β -secretase meet after endocytosis, through clustering APP- or β -secretase-containing rafts within endosomes^[21].

6 MARCKS proteins

MARCKS is a family of prominent substrates of protein kinase C (PKC), and is expressed at a very high level in the nervous system^[33]. MARCKS is localized to the plasma membrane and has 2 regions: one is the amino-terminal myristate inserting hydrophobically into the bilayer, and the other is an effector domain located in the middle of the molecule, which is a cluster of basic residues with 4 serine residues, electrostatically interacting with acidic lipids (such as PIP₂) in the bilayer. MARCKS can cross-link the major part of the cell cytoskeleton—filamentous actins. Phosphorylation by PKC or interaction with Ca²⁺ can introduce negative charges into the basic cluster, reducing the electrostatic interaction of MARCKS with acidic lipids, causing translocation of MARCKS from membrane to cytoplasm. Thus, the activity of actin-binding and electrostatic interaction with PIP₂ can be inhibited^[34]. Previous experiments have suggested the involvement of MARCKS in brain development regulation, postnatal survival, cellular migration, adhesion, endophagocytosis, exophago-cytosis, and neurosecretion. Besides, MARCKS is critical for learning and memory, since studies find that both heterozygous knockouts with a half reduction in MARCKS expression and transgenic mice overexpressing exogenous MARCKS show significant impairment of spatial learning^[35].

7 A possible role of MARCKS in AD

MARCKS can interact with PIP₂ (Fig. 1), latter of which plays a critical role in endocytosis cell signal pathway on the lipid raft at the inner surface of the cell membrane. F-actin binds to MARCKS in the area near the membrane at the inner surface of the cell membrane^[36], to maintain the cell morphology. When MARCKS leaves the membrane (Fig. 2), binding of MARCKS with PIP₂ and actins will be abandoned. Then the released PIP₂ and F-actin bind to other actin-binding proteins, by which endocytosis could be caused. PIP₂ is concentrated in lipid rafts^[37,38]. Although it constitutes only about 1% of the phospholipids in the cytoplasmic leaflet of the plasma membrane, it is responsible for a wide range of membrane-related phenomena, including the regulation of endocytosis. For example, it plays important roles in the se-

Fig. 1 The relation between APP proteolytic process and MARCKS on lipid rafts. When MARCKS binds to PIP₂ on the lipid raft, actins will bind to the area near the membrane to maintain the morphology of neurons. Thus endocytosis is inhibited. Meanwhile, APP, β -secretase and γ -secretase are located on separate small lipid rafts, which precludes their meeting and A β generation.

Fig. 2 The role of MARCKS in endocytosis that induces A β production. After MARCKS translocation, PIP₂ and actins are released. PIP₂ will bind to some endocytosis signal proteins and actins will bind to actin-binding proteins, which can induce endocytosis. Endocytosis then induces invagination of the membrane. This process can make separate lipid raft form a large one, by which APP, β -secretase and γ -secretase can meet together, and then amyloidogenic pathway can be induced.

quential recruitment of clathrin coat components and accessory proteins to endocytic sites^[39,42].

Recent research shows that oligomeric A β could decrease the level of PIP₂ in primary cultured cortical neurons, and the normal balance of PIP₂ in brain could inhibit the synaptic dysfunction induced by oligomeric A β ^[43]. It is also found that FAD-associated presenilin mutations cause imbalance in PIP₂ metabolism, and the alteration of cellular PIP₂ closely correlates with A β level^[44]. Therefore, it could be concluded that the disruption of PIP₂ system may be one of the mechanisms for synaptic dysfunction in AD. Besides, PIP₂ is also known to be involved in cellular actin reorganization and motility^[45], both of which are required for clathrin-mediated endocytosis^[46]. Increasing evidence has highlighted the importance of actin cytoskeleton during endocytosis. Actin dynamics acts at multiple steps in endocytic pathway, such as the initial internalization^[47] and the movement of endosomes^[48].

MARCKS may be a key linker between actin cytoskeleton and PIP₂-mediated endocytosis signal pathway. The actin cytoskeleton assembly requires accumulation of actins at PIP₂-containing rafts and the presence of MARCKS effector domain^[41]. MARCKS presents as a 'pipmodulins' to control the level of free PIP₂ in the plasma membrane. MARCKS translocation can cause 2 important processes of endocytosis. One involves the leaving of released filamentous actins from the area near plasma membrane, and the promotion of actin filament disassembly. This causes a local softening of the actin cytoskeleton with increased plasticity and endocytosis^[49-52]. The other is the increase in the level of free PIP₂. The free PIP₂ then interacts with endocytosis signal proteins, such as Neural Wiskott-Aldrich Syndrome Protein (N-WASP) which is very important for endocytosis^[37]. So MARCKS may be an important linker between the endocytosis pathway and PIP₂ signal on lipid rafts (Fig. 1, 2).

8 Conclusion

It has been proposed that APP, β - and γ -secretases are all located on the PIP₂-containing lipid raft. MARCKS can bind to the membrane and hide PIP₂, an important signal lipid for endocytosis. Endocytosis pathway is essential for A β

production. By endocytosis, small lipid rafts may cluster together to form larger platforms for the meeting of APP, γ - and β -secretases, causing A β production. Through the actin-binding sites, MARCKS may act as a linker between lipid raft and endocytosis in the process of A β production. Thus, MARCKS provides a new therapeutic target for AD treatment, through regulating the pathway of endocytosis to reduce A β production.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (No. 30701137).

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豆蔻酰化的富丙氨酸的蛋白激酶 C 的底物在阿尔茨海默病胞吞过程中的作用

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摘要: β 淀粉样蛋白(amyloid β , A β)在阿尔茨海默病(Alzheimer's disease, AD)的发病过程中的重要作用已为人熟知。淀粉样前体蛋白(amyloid precursor protein, APP)的水解过程也因此成为 AD 研究的重点。APP、 β -和 γ -分泌酶都位于脂筏上, 三者的相遇是产生 A β 的必要步骤, 而胞吞作用则能使分布在微小脂筏上的 APP、 β -和 γ -分泌酶集中到较大的脂筏上。另一方面, 豆蔻酰化的富丙氨酸的蛋白激酶 C 的底物(myristoylated alanine-rich C kinase substrate, MARCKS)被蛋白激酶 C 磷酸化或与钙离子作用后, 会离开细胞膜进入细胞质, 进而引起在胞吞作用中起重要作用的肌动蛋白和 4, 5-二磷酸肌醇(PIP₂)的释放。因此, 本文提出假说, 认为 MARCKS 通过调节自由态 PIP₂ 的水平和肌动蛋白的运动, 引发胞吞作用, 进而在 A β 的产生过程中起重要作用。

关键词: 阿尔茨海默病; 胞吞; 豆蔻酰化的富丙氨酸的蛋白激酶 C 的底物; 脂筏; 4, 5-二磷酸肌醇; 肌动蛋白细胞骨架