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Protein Prenylation and Synaptic Plasticity: Implications for Alzheimer's Disease

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Abstract

Protein prenylation is an important lipid posttranslational modification of proteins. It includes protein farnesylation and geranylgeranylation, in which the 15-carbon farnesyl pyrophosphate or 20-carbon geranylgeranyl pyrophosphate is attached to the C-terminus of target proteins, catalyzed by farnesyl transferase or geranylgeranyl transferases, respectively. Protein prenylation facilitates the anchoring of proteins into the cell membrane and mediates protein-protein interactions. Among numerous proteins that undergo prenylation, small GTPases represent the largest group of prenylated proteins. Small GTPases are involved in regulating a plethora of cellular functions including synaptic plasticity. The prenylation status of small GTPases determines the subcellular locations and functions of the proteins. Dysregulation or dysfunction of small GTPases leads to the development of different types of disorders. Emerging evidence indicates that prenylated proteins, in particular small GTPases, may play important roles in the pathogenesis of Alzheimer's disease. This review focuses on the prenylation of Ras and Rho subfamilies of small GTPases and its relation to synaptic plasticity and Alzheimer's disease.

Keywords

Protein prenylation; farnesylation; geranylgeranylation; small GTPases; synaptic plasticity; Alzheimer's disease

Introduction

Many proteins undergo posttranslational modifications that allow for proper protein folding, trafficking, and function [1]. These modifications often include the addition of functional groups such as phosphates, lipids and carbohydrates. The functions of proteins are regulated by posttranslational modifications. One type of lipid posttranslational modification is prenylation [2]. Prenylation refers to the addition of short-chain lipid molecules called isoprenoids to the C-terminus of target proteins. These lipid attachments facilitate the anchoring of proteins to the cell membrane and mediate protein-protein interactions. Prenylated proteins are involved in regulating a variety of cellular functions including

synaptic plasticity and in the pathogenesis of a number of diseases including Alzheimer's disease (AD).

AD is the most common cause of dementia, affecting approximately 11% of the population aged 65 years and older [3]. AD is a neurodegenerative disorder characterized clinically by impaired episodic memory. The pathological hallmarks of AD are intracellular neurofibrillary tangles and deposits of aggregated amyloid- β protein (A β) in neuritic plaques and cerebral vessels [4]. Importantly, failures of synaptic plasticity are thought to represent early events in AD progression [5]. However, the relationship between the neuropathology and the behavioral changes is not fully understood. Emerging evidence indicates that alterations in the level and function of some small GTPases may contribute to the pathogenesis of AD [6,7]. The focus of this review is on the prenylation of small GTPases, in particular the Ras and Rho subfamilies of proteins, and its relation to synaptic plasticity and AD.

Isoprenoids and Protein Prenylation

Isoprenoids are short-chain lipid molecules formed in the mevalonate pathway for cholesterol biosynthesis [8] (Fig. 1). The 15-carbon isoprenoid, farnesyl pyrophosphate (FPP), is a major branching point in the mevalonate pathway. FPP serves as a substrate for several enzymes, including squalene synthase (SS), farnesyl transferase (FT), and GGPP synthase (GGPPS) that produces the 20-carbon geranylgeranyl pyrophosphates (GGPP). FPP is also a precursor for the synthesis of long-chain isoprenoids such as dolichol and ubiquinone (coenzyme Q), and heme. FPP and GGPP serve as lipid donors for protein prenylation.

During protein farnesylation and geranylgeranylation, collectively called protein prenylation, FPP and GGPP are covalently attached to the C-terminus of target proteins, respectively [2]. Farnesylation is catalyzed by protein farnesyl transferase (FT) and occurs on cysteine residues present in tetrapeptide recognition sequences (CaaX, in which C is cysteine, a is an aliphatic amino acid and X is variable) located at the C-termini of their cognate protein substrates. In contrast, geranylgeranylation is catalyzed by two different protein geranylgeranyl transferases. Geranylgeranyl transferase-1 (GGT-1) acts on substrates that contain C-terminal tetrapeptide sequences similar to but distinct from FT substrates, whereas geranylgeranyl transferase-2 (GGT-2 or RabGGT) recognizes more structurally complex sequences and exclusively prenylates Rab proteins [2,9]. Protein prenylation is an important posttranslational modification that allows proteins to anchor to the cell membrane or other subcellular locations and mediates protein-protein interactions [10].

Statins are drugs commonly used to regulate cholesterol levels. Statins work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate limiting step in the mevalonate pathway for cholesterol biosynthesis that converts acetyl-CoA to mevalonate (Fig. 1). Inhibition of HMG-CoA reductase results in a decreased level of FPP and GGPP, and thus, may lead to decreased farnesylation and geranylgeranylation of proteins [11,12]. As such, it is difficult to dissect the roles of farnesylation and geranylgeranylation using

statins. To this end, drugs have been developed to specifically target FT and GGT-1 [13]. Farnesyl transferase inhibitors (FTIs) and geranylgeranyl transferase-1 inhibitors (GGTIs) are powerful tools for studying the function of specific prenylation pathways. These drugs are currently under investigation for the treatment of cancers and other disorders [14].

Over 100 proteins are known to undergo prenylation [10,13]. They include heterotrimeric G protein subunits and nuclear lamins but the largest and most extensively studied group is the Ras superfamily of small GTPases.

Ras Superfamily of Small GTPases

The Ras GTPase superfamily consists of over 150 known members, divided between five major subfamilies: Ras, Rho, Rab, Arf/Sar and Ran [15]. Specific small GTPases regulate a number of effector proteins and may have different final intracellular locations, and in some cases, differential prenylation can affect the subcellular distribution and function of small GTPases [16,17].

In general, small GTPases act as molecular switches that are activated, or 'turned on' by guanine nucleotide exchange factors (GEFs) and inhibited, or 'turned off' by GTPase-activating proteins (GAPs) [18,19]. GEFs promote the dissociation of guanosine diphosphate (GDP) from small GTPases [20]. This dissociation step allows the exchange of GDP for guanosine triphosphate (GTP). A small GTPase is considered 'active' when GTP is bound. Antagonistically, GAPs enhance the rate of the weak intrinsic GTP hydrolysis activity of small GTPases [21]. Small GTPases depend on prenylation for proper cellular localization and function [10]. Inhibiting small GTPase prenylation affects many cellular functions such as cytoskeletal stability and the efficiency of vesicular transport [22]. More recent studies have also revealed that the interplay between small GTPase GEFs and GAPs regulates spine morphogenesis and synapse development [23]. Interestingly, GGT-1 itself has been shown to have a direct role in neuromuscular junction formation and maintenance by controlling acetyl choline receptor rearrangement during development [24]. In addition to morphological changes, small GTPases are involved in multiple signaling pathways that regulate synaptic plasticity [25].

Synaptic Plasticity

In its most general definition, synaptic plasticity is the strengthening or weakening of the synapse between two neurons over time [26]. Synaptic plasticity has many underlying mechanisms, including pre-synaptic changes regulating the amount of neurotransmitter released, and post-synaptic changes such as the incorporation of new neurotransmitter receptors [27]. In general, both the strengthening and weakening of a synapse depends on calcium uptake. Two major molecular mechanisms of synaptic plasticity in the hippocampus include the regulation and activity of N-methyl D-aspartate (NMDA) and α -amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors [28] (Fig. 2). Notably, before NMDA receptors open their ion channel, glutamate must be present at the receptor while the post-synaptic cell is depolarized [29]. This is due to a magnesium block in the NMDA channel pore that must be expelled by a reduction in the voltage across the post-synaptic cell membrane [30]. Once open, NMDA channels allow for calcium to rush

into the cell and trigger downstream signaling cascades that alter the synaptic strength between the two cells [30,31]. These NMDA receptors act as a ‘coincidence detector’ because two events need to occur within a narrow temporal window to allow calcium to flow into the post-synaptic cell [32].

Calcium influx from NMDA receptors is necessary for the activation of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) [33]. The activation of NMDA receptors is a mechanism to transfer the information of mutual depolarization across the synapse. If the two cells continue to fire strongly together, their synapses will strengthen over time by the addition of AMPA and NMDA receptors to the post-synaptic cell membrane, or phosphorylation of the subunits of existing AMPA and NMDA receptors in the membrane [34,35]. The changes in synaptic potentiation exist in equilibrium, and therefore, AMPA and NMDA receptors can be removed/dephosphorylated from synapses.

Synaptic plasticity can be divided into two major categories, short-term plasticity, and long-term plasticity. Long-term plasticity can be further separated into long-term depression (LTD), early long-term potentiation (E-LTP), and late long-term potentiation (L-LTP) [36-38]. LTD is the weakening of synaptic strength over time, often by removal or dephosphorylation of post-synaptic receptors. E-LTP is the enhancement of synaptic strength that is not dependent on protein synthesis. L-LTP has the longest lasting effects, and is dependent on synthesis of new proteins in response to increased synaptic activity. Small GTPases are involved in regulating multiple aspects of synaptic plasticity and the following sections will briefly discuss the roles of Ras and Rho subfamilies of proteins in synaptic function.

Ras and Synaptic Plasticity

Ras subfamily GTPases were originally studied for their role in oncogenesis. Constitutively active mutations in Ras small GTPases occur in 8% to 93% of cancers depending on the tumor type [39]. This underscores the importance of proper regulation of small GTPases. Normally, Ras small GTPases play crucial roles in regulating cell proliferation, differentiation, cell survival, and memory formation [40,25]. The well-known members of Ras subfamily of small GTPases include H-Ras, K-Ras, and N-Ras. Ras small GTPases primarily undergo farnesylation but some of them can also undergo geranylgeranylation. For example, while H-Ras is exclusively farnesylated, K-Ras and N-Ras can be geranylgeranylated when farnesyltransferase is inhibited [13]. Major downstream signaling cascades of Ras include mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinase (ERK), and phosphoinositide 3-kinase (PI3K), which regulate glutamate receptor trafficking during synaptic plasticity (Fig. 2) [25,41].

Several lines of evidence indicate that H-Ras plays a negative role in regulating synaptic plasticity and memory function. In a mouse model of neurofibromatosis type 1 mental retardation, which is characterized by the hyperactivity of Ras, learning/memory and synaptic function are severely impaired [42,43]. Treatment with an FTI or a statin rescues hyperactive Ras-induced synaptic and memory impairment [42,43]. Similarly, H-Ras overexpression negatively affects the NMDA receptor transmission by decreasing the level

of tyrosine phosphorylation of the NMDA receptor NR2A subunit [44]. In contrast, mice deficient in H-Ras expression display enhanced tyrosine phosphorylation of NMDA receptors and NMDA receptor-mediated hippocampal LTP [45]. These data support the role of Ras small GTPases in regulating NMDA receptor dependent synaptic plasticity.

Rho and Synaptic Plasticity

The Rho subfamily of GTPases primarily undergoes geranylgeranylation, although some are exclusively farnesylated (e.g., RhoE). Others, such as RhoB, can be either farnesylated or geranylgeranylated [46,47]. Interestingly, geranylgeranylated and farnesylated RhoB exhibit distinct and opposite functions. Geranylgeranylated RhoB inhibits cell growth, whereas farnesylated RhoB promotes cell growth and transformation [16,17]. However, for some Rho GTPases, although their functions depend on being prenylated, either geranylgeranylated or farnesylated form works equally. For example, RhoA is exclusively geranylgeranylated under physiological conditions; when RhoA is mutated to become susceptible to farnesylation, the farnesylated RhoA shows similar subcellular location and functions as the geranylgeranylated RhoA [48].

The Rho subfamily of GTPases is one of the major regulators in synaptic plasticity, both in dendrite morphogenesis and stability as well as in growth cone motility [49,50,19]. Rho proteins are well documented for their role in the regulation of actin rearrangement in neuronal cytoskeletons. Specifically, three major Rho proteins, RhoA, Rac1, and Cdc42, regulate neuronal structures and synaptic connectivity [49,50,19]. When activated by GEFs, Rho small GTPases interact with effector proteins, initiating signaling cascades that control actin cytoskeletal rearrangement, microtubule rearrangement, transcription, membrane trafficking, and act as key regulators of dendritic growth and spine morphogenesis [49,50,19] (Fig. 2).

The interaction between the Rho GTPases determines the complexity of the dendritic tree and the formation of spines. RhoA, Rac1, and Cdc42 play differential roles in regulating dendritic growth and spine formation. Activation of Rac1 and Cdc42 promotes dendritic branching/remodeling and spine formation, whereas activation of RhoA exhibits opposite function, reducing dendritic growth/complexity and spine density/length [50]. Rac1 is highly expressed in the hippocampus of adult mice [51]. The hippocampus is well known for its synaptic plasticity and its importance in developing associative memories [37,52]. Rac1 plays an important role in the formation of neuronal synapses at their correct locations. Specifically, *in vitro* studies show that NMDA receptor activation induces membrane translocation and activation of Rac1 in the CA1 region of the hippocampus [51]. Activation of tyrosine kinase receptor B (TrkB) by brain-derived neurotrophic factor (BDNF) leads to the activation of Rac1 and induces changes in cellular morphology [53]. Notably, BDNF-dependent dendritic morphogenesis requires the activation of GGT-1, the enzyme that catalyzes the geranylgeranylation of Rac1 and other Rho proteins [54]. In addition, TrkB is physically associated with GGT-1 and neuronal activity enhances this association and GGT-1 activity, further promoting dendritic spine morphogenesis [54]. Conversely, activation of RhoA inhibits dendritic growth and spine formation in multiple model systems [50]. The negative role of RhoA on dendritic growth and spine morphogenesis is partly

mediated by the RhoA effector Rho-kinase (ROCK) [55]. Specific inhibitors of ROCK can block active RhoA-induced dendritic simplification [55]. The balance between the positive and negative effects of Rac1/Cdc42 and RhoA guarantees the proper development of dendrites and dendritic spines that are important postsynaptic structures regulating synaptic plasticity.

Implications for Alzheimer's Disease

AD is a progressive neurodegenerative disease with a behavioral characterization of impaired episodic memory. Pathologically, AD is defined by amyloid plaques and tau tangles that have been seen in post-mortem brain tissues. However, the relationship between the neuropathology and the behavioral changes is not completely understood.

In the brain of AD patients, A β accumulates as the disease progresses. The structural integrity of synapses degrades rapidly during β -amyloidosis [56], with the longer amyloidogenic A β 42 being more potent than A β 40 in disrupting synaptic plasticity [57]. One of the mechanisms by which A β impairs synaptic function is by promoting endocytosis of NMDA receptors and thereby reducing the presence of NMDA receptors at the cell surface [58]. Importantly, the impairment of synaptic function in the hippocampus occurs prior to the appearance of insoluble amyloid plaques and neuronal cell death [5]. However, inhibition of A β -producing enzymes under normal conditions results in abnormalities in synaptic function [59]. These findings suggest that A β itself may have normal physiological functions which are disrupted by abnormal accumulation of A β during AD pathology.

Emerging evidence indicates that isoprenoids/protein prenylation and small GTPases affect multiple aspects of AD (Fig. 3) [6,7]. For example, statin-induced depletion of isoprenoids leads to reduced levels of protein prenylation and promotes non-amyloidogenic processing of APP and reduces the production of A β [60-63]. Interestingly, while geranylgeranylated RhoA-mediated activation of ROCK increases A β secretion via modulation of γ -secretase [64], specific inhibition of farnesylated RhoB/ROCK pathway promotes α -secretase activity [60]. Of note, although inhibitors of ROCK reduce total A β secretion, targeting ROCK by expression of dominant-negative or constitutively active ROCK mutants failed to modulate A β secretion [65]. Additional *in vitro* experiments show that statin-induced low isoprenoid conditions cause the accumulation of intracellular APP, the C-terminal fragment of APP produced by β -secretase cleavage (β -CTF), and A β , which can be rescued by GGPP supplementation, suggesting the involvement of geranylgeranylated target proteins [61]. The study also shows that low isoprenoid levels inhibit the trafficking of APP through the secretory pathway [61]. A more recent study further demonstrates that low isoprenoid conditions induced by physiologically relevant doses of statins preferentially inhibit the geranylgeranylation of Rab family proteins involved in vesicle trafficking and thereby affects the trafficking and intracellular localization of APP [62]. Inhibition of Rac also regulates APP expression and processing [66,67]. In contrast, supplementation of FPP and/or GGPP stimulates the production of A β [63,64,68].

Intriguingly, the interplay between isoprenoids/prenylated proteins and APP/A β metabolism appears to be reciprocal. It has been shown that A β and other APP cleavage products such as

APP intracellular domain (AICD) may directly regulate the activities of the enzymes in the mevalonate pathway thereby changing the levels of isoprenoids and other lipids [69,70]. Consistent with these findings, the levels of FPP and GGPP are elevated in the brains of patients with AD [71], suggesting that the abundance of prenylated proteins could be increased in AD brains. Indeed, the level of Ras (both cytosolic and membrane/prenylated fractions) in the brain is increased in the early stage of AD [72,73], suggest that upregulation of Ras may play an important role in the pathogenic cascade leading to AD. A β causes cellular dislocation and dysfunction of Rac and its effector protein PAK [74,75]. Also, the level of prenylated RhoA is increased in A β -treated neuroblastoma cells and in the neurons surrounding A β plaques in AD mice [76]. Conversely, a recent study shows that a toxic level of oligomeric A β 42 inhibits protein prenylation [77].

In addition to APP/A β metabolism, prenylation/GTPases have been shown to be involved in other aspects of AD pathology. For instance, inhibition of prenylation of Rho GTPases leads to attenuation of A β -induced neuroinflammation [78,79]. Limiting the availability of isoprenoids for prenylation has been shown to protect neurons from A β -induced apoptosis via activating pro-survival signaling pathways [80-82]. Activation of the prenylated protein Rac1 has been shown to contribute to increased oxidative stress in AD [83,84]. Inhibition of Rho prenylation decreases total and phosphorylated tau levels [85]. We and others have also shown that manipulation of isoprenoid and protein prenylation levels modulates synaptic plasticity and cognitive function in animal models [86-88,25,42]. Intriguingly, inhibiting the level of FPP/farnesylation, but not GGPP/geranylgeranylation, enhances hippocampal synaptic plasticity in brain slices of mature C57BL/6 mice [87]. Consistent with these results, our most recent study indicates that haplodeficiency in farnesyl transferase, but not geranylgeranyl transferase-1, rescues cognitive function as well as attenuates A β -associated neuropathology and neuroinflammation in a mouse model of AD [89]. Taken together, these findings strongly suggest that alteration of small GTPases is implicated in the pathogenesis of AD and that modulation of protein prenylation, in particular protein farnesylation, may present a potential therapeutic strategy for AD.

Concluding Remarks/Perspectives

Protein prenylation is a critical lipid posttranslational modification of many important proteins. Particularly, it plays a key role in determining the cellular localization and functions of small GTPases. Small GTPases control signaling pathways that regulate a plethora of cellular functions including synaptic plasticity, and dysregulation or dysfunction of small GTPases leads to different types of disorders. Emerging evidence indicates that protein prenylation plays an important role in the development of AD. However, clinical trials using statins in patients with AD have not shown consistent benefits [90,91]. While differences in the blood-brain barrier permeability and the dose of statins, the population of subjects, and the stage of the disease at which statins are administered could all contribute to the discrepancies in clinical outcomes, one critical missing point is the fact that statins inhibit the production of FPP and GGPP simultaneously [71] and thus may affect both farnesylation and geranylgeranylation pathways. Importantly, farnesylated and geranylgeranylated proteins are involved in regulating distinct cellular functions [18]. Results from recent studies suggest that specific inhibition of protein farnesylation but not

geranylgeranylation enhances synaptic and cognitive function as well as reduces AD pathology, suggesting the potential of FTIs as therapeutic agents for AD.

Several FTIs are in clinical trials mainly for cancer treatment [14]. FTIs have also been proposed to treat neurodegenerative diseases in a patent application [92] and one FTI (LNK-754) has been tested in Phase I clinical trials for safety, tolerability and pharmacokinetics in healthy elderly volunteers and in subjects with mild AD (<http://clinicaltrials.gov>).

Further studies are needed to elucidate the role of protein prenylation, in particular farnesylation, on the onset and progression of AD. Until then, FTIs developed originally for the treatment of cancers may translate well to the treatment of AD.

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Fig. 1. The mevalonate pathway

HMG-CoA reductase is a rate-limiting enzyme in the mevalonate pathway. Statins inhibit the activity of HMG-CoA reductase and limit the production of isoprenoid intermediates and cholesterol. Farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) serve as lipid donors for protein prenylation. Farnesyl transferase inhibitors (FTIs) and geranylgeranyl transferase-1 inhibitors (GGTIs) block protein farnesylation and geranylgeranylation, respectively (see text for details). PP, pyrophosphate; FPPS, farnesyl PP synthase; GGPPS, geranylgeranyl PP synthase; SS, squalene synthase; FT, farnesyl transferase; GGT-1, geranylgeranyl transferase-1; GGT-2, geranylgeranyl transferase-2 (a.k.a., RabGGT).

Fig. 2. Schematic diagram of a synapse

A) At resting membrane potentials, NMDA receptors are blocked by Mg^{2+} . Low intracellular concentrations of Ca^{2+} prevent the autophosphorylation of Ca^{2+} /calmodulin-dependent protein kinase (CaMKII). **B)** Post-synaptic depolarization pushes the Mg^{2+} out of the NMDA channel pore, allowing Ca^{2+} to enter the cell. Glutamate (Glu) from the pre-synaptic cell binds to AMPA and NMDA receptors to depolarize the post-synaptic cell. The rise in intracellular Ca^{2+} promotes CaMKII autophosphorylation. Once phosphorylated, CaMKII phosphorylates AMPA subunits to enhance their conductance. CaMKII also promotes the exocytosis of receptor containing vesicles and thereby increases the presence of receptors at the synapse. Furthermore, CaMKII activates RasGEFs (guanine exchange factors) and promotes the turnover of inactive Ras-GDP to active Ras-GTP. Downstream signaling cascades include mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT). When activated (phosphorylated), ERK and AKT facilitate exocytosis of glutamate receptors during synaptic plasticity. In addition, neuronal activity activates Rho GTPases. Active (GTP-bound) Rac1/Cdc42 enhance while RhoA inhibits synapse/spine formation.

Fig. 3. Schematic diagram of interplay between prenylated proteins and AD pathology