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Invited review

Palmitoylation in Alzheimer's disease and other neurodegenerative diseases

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ABSTRACT

Posttranslational modifications of proteins are important regulatory processes endowing the proteins functional complexity. Over the last decade, numerous studies have shed light on the roles of palmitoylation, one of the most common lipid modifications, in various aspects of neuronal functions. Major players regulating palmitoylation are the enzymes that mediate palmitoylation and depalmitoylation which are palmitoyl acyltransferases (PATs) and protein thioesterases, respectively. In this review, we will provide and discuss current understandings on palmitoyation/depalmitoylation control mediated by PATs and/or protein thioesterases for neuronal functions in general and also for Alzheimer's disease in particular, and other neurodegenerative diseases such as Huntington's disease, schizophrenia and intellectual disability.

Contents

Abbreviations: ABCA1, ATP-binding cassette transporter A1; AD, Alzheimer's disease; ADAM17, a disintegrin and metalloproteinase 17; AICD, APP intracellular domain; AKAP79, A-kinase anchoring protein 79; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; APP, amyloid precursor protein; APT, acyl protein thioesterase; BACE1, β-site APP cleaving enzyme 1; CI-MPR, cation-independent mannose 6-phosphate receptor; CKAP4, cytoskeleton-associated protein 4; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CSP, cysteine-string protein; CTF, C-terminal fragment; D2R, D2 dopamine receptor; eNOS, endothelial nitric oxide synthase; $GABA_AR\gamma2$, γ-aminobutyric acid (GABA) A receptor subuint γ2; GAD65, glutamate decarboxylase of 65-kDa; GAP-43, growth associated protein of 43-kDa; GCP16, Golgi complex associated protein of 16-kDa; GluA1/2, AMPA receptor subunit 1 and 2; GODZ, Golgi-specific DHHC zinc finger protein; GPM6A, glycoprotein M6A; GRIP, glutamate receptor interacting protein; HD, Huntington disease; HIP, huntingtin-interacting protein; ID, intellectual disability; IP3R, inositol-1,4,5-triphosphate (IP3) receptor; LOAD, late-onset sporadic Alzheimer's disease; LTD, long-term depression; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic current; NCAM140/180, neural cell adhesion molecule of 140-kDa/180-kDa; Ncdn, neurochondrin; NCL, neuronal ceroid lipofuscinosis; NDE1, nuclear distribution factor E homolog-1; NDEL1, NDE-like 1; NFT, neurofibrillary tangle; NIDD, nNOS-interacting DHHC domain-containing protein with dendritic mRNA; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; PaCCT, palmitoyltransferase conserved C-terminus; PEN2, presenilin enhancer 2; PHF, paired helical filament; PICK1, protein interacting with C-kinase 1; PI4KIIα, phosphatidylinositol 4-kinase IIα; PKA, protein kinase A; PPT, palmitoyl protein thioesterase; PSD-95, postsynaptic density protein of 95-kDa; Selk, selenoprotein K; SFV, semliki forest virus; SH3, Src homology 3; SNAP-25, synaptosomal-associated protein of 25-kDa; SPRED-1/3, sprouty-related, EVH1 domain-containing protein 1 and 3; SV, synaptic vesicle; TARP, transmembrane AMPA receptor regulatory protein; TGN, the *trans*-Golgi network; VAMP2, vesicle-associated membrane protein 2; VSV, vesicular stomatitis virus; XLID, X-linked intellectual disability; Yck2, yeast casein kinase 2.

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1. Introduction

Protein posttranslational modifications (PTMs), including phosphorylation, ubiquitination, sumoylation, nitrosylation, glycosylation, and lipidation are the key regulatory steps that contribute to the functional complexity of proteins. Of these PTMs, lipidation increases the hydrophobicity of proteins, which make the proteins to be associated with membranes of intracellular organelles such as the endoplasmic reticulum (ER), Golgi apparatus, endosomes, mitochondria and plasma membrane. Myristoylation, prenylation and palmitoylation are the most common lipid modifications and play roles in protein trafficking, targeting, and function [1–6]. Of these three lipid modifications, only palmitoylation is reversible [7,8] that allows more dynamic regulation of protein function in various aspects of cellular signaling. Intriguingly, palmitoylation is most often observed in neuronal cells and it indeed plays critical roles in neuronal function [9].

Protein palmitoylation is occurred by the covalent attachment of a 16-carbon palmitate to internal cysteine residues of proteins via thioesther bonds. This process is catalyzed by a family of palmitoyl acyltransferases (PATs) (Fig. 1), containing a conserved Asp-His-His-Cys (DHHC) motif [9–12], and many of them have been reported to be expressed in neurons [13,14]. Roles of palmitoylation in neuronal function have begun to receive attention since a synaptosomal-associated protein 25 (SNAP-25) was reported as a palmitoylated synaptic protein [15–19]. Since then, there have been extensive studies on the roles of palmitoylation in protein targeting and many other aspects of neuronal function, including intracellular trafficking pathway mechanisms underlying synaptic transmission and plasticity [20–28]. Disruption of protein palmitoylation has been implicated in pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Huntington's disease (HD), schizophrenia and intellectual disability (ID) [9,29,30]. DHHC proteins were selectively paired with their specific substrates, and the palmitoylation through DHHC-substrate interactions is closely involved in their function. In this review, we provide the current understandings on the DHHC PAT proteins, especially whose respective substrate pairs were identified, the functions based on the DHHC-substrate pair, and the roles of palmitoylation and depalmitoylation in neurodegenerative diseases with an intense focus on the AD.

2. Palmitoylation

2.1. Subcellular localization of DHHC PAT proteins

There are at least 23 mammalian DHHC proteins that exhibit specific localizations in intracellular compartments. The intracellular colocalization analysis of all mammalian DHHCs exogenously expressed in *in vitro* with endogenous intracellular organelle marker proteins revealed that the majority of DHHC proteins localize to the ER and Golgi, and a small number of DHHC proteins localize to post-Golgi membranes, including endosomes and synaptic vesicles [31,32] (Table 1). Because most of current knowledge on the subcellular localization of DHHC proteins is based on co-expression studies, it will be important to obtain more reliable findings with endogenous DHHC proteins. It will also need to investigate a differential intracellular distribution of DHHC proteins in different cell types. Indeed, DHHC2 that was reported as a Golgi-residency in HEK293T cells [31] was shown to localize on dendritic vesicles in cultured hippocampal neurons [23] and the plasma membrane in PC12 cells [33]. DHHC21 also displayed different localization patterns in various cell types; it was located on the plasma membrane in HEK293 T cells [31] and to the Golgi in primary keratinocytes [34]. In COS-7 cells, DHHC21 was found to localize primarily to the Golgi, while some were still observed on the plasma membrane [35]. DHHC5 was mainly located to dendritic shaft in cultured hippocampal neurons [28] and to the plasma membrane in HEK293 T cells [31]. DHHC8 was largely localized to dendrites, mainly to the synaptic region in spines [28] or to dendritic vesicles in cultured hippocampal neurons [36]. In addition, several among the 23 DHHCs exhibited different localizations in cultured hippocampal neurons (*unpublished data in the Park laboratory)* from the ones reported in HEK293T cells [31].

There has been no report on how the DHHC proteins arrive at their respective intracellular localizations till the study on 2011, which showed the ER sorting signals for DHHC4 and DHHC6 [37]. The KXX and KKXX motif (last X indicates the last amino acid of the proteins) at the extreme C-termini of DHHC4 and DHHC6, respectively, were identified and characterized as the ER targeting signals. The fact that the dilysine signals are sufficient for their ER localization was revealed by motif swapping experiment with a Golgi-resident DHHC3 protein [37].

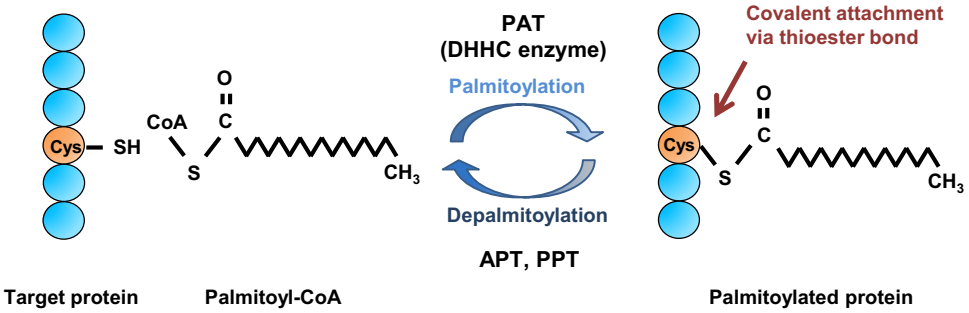

Fig. 1. Palmitoylation-depalmitoylation cycle.
Palmitoylation is achieved by attaching a 16 carbon-containing saturated fatty acid palmitate to specific cysteine residues of target proteins via thioester bonds, which is catalyzed by palmitoylacyltransferases (PATs), also known as DHHC enzymes. Reversibly, depalmitoylation is mediated by releasing the palmitate group from the palmitoylated proteins, which is catalyzed by acyl protein thioesterases (APT) or palmitoyl protein thioesterase (PPT).

Table 1
Subcellular localization of DHHC PAT proteins.

*zDHHC	Alternative names	Intracellular localization	References
1	DHHC1	ER	[31]
		EE	[69]
2	DHHC2	ER/Golgi	[31]
		Dendritic vesicles in neuron	[23]
		PM, recycling endosome	[33,262]
3	DHHC3, GODZ, Erf2	Golgi	[24,31,72,147] (in neurons)
4	DHHC4	ER	[37]
		Golgi	[31]
5	DHHC5	PM	[31]
		Endosomes in dendritic shafts	[28]
6	DHHC6	ER	[31,37]
7	DHHC7	Golgi	[31,147] (in neurons)
8	DHHC8	Golgi	[31,36]
		Dendritic vesicles	[36]
		Spines in neuronal cells	[28]
9	DHHC9	ER/Golgi	[31,85]
11	DHHC10	ER	[31]
		EE	[69]
12	DHHC12, AID	ER/Golgi	[31]
13	DHHC22, HIP14L	ER/Golgi	[31,263]
14	DHHC14	ER	[31]
15	DHHC15	Golgi	[31,33,147] (in neurons)
16	DHHC16	ER	[264]
17	DHHC17,	Golgi	[31,40,41,263]
	HIP14,	Intracellular vesicles	[40]
	Akr1p	Presynaptic terminals	[265]
18	DHHC18	Golgi	[31]
19	DHHC19	ER	[31]
20	DHHC20	PM	[31]
21	DHHC21	PM	[31,35]
		Golgi	[34,35]
22		Unknown	
23	DHHC11,	ER	[31]
	NIDD	PM (synaptic)	[266]
24	DHHC13	ER	[31]

ER, endoplasmic reticulum; EE, early endosome; PM, plasma membrane.
* Used in the text.

2.2. Substrate specificity

Such subcellular localizations of DHHC proteins have been considered as a determinant of substrate specificity [9,23]. In contrast, however, there was a report that palmitoylation is restricted only to the Glogi [38]. Defining the localization of individual DHHC proteins is still under construction because the localization would be affected by the cell types and experimental conditions [29,39] and also because the functional intracellular localization of each DHHC protein depends on its substrates.

The fact that DHHC proteins exhibit substrate specificity despite the commonly shared active region, the DHHC – cysteine rich domain (CRD) has implied the possibility of existence of regulatory domains outside of the common active region. Indeed, ankyrin repeats of DHHC17 [40,41], Src homology 3 (SH3) domain of DHHC6 [42], and PDZ-binding motif of DHHC3, DHHC5, and DHHC8 [9,28,43,44] were identified as the regulatory regions outside DHHC – CDR to affect the recruitment of specific substrates and their catalytic activity. There is another report showing that regions distinct from the palmitoylated cysteine residues are important for the specific substrate recognition by DHHC proteins. The yeast vacuolar protein 8 (Vac8) contains 11 armadillo repeats which are involved in protein-protein interactions [45,46] and is palmitoylated by DHHC Pfa3 [47]. The 11th armadillo repeat of Vac8 was revealed as an important region for Pfa3 recognition [48].

Palmitoylation occurs at the various cysteine residues located at diverse region of various substrates [49]. For instance, palmitoylated cysteines have been found in the N-terminal region of the postsynaptic density 95 (PSD-95), the growth-associated protein (GAP-43) and Gα, the internal region of SNAP-25, the cysteine string protein (CSP), and glutamate decarboxylase 65 (GAD65), the C-terminal region of H-Ras, N-Ras and Rho B, and the juxtamembrane or transmembrane region of various transmembrane proteins [9]. The consensus sequences for other lipidations such as myristoylation and isoprenylation were already identified as glycine in the N-terminal MGXXXS/T (M, Met; G, Gly; S, Ser; T, Thr; X, any amino acid) for myristoylation and cysteine in the C-terminal CAAX motif (C, Cys; A, an aliphatic amino acid; X, any amino acid) for isoprenylation [49]. Regarding the consensus sequence for palmitoylation, a very recent report identified a novel sequence motif that is recognized by the ankyrin repeat domain of DHHC17 and DHHC13, which is the first demonstration of a motif as consensus sequences of substrates recognized by ankyrin repeat-containing DHHCs [50]. A number of DHHC17 substrates and DHHC17- and DHHC13-interacting palmitoylated proteins, including SNAP-25b, SNAP-23, CSPα, huntingtin, cytoplasmic linker protein 3 (CLIP3), and microtubule associated protein 6 (MAP6) contain a ΨβXXQP (Ψ, an aliphatic amino acid; β, a C-β branched amino acid Val, Ile, or Thr; X, any amino acid; Q, Gln; P, Pro) motif. The consensus sequence was recognized by DHHC17 and DHHC13 via the ankyrin repeats domain in their cytosolic N-terminus [50]. The consensus sequences for the recognition by and catalytic activity of most DHHC proteins will need to be identified.

3. Palmitoyl acyltransferases (PATs)

3.1. Structure of DHHC PAT proteins

Most PATs are predicted to have four transmembrane domains (TMDs) (Fig. 2). Both N- and C- termini and DHHC – CRD of PATs are faced toward the cytoplasmic side. The DHHC – CRD, consisting of 51 amino acids is located in the cytoplasmic loop between the second and third TMDs, while it is more proximal to the third TMD. A smaller subset of the DHHCs such as DHHC13 and DHHC17 have six predicted TMDs with ankyrin repeats-containing N-terminal region and a DHHC-CRD located in the cytoplasmic loop between the fourth and fifth TMD [51] (Fig. 2). Most DHHCs also have additional conserved domains, a DPG (Asp-Pro-Gly) and a TTXE (Thr-Thr-X-Glu) motif, which are found to lie on the cytoplasmic side adjacent to the second and fourth TMDs (Fig. 2A–D) or fourth and sixth TMDs (Fig. 2E and F), respectively. The role of these motifs in PAT activity needs to be addressed [52]. There is another motif, the PaCCT (palmitoyltransferase conserved C-terminus) motif containing 16 amino acids proximal to the C-terminus following the forth TMD, and this motif was reported to be required for the function of yeast PATs, Swf1 and Pfa3 [53]. The DHHC – CRD is a zinc finger domain which is similar to the C_2H_2 zinc finger motif [54] and is sufficient to be considered as a candidate for zinc binding site. Indeed, several DHHC proteins, including DHHC1, DHHC4, DHHC6, DHHC14, DHHC16, and DHHC22 are predicted to have zinc binding capacity [32].

3.2. Enzymatic activity of PATs

Although the PTM palmitoylation had been studied for far over the three decades since it was first described [55], the mechanism in which molecules are involved had been unknown till 2002 when the two yeast PATs were identified [56,57]. A yeast work reported Akr1 as a PAT for the yeast casein kinase 2 (Yck2) [57]. Mutations within the DHHC – CRD of Akr1 eliminated the PAT activity, suggesting that the DHHC – CRD is the catalytic core for PAT activity. A yeast genetic screening with a palmitoylation-dependent Ras2 allele identified Erf2 which contains the DHHC motif as a PAT for Ras2. Expression of Ras2 in an *erf2Δ* deletion strain reduced the palmitoylation level of Ras2 [58]. In addition, mutations on conserved residues within the DHHC-CRD of Erf2 abolished Ras PAT activity of Erf2 [56,58]. Unlike Akr1, Erf2 required Erf4 as a cofactor for its Ras PAT activity [56]. These studies indicated that DHHC sequence is critical for the PAT activity of Akr1 and Erf2, initially suggesting that DHHC family proteins are PATs. To date, a number of DHHC family proteins have been predicted in various species, including the yeast *Saccharomyces cerevisiae* (7 genes) [57], *Caenorhabditis elegans* (15 genes) [59], the fruit fly *Drosophila* (22 genes) [60], the mouse and human (23 genes) [9,32], and even the plant *Arabidopsis* (24 genes) [61,62]. Among these DHHC proteins, 6 (Akr1, Erf2, Swf1, Pfa3, Pfa4 and Pfa5) in yeast [47,52,57,63–66], 20 (DHHC1 – 9, DHHC11 – 21) in mammals [25,42,67–69], and 2 (TIP1 and PAT10) in plants have already been confirmed as PATs [70,71]. Other DHHCs need to be addressed for their catalytic activity as PATs.

3.3. DHHC PAT – substrate pairs

In 2004, three groups of researchers for the first time reported on the mammalian DHHCs and their substrates [10,41,72] (Table 2). DHHC3, also known as Golgi-specific DHHC zinc finger protein (GODZ) [73] palmitoylates the γ2 but not α or β subunit of γ-aminobutyric acid (GABA) A ($GABA_A$) receptors [72], and the DHHC3-mediated palmitoylation of the γ2 subunit affects the trafficking and targeting of postsynaptic $GABA_A$ receptors [72,74,75].

Besides the function of DHHC3/GODZ in the inhibitory synapses through the palmitoylation of $GABA_A$ receptors and GAD65 [72,74–76], DHHC3/GODZ also displayed a catalytic activity for the excitatory glutamate receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors [77] and *N*-methyl-D-aspartate (NMDA) receptors [21]. The AMPA receptors palmitoylated on the second TMD at C585 in GluA1 and at C610 in GluA2 increased Golgi accumulation and reduced surface expression of the receptors whereas the C-terminal palmitoylated AMPA receptors at C811 in GluA1 and at C836 in GluA2 were normally expressed on the surface and this C-terminal palmitoylation inhibited the AMPA receptor interaction with the 4.1 N protein [77] that has previously been reported to stabilize the surface expression of AMPA receptors [78] and thus promoted AMPA receptor endocytosis [77]. NMDA receptor subunits GluN2A and GluN2B have two distinct clusters of palmitoylation sites in their C-terminal region. DHHC3/GODZ also palmitoylates the cysteine cluster in the middle of C-terminus of GluN2A and GluN2B (C1214, C1217, C1236, and C1239 in GluN2A; C1215, C1218, C1239, C1242, and C1245 in GluN2B) [21]. Similar to the case of AMPA receptors, DHHC3/GODZ-mediated palmitoylation of NMDA receptors increased Golgi accumulation and reduced surface expression of the receptors [21]. Given that DHHC3/GODZ plays a role in both inhibitory and excitatory synapses, it is highly conceivable that DHHC3/GODZ might be a crucial factor to regulate the excitation and inhibition balance in the brain, whose disturbance could lead to various neurological disorders.

PSD-95 is undoubtedly a major palmitoylated synaptic protein in neuronal cells [79] and the significance of PSD-95 palmitoylation has been addressed in multiple studies [79–81]. DHHC2, DHHC3/GODZ, DHHC7 and DHHC15 were identified as PATs for PSD-95 [10]. Turnover of palmitoylation cycle of PSD-95 is rapid [81], and its palmitoylation regulates the postsynaptic targeting of PSD-95 in cultured hippocampal neurons [79,80]. Interestingly, depalmitoylation of PSD-95 is required for the rapid endocytosis of AMPA receptors [81], suggesting that DHHC2, DHHC3/GODZ,

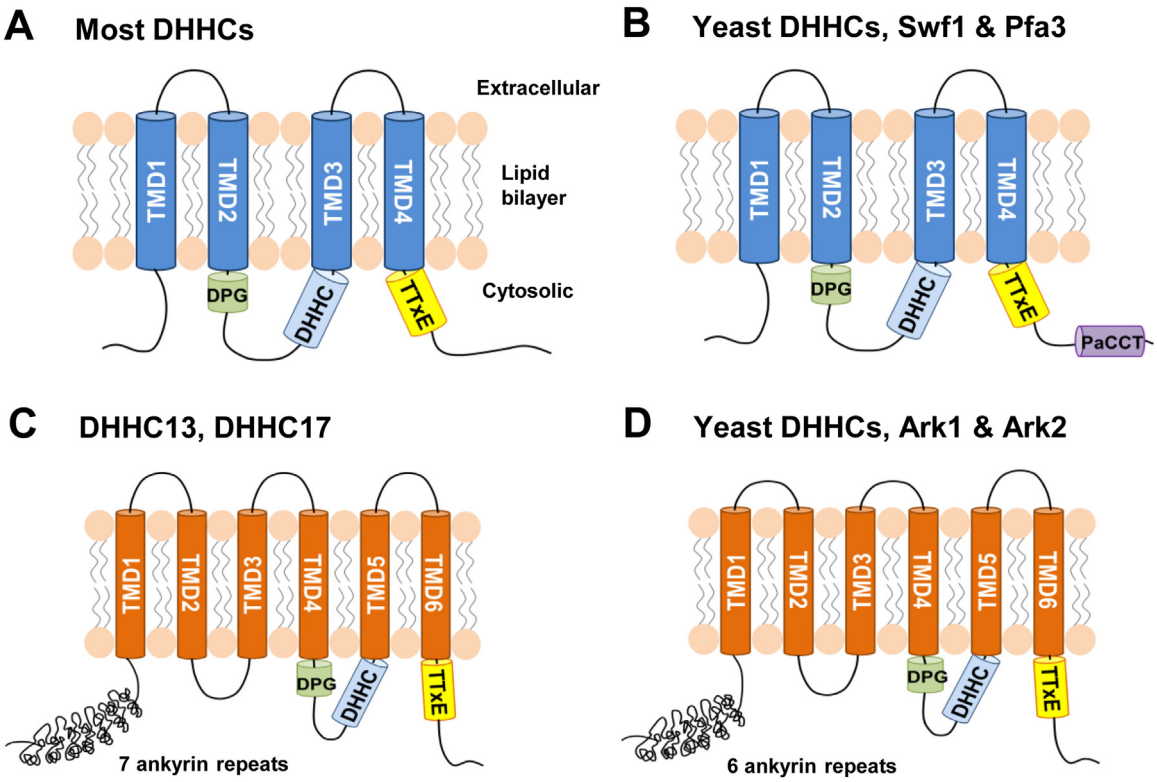

Fig. 2. Schematic illustration of structures of mammalian and yeast DHHC protein family.
(**A** – **B**) DHHC proteins mostly have four transmembrane domains (TMD1 – 4), a conserved cysteine-rich domain-containing DHHC motif in the cytoplasmic loop proximal to the TMD3, and other conserved domains, DPG (Asp-Pro-Gly) motif immediately next to the C-terminus of TMD2 and TTxE (Thr-Thr-X-Glu) motif adjacent to the C-terminus of TMD4. Swf1 and pfa3, the yeast DHHCs, have the PaCCT (Palmitoyltransferase Conserved C-Terminus) motif towards the C-terminus after TMD4 and TTxE motif (**B**). (**C** – **D**) DHHC13 and DHHC17 have six TMDs and an N-terminal extension containing seven ankryin repeats (**C**) while the yeast DHHCs Ark1 and Ark2 have six ankryin repeats at the N-terminal cytosolic region (**D**).

DHHC7 or DHHC15 regulates AMPA receptor trafficking and AMPA receptor-mediated synapse function via PSD-95 palmitoylation. Intriguingly, a synaptic activity blocker tetrodotoxin-induced palmitoylation of PSD-95 is mediated only by DHHC2 but not by DHHC3/GODZ. Following the blockade of synaptic activity, dendritically localized DHHC2 rapidly translocates to the postsynaptic plasma membrane where DHHC2 induces palmitoylation of PSD-95, synaptic accumulation of PSD-95 and synaptic recruitment of AMPA receptors [23]. Thus, it would be important to test whether DHHC2 is involved in an activity-dependent synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD). Indeed, a recent work demonstrated that knockdown of DHHC2 failed to express the features of LTP such as AMPA receptor-mediated synaptic potentiation and spine enlargement in cultured hippocampal neurons, and it was also shown that palmitoylation of protein A-kinase anchoring protein 79 (AKAP79) by DHHC2 is essential for the synaptic potentiation [82].

DHHC5 has been reported to interact with PDZ3 domain of PSD-95 through its C-terminus [43]. In the study using mice homozygous for a hypomorphic allele of the DHHC5 gene, which express DHHC5 at low levels, DHHC5 was highly enriched in PSD and the contextual fear conditioning was markedly impaired [43]. These findings suggested a role for DHHC5 in postsynaptic function and learning and memory. Indeed, a couple of studies have reported the importance of DHHC5 for postsynaptic trafficking of AMPA receptors and synaptic plasticity [28,83]. Glutamate receptor interacting protein 1b (GRIP1b) was identified as a neuronal substrate for DHHC5 and also for DHHC8 using yeast two-hybrid (Y2H) screening with DHHC8 C-terminal region containing PDZ motif as a bait [28]. In cultured hippocampal neurons, DHHC5 and DHHC8 were largely localized to dendrites, mainly to dendritic shafts and synaptic region in the spine, respectively. Palmitoylated GRIP1b by DHHC5 and DHHC8 was targeted to dendritic endosomes and accelerated activity-dependent AMPA receptor recycling [28]. In addition, δ-catenin, an intracellular binding protein of cadherin that functions as a synaptic adhesion molecule, was found as a substrate for DHHC5 and it was transiently palmitoylated at last two cysteines C960 and C961 in the C-terminus among 18 cysteine candidates following enhanced synaptic activity [83]. Palmitoylation of δ-catenin increased its interaction with cadherin at synapses and was required for activity-induced spine enlargement, AMPA receptor insertion into the synaptic plasma membrane, and an increase in miniature excitatory postsynaptic current (mEPSC) amplitude. In mice, contextual fear conditioning increased palmitoylation of δ-catenin and its associations with N-cadherin [83]. DHHC5 also palmitoylated flotillin-2 that is a lipid raft protein [84] and was suggested to be important for development because the mice homozygous for a hypomorphic allele of the DHHC5 gene had a birth rate that was half the expected rate [43] (Table 3).

A mammalian orthologue of Akr1, DHHC17 [11] which was identified as a huntingtin-interacting protein, HIP14 [40] exhibited substrate specificity for SNAP-25, PSD-95, GAP-43, GAD65, synaptotagmin I, and huntingtin, but not for paralemmin and synaptotagmin VII [41]. Similar to PSD-95 palmitoylating DHHCs, DHHC17/HIP14 is also involved in the palmitoylation-dependent vesicular trafficking and clustering of several palmitoylated proteins [41].

There are a few DHHC proteins whose PAT activity has been reported to require a cofactor [42,85,86] although the majority of DHHC proteins appear to have a catalytic activity independently without other protein cofactors [87]. Yeast Ras is palmitoylated by a PAT Erf2 in a form of complex with Erf4 as a cofactor [56].

Table 2
DHHC-substrate pairs and related neurodegenerative diseases.

*zDHHC	Specific substrates	References for substrates	Related diseases	References for diseases
1	Ncdn	[69]		
2	PSD-95; eNOS; CD9/CD151; AKAP79;	[10,267]; [35]; [268]; [82];		
	NDE1/NDEL1; CKAP4; $G_{\alpha i2}$; GAP-43;	[269]; [270];[271]; [10];		
	ABCA1; Lck; SNAP-25; PI4KIIα	[272]; [87]; [33]; [273]		
3	$GABA_AR2$; PSD-95; GluA1/2; eNOS;	[72]; [10]; [77]; [35];		
	GluN2A/2B; CaMKIGs (CLICK-III); CSP;	[21]; [274]; [275];		
	NCAM140/180; GluN2A/2B; GAP-43;	[276]; [21]; [10];		
	GAD65; NDE1/NDEL1; BACE1;	[76];[269]; [151];		
	$G_{\alpha q}$, $G_{\alpha s}$, $G\alpha i_2$; SNAP-25/-23; STREX;	[271]; [33]; [88];		
	Stathmin 2/SCG10; Ncdn; PI4KIIα; D2R	[147]; [69]; [273]; [277]		
4	BACE1; D2R	[151]; [277]		
5	STREX; GRIP1b; flotillin-2; δ-catenin	[88]; [28]; [84]; [83]		
6	Calnexin; IP3R	[68]; [42]		
7	PSD-95; eNOS; $GABA_AR2$; GAP-43; NCAM140/180; CSP; NDE1/NDEL1;	[10]; [35]; [74]; [10]; [276]; [275]; [269];	Alzheimer's disease	[142]
	BACE1; APP; $G_{\alpha q}$, $G_{\alpha s}$, $G\alpha i_2$;	[151]; [142]; [271];		
	SNAP-25/-23; STREX; Sortillin;	[33]; [88]; [278];		
	Stathmin 2/SCG10; PI4KIIα	[147]; [273]		
8	eNOS; PSD-95; Paralemmin-1, GAD65;	[35]; [239]; [76];	Schizophrenia	[36,237,239,240]
	ABCA1; GRIP1b; PICK1; D2R; Cdc42, Rac1	[272]; [28]; [187]; [277]; [240]	Bipolar disorder	[36,236]
9	H-Ras, N-Ras; STREX	[85]; [88]	X-linked intellectual disability	[248,251–253]
11	Ncdn	[69]		
12	ABCA1; Gephyrin	[272];[279]	Alzheimer's disease	[139]
13	Huntingtin, GAD65; SNAP-25	[76],[229](huntingtin); [230]	Huntington's disease	[229,230]
14	PI4KIIα	[273]		
15	PSD-95; CSP; SNAP-25b; ABCA1;	[10]; [275]; [33]; [272];	X-linked intellectual disability	[250]
	$GABA_AR2$; BACE1;	[74]; [151];		
	CD151; CI-MPR, sortillin;	[268]; [278];		
	Stathmin 2/SCG10; GAP-43; PI4KIIα	[147]; [10];[273]		
17	Lck; CSP; huntingtin, GAD65, GluA1/2;	[10]; [275]; [41,76];	Huntington's disease	[40,41,224,226,227]
	SNAP-25/-23;	[41] (SNAP-25), [33];		
	Stathmin 2/SCG10; PSD-95, GAP-43;	[147];[10];		
	GPM6A, SPRED1/3; CLIPR-59; STREX	[232]; [280]; [88]		
18	H-Ras, N-Ras; H-Ras, Lck	[85]; [10]		
19	R-Ras	[281]		
20	ABCA1; BACE1; δ-catenin	[272]; [151]; [83]		
21	Fyn, Lck, eNOS; eNOS; ABCA1;	[34]; [35]; [272];	Alzheimer's disease	[142]
	APP; $G_{\alpha i2}$; PI4KIIα	[142]; [271]; [273]		

* Used in the text.

By a sequence homology search of yeast Erf2 – Erf4 complex, the mammalian DHHC9 – Golgi complex associated protein of 16 kDa (GCP16) complex was uncovered to have a PAT activity specific for H-Ras and N-Ras. GCP16 as a cofactor is required for DHHC9 autopalmitoylation and Ras palmitoylation [85]. Recently, another PAT DHHC6 has been shown to palmitoylate the Ca^{2+} channel protein, inositol-1,4,5-triphosphate receptor (IP3R) in the ER membrane, and the selenoprotein K (Selk) whose expression is sensitive to dietary selenium levels functions as a cofactor in the DHHC6-mediated IP3 R palmitoylation as revealed by that Selk deficiency decreased palmitoylation and stability of the IP3 R [42,86]. Interestingly, Selk contains an SH3 domain while DHHC6 is also predicted to contain an SH3 domain. Thus, DHHC6/Selk complex could be formed through SH3/SH3 interaction for the DHHC6 enzyme activity [42], suggesting the SH3 domain as a regulatory domain in DHHC6/Selk-mediated palmitoylation. Calnexin that is a major ER chaperone involved in glycoprotein folding was reported to be palmitoylated by DHHC6 with no requirement of other cofactors [68]. It seems that requirement of cofactors for PAT activity is not dependent on DHHC proteins rather it may depend on the substrates because STREX channel palmitoylation by DHHC9 [88] and calnexin palmitoylation by DHHC6 [68] do not require any cofactors for their PAT activity. More pairs of different DHHCs and their substrates are summarized in Table 2.

4. Depalmitoylating enzymes

In contrast to the intensive studies on PATs, current understandings on the depalmitoylating enzymes are relatively very limited although they surely are the key players along with the PATs in the

Table 3
Depalmitoylating enzymes, their substrates and related neurodegenerative diseases.

Enzyme	Gene	Substrates	References for substrates	Associated diseases	References for diseases
APT1	*lypla1*	H-Ras, RGS, $G_s\alpha$	[94,95,99]		
		eNOS	[96]		
		SNAP-23	[97]		
		G protein of VSV, HEF and HA proteins of influenza virus, E2 glycoprotein of SFV	[98]		
		Gα13	[101]		
		CD95	[103]		
APT2	*lypla2*	H-Ras, N-Ras	[105]		
		GAP-43	[106]		
		CD95	[103]		
PPT1	*cln1*	H-Ras, Gα	[110]	Infantile neuronal ceroid lipofuscinosis	[113]
		VAMP-2, SNAP-25	[121]		
				Adult neuronal ceroid lipofuscinosis	[123]
		CSP	[123]		

dynamic control of palmitoylation of substrate proteins (Fig. 1). Based on current knowledge, depalmitoylating enzymes include two acyl protein thioesterases (APTs), APT1 and APT2, and the palmitoyl protein thioesterase 1 (PPT1) (Table 4).

4.1. Acyl protein thioesterase 1 (APT1)

APT1, encoded by *lypla1* gene, belongs to members of the α/β-hydrolase family of serine hydrolases as revealed by crystal structure, which contain the catalytic triad Ser – His – Asp, a typical feature of α/β-hydrolases [89–92]. APT1 was originally purified from rat liver as a lysophospholipase [89,93] and later characterized as a thioesterase in yeast [94]. APT1 has been shown to depalmitoylate $G_s\alpha$, regulator of G protein signaling (RGS) protein, H-RAS [95], eNOS [96] and SNAP-23 *in vitro* [97]. It has also been shown to deacylate the G protein of vesicular stomatitis virus (VSV), HEF and hemagglutinin proteins of influenza virus, and the E2 glycoprotein of Semliki Forest virus (SFV) *in vitro* [98]. Unlike the E2, E1 glycoprotein of SFV was not deacylated by APT1 [98], demonstrating the substrate specificity of APT1. Palmostatin B, a small molecule inhibitor of APT1 [99] has been shown to interrupt palmitoylation and depalmitoylation cycle at the level of depalmitoylation and thus to disturb the steady-state localization of Ras, identifying APT1 as a thioesterase [99,100]. In hippocampal neurons, APT1 has been shown to be expressed in neuronal dendrites at the level of mRNA and to regulate dendritic spine size [101,102]. Knockdown of APT1 by shRNAs or enzymatic activity inhibitors of APT1, FD196 and FD253 decreased dendritic spine volume. MicroRNA-138 (miR-138) downregulated APT1 expression [101,103], which led to the shrinkage in spine volume presumably through the enhanced palmitoylation level of $G_{\alpha 13}$ caused by inhibited $G_{\alpha 13}$ depalmitoylation.

APT2, encoded by *lypla2* gene, was identified from mouse embryo as a new lysophospholipase named lysophospholipase II, and displayed 64% amino acid sequence identity with APT1. Similar to APT1, APT2 was predicted to contain the Ser – His – Asp catalytic triad [104]. A PT2 has also been reported to depalmitoylate H-Ras like APT1. However, it has more efficient catalytic activity than APT1 in depalmitoylating a biologically active semisynthetic N-Ras *in vitro* [105]. Overexpression of APT2, but not APT1, causes rapid depalmitoylation of the GAP-43 [106], demonstrating the substrate specificity of APT2. A recent report has shown that APTs regulate the apoptosis mediated by the cluster of differentiation 95 (CD95) in primary chronic lymphocytic leukemia (CLL) cells [103]. APT1 and APT2 were shown to promote depalmitoylation of CD95 through a direct interaction with CD95 and thus to impair CD95-mediated apoptosis. This impairment was reverted by a specific downregulation of APTs by siRNAs, miR-138, miR-424 or palmostatin B [103].

Unlike palmitoylation, depalmitoylation has been considered to occur everywhere in the cell and to lack any consensus sequence or substrate specificity [38]. However, a few studies have reported the substrate specificity of APTs such as APT1-specific deacylation of E2 glycoprotein of SFV [98] and APT2-specific deacylation of GAP-43 [106]. It remains, however, to be solved how APTs can efficiently access their substrates. APTs, including both APT1 and APT2 were identified to be palmitoylated [107,108]. Thus, it is be plausible that palmitoylation of cytoplasmic APTs may facilitate to be localized to the membrane and to interact with their substrates.

4.2. Palmitoyl protein thioesterase 1 (PPT1)

PPT1, encoded by *cln1* gene, is also a member of the α/β-hydrolase family harboring the classical catalytic triad, Ser – His – Asp [109]. It was characterized as a thioesterase through the observations that PPT1 catalyzes depalmitoylation of H-Ras and Gα *in vitro* [110,111]. PPT1 itself, like APT1 and APT2, is also palmitoylated at C6 by DHHC3 and DHHC7. In addition, regulation of the PPT1 enzymatic activity depended on its palmitoylation [112]. Interestingly, defects in the PPT1 gene were identified in the infantile type of neuronal ceroid lipofuscinosis (NCL, also known as Batten disease), a severe brain disease in childhood, which is characterized by early loss of vision and a massive loss of cortical neurons [113]. Although PPT1 was interestingly found to be targeted to lysosomes [114–116], PPT1 mutant (R122W), the most common infantile NCL mutation was not targeted to the lysosomes, but it was rather retained in the ER and remained enzymatically inactive [113,114], suggesting PPT1 as being involved in a lysosomal enzyme deficiency, infantile NCL. As expected from the fact that PPT1 gene is linked to the infantile NCL which is a neurodegenerative disorder, PPT1 has been implicated to play roles in the neuronal functions. PPT1 is widely expressed in the brain, localizes synaptosomes and synaptic vesicles (SVs), and colocalizes with presynaptic proteins, synaptophysin or GAP-43 [117–121]. PPT1 deficiency caused persistent membrane retention of palmitoylated SV proteins such as vesicle-associated membrane protein 2 (VAMP2) and SNAP-25 and disturbed the maintenance of SV pools, plausibly contributing to the abnormal neurotransmission and ultimately to infantile NCL pathology [121]. PPT1 mutant mice lacking the exon 4 exhibited a prominent loss of GABAergic interneurons in the brain [122]. A recent study reported that CSP is depalmitoylated by PPT1 and hence a substrate for PPT1 [123].

4.3. Other palmitoyl thioesterases: PPT2 and APTL1

PPT2 was isolated as a second lysosomal hydrolase which was shown to share an 18% homology at the level of amino acid with PPT1 and to possess palmitoyl-CoA thioesterase activities comparable with PPT1 [124]. However, PPT2 did not depalmitoylate the H-Ras [124], which was depalmitoylated by PPT1 in the past study [110], suggesting the substrate specificity and differential functions of PPT2 distinct from PPT1. Indeed, knockout mice studies have provided the evidence that PPT2 could serve a distinct role in the brain apart from PPT1 [125]. PPT2 knockout mice showed the milder NCL phenotypes such as reduced clasping behavior, enhanced survival rate, and lesser autofluorescent storage material compared to the PPT1 knockout phenotypes. Smaller lipid binding pocket of PPT2 than that of PPT1 revealed by crystal structure [126] could further support the distinct role of PPT2 and may explain the preference of PPT2 thioesterase activity for palmitoyl-CoA over the palmitoylated proteins [124].

APTL1, encoded by *lyplal1* gene, is a homologue of APT1 with 31% identity at the amino acid sequence level. APTL1 also contains the catalytic triad conserved [127]. Unlike APT1 but similar to PPT2, APTL1 features a narrow substrate-binding pocket which prefers short-chain substrates, thus showing a limited function as a palmitoyl thioesterase [128]. Currently, there is no report on the "protein" substrates for PPT2 and APTL1 with the possibilities that they may not serve as thioesterases for the palmitoylated proteins or the protein substrates for PPT2 and APTL1 may exist but have yet to be identified. Given that there are at least 23 DHHC PATs with specific substrates, it is well worth paying continuous effort to identify more potential thioesterases and test whether they play a role as thioesterases.

5. Palmitoylation in Alzheimer's disease

Protein palmitoylation is an important process to regulate physiological function of the brain. Indeed, numerous studies have reported that defects in palmitoylation step or in the enzymes for palmitoylation and depalmitoylation are associated with several neurological disorders such as AD, HD, schizophrenia, ID, and NCL. In this section, we will review the work providing evidence for the involvement of palmitoylation in several neurological disorders, in particular with more intensive focus on the AD.

5.1. Amyloidogenic and non-amyloidogenic process of amyloid precursor protein

Alzheimer's disease (AD) is the most common form of neurodegenerative disorders characterized by neuronal dysfunctions that lead to a cognitive decline and progressive memory loss. The most well-known neuropathological feature of AD is the formation of amyloid plaques [129] by neurotoxic extracellular β-amyloid (Aβ) aggregation in the brain [130–133]. Aβ is a 38 – 43 amino acid fragment derived from the sequential proteolytic processing of amyloid precursor protein (APP) by β-secretase (β-site APP cleaving enzyme 1, BACE1) and γ-secretase [132,134]. APP in non-amyloidogenic pathway is primarily cleaved by the α-secretase whereas APP in amyloidogenic pathway is internalized and cleaved by the β-secretase/BACE1 on endosomes and then by the γ-secretase complex to generate Aβ. Although most Aβ peptides are secreted to extracellular space, some Aβ peptides may aggregate in late endosomes or lysosomes contributing to intracellular Aβ accumulation [135,136]. A recent work has suggested a differential role of intracellular Aβ presumably depending on the degree of intracellular Aβ accumulation by examining a rapid synaptic delivery of GluA1 in response to intracellularly applied Aβ [137]. Genetic mutations responsible for early-onset familial AD (FAD) are isolated in APP and presenilin, an essential component of γ-secretase complex [138].

5.2. Palmitoylation and Aβ production

Co-immunoprecipitation assay revealed that DHHC12 is an alcadein and APP interacting DHHC protein (AID) [139]. DHHC12/AID suppressed APP trafficking by tethering APP in the Golgi, which attenuated its further trafficking to the *trans*-Golgi network (TGN) and the plasma membrane and inhibited APP metabolism, including Aβ generation, which was dependent on the DHHC motif of DHHC12/AID (Fig. 3). A mutant DHHC12/AID of which palmitoyl transferase activity was impaired by replacing the DHHC with the Ala-Ala-His-Ser (AAHS) still showed the suppressed APP trafficking and metabolism but significantly facilitated α-cleavage of APP through the activation of a disintegrin and metalloproteinase 17 (ADAM17) [139], a major α-secretase [140,141] indicating that amyloidogenic pathway producing Aβ was DHHC12/AID-mediated palmitoylation independent while non-amyloidogenic α-cleavage of APP was DHHC12/AID-mediated palmitoylation dependent. A recent study provided more direct evidence on the involvement of palmitoylation in the AD pathogenesis by showing that APP is palmitoylated *in vitro* and *in vivo* and APP palmitoylation regulates amyloidogenic process [142] (Fig. 3). It was found that APP is palmitoylated at C186 and C187 in N-terminal region structured toward the extracellular area. APP was not palmitoylated in the APP mutants with the cysteine residues at C186 and C187 replaced with serines such as APP-C186S, APP-C187S, and APP-C186,187S, and such palmitoylation-deficient APP mutants were retained in the ER (Fig. 3). DHHC7 and DHHC21 were shown to palmitoylate APP and overexpression of DHHC7 and DHHC21 increased Aβ production as well as APP palmitoylation. Palmitoylated APP enriched in lipid rafts was shown as a better substrate for BACE1 than α-secretase and the palmitoylation increased the BACE1-mediated cleavage of APP in lipid rafts [142], indicating that APP palmitoylation enhances amyloidogenic pathway producing Aβ (Fig. 3). Therefore, some strategies targeting the prevention of APP palmitoylation by developing specific inhibitors might need to be adopted to prevent and/or treat AD.

Palmitoylation of an APP interacting protein SCG10/stathmin 2 [143] which is a member of stathmin family and specifically expressed in neurons [144] was shown to be important in the APP processing [143]. SCG10/stathmin 2 was palmitoylated at C22 and C24 in N-terminal region [145,146], and SCG10/stathmin 2 palmitoylation mediated by Golgi-resident DHHC3/GODZ, DHHC7, and DHHC15 [147] contributed to its membrane association and APP processing [143]. SCG10/stathmin 2 was shown to directly interact with the KFFEQ motif of the APP intracellular domain (AICD) [143]. Overexpression of SCG10/stathmin 2 increased sAPPα and decreased $A_{\beta 1-40}$ in cultured mouse cortical neurons overexpressing APP, indicating that SCG10/stathmin 2 promotes the non-amyloidogenic processing of the APP (Fig. 3). Consistently, SCG10/stathmin 2 overexpression reduced Aβ accumulation and amyloid plaque formation in the hippocampus of APP_{Swe}/PS1ΔE9 mice [143], an AD model harboring APP Swedish mutations (APP_{Swe}) and exon 9 deletion (ΔE9) of the presenilin 1 [148]. Knockdown of SCG10/stathmin 2 decreased α-secretase cleavage products, sAPPα and C-terminal fragment α (CTFα), and it increased $A_{\beta 1-40}$ and $A_{\beta 1-42}$. Overexpression of palmitoylation-deficient SCG10/stathmin 2 mutant decreased the level of $A_{\beta 1-40}$ and $A_{\beta 1-42}$ in a significantly lesser degree compared to SCG10/stathmin 2-WT, indicating that palmitoylation of SCG10/stathmin 2 affects the APP processing. Therefore, these results suggest that identifying a PAT for SCG10/stathmin 2 would be the next step to investigate and developing methods blocking the palmitoylation of

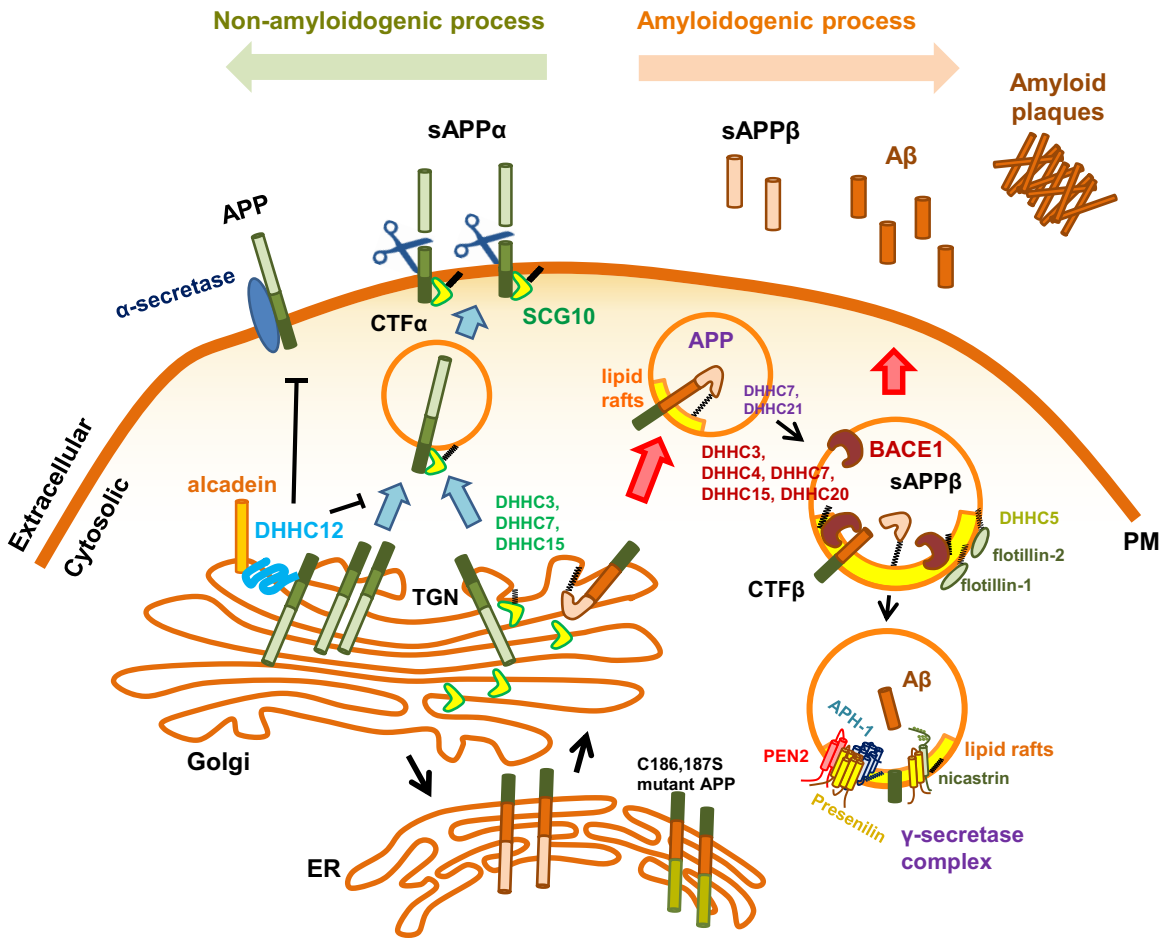

Fig. 3. Palmitoylation of AD-related proteins and the role of palmitoylation in AD pathogenesis.
In the non-amyloidogenic process, an alcadein and APP interacting DHHC protein DHHC12/AID suppresses APP trafficking in the Golgi and further to the late secretary pathway and also inhibits APP metabolism, including Aβ generation. DHHC12/AID negatively regulates the α-secretase activity in non-amyloidogenic process. SCG10/stathmin 2 is palmitoylated at C22 and C24 in N-terminal region by Golgi-resident DHHC3/GODZ, DHHC7 and DHHC15, interacts with AICD, and promotes APP trafficking from Golgi to the plasma membrane, affecting non-amyloidogenic processing of APP in a palmitoylation-dependent manner. In the amyloidogenic process, APP is palmitoylated at C186 and C187 in N-terminal region toward the extracellular area, and the palmitoylation of APP enhances amyloidogenic pathway producing Aβ. DHHC7 and DHHC21 increased APP palmitoylation and Aβ production as well. Palmitoylation-deficient APP mutants (APP-C186S, APP-C187S, and APP-C186,187S) are retained in the ER whereas palmitoylated APP is enriched in lipid rafts, resulting in upregulation of APP cleavage by BACE1. BACE1 is palmitoylated at C478, C482, and C485 within the C-terminal cytosolic region and at C474 within the transmembrane domain. DHHC3/GODZ, DHHC4, DHHC7, DHHC15, and DHHC20 promote palmitoylation of BACE1, which may facilitate the amyloidogenic processing of APP by targeting BACE1 to lipid rafts. Palmitoylation-mediated subcellular localization of BACE and the contribution of BACE1 palmitoylation to the AD are still unclear. Flotillins/reggies are palmitoylated at C34. Palmitoylation of flotillin-2/reggie-1 can be regulated by DHHC5. Flotillin-1/reggie-2 directly binds to the cytoplasmic tail of BACE1 and both flotillins are putative regulators for the trafficking of APP and BACE1, with being implicated in AD pathology. Among subunits of γ-secretase complex, nicastrin and APH-1 were reported to be palmitoylated, and the palmitoylation of nicastrin and APH-1 plays a role in the protein stability, their raft localization, and the modulation of Aβ deposition in the brain.

SCG10/stathmin 2 could be useful source for the therapeutic target for AD.

5.3. *BACE1 palmitoylation and APP processing*

BACE1, an aspartyl protease containing a long extracellular catalytic domain and a single TMD [149] has also been reported to be palmitoylated at C478, C482, and C485 within the C-terminal cytosolic region [150] and at C474 within the TMD [151]. DHHC3/GODZ, DHHC4, DHHC7, DHHC15 and DHHC20 were isolated as PATs for BACE1 and significant amount of BACE1 was targeted to lipid rafts in a palmitoylation-dependent manner [151].

The role of palmitoylation of BACE1 in Aβ production has been contradictory to date. Non-palmitoylated form of BACE1 lacking the TMD and cytoplasmic tail was reported to enhance amyloidogenic processing of APP, leading to Aβ production unlike BACE1 wildtype [150]. In contrast, when the BACE1 was engineered to be exclusively located to lipid rafts by adding glycosylphosphatidylinositol (GPI) anchor to the ectodomain of BACE1 (BACE1-GPI), both sAPPβ secretion and Aβ production were upregulated [152]. Given that BACE1 is located to lipid rafts depending on its palmitoylation, BACE1 palmitoylation would promote Aβ production. Indeed, palmitoyltransferase inhibitor cerulenin decreased Aβ production, supporting the idea that palmitoylation of BACE1 would be required for Aβ production [153,154]. While these controversial findings on the role of BACE1 palmitoylation in Aβ production were reported, two surprising reports were made on no influence of BACE1 palmitoylation on Aβ production [151,155]. Palmitoylation-deficient BACE1 whose 4 cysteines (C474, C478, C482, and C485) were substituted by alanine residues (BACE1-CA4) exhibited non-raft localization and did not affected the BACE1 processing of APP or secretion of Aβ, indicating that palmitoylation of BACE1 is not required for APP processing and also even lipid rafts localization of BACE1 is not important for its cleavage activity of APP [151,155]. So far, the contribution of BACE1 palmitoylation to Aβ production and AD is still unclear, and it needs further investigation.

5.4. γ-Secretase complex palmitoylation and APP processing

γ-Secretase acts on CTFβ (CTF99) to generate the AICD and the Aβ subsequent to BACE1. The γ-secretase is a multiprotein complex, consisting of at least four catalytic subunits [156], presenilins [156,157], the presenilin enhancer 2 (PEN2) [158], the anterior pharynx-defective 1 (APH-1) [159], and nicastrin [160] (Fig. 3). Although presenilins, PEN2, APH-1, and nicastrin have been known to be sufficient for γ-secretase processing of APP, a report identified a type I transmembrane protein p23 as a component of γ-secretase that modulates γ-secretase activity and regulates secretory trafficking of APP [161,162]. Nicastrin and APH-1 were reported to be palmitoylated at transmembrane C689 in nicastrin and at cytosolic C182 and C245 in APH-1 [163]. Co-overexpression of palmitoylation-deficient nicastrin and APH-1 caused a protein instability and reduced their lipid raft association whereas the palmitoylation deficiency of nicastrin and APH-1 did not influence Aβ40, Aβ42, CTFβ, P3, CTFα and AICD production, suggesting that palmitoylation of nicastrin and APH-1 plays a role in the protein stability and raft localization but not in γ-secretase activity and amyloidogenic and non-amylodogenic processing of APP [163]. The same group generated transgenic mice co-expressing palmitoylation-deficient APH1aL and nicastrin in the forebrain and found that palmitoylation deficiency did not affect the ability of APH1aL, an isoform of APH-1 and nicastrin to form enzymatically active γ-secretase complexes [164]. However, interestingly, the transgenic mice co-expressing palmitoylation-deficient APH1aL and nicastrin exhibited a significant but moderate reduction of amyloid deposits in the forebrain and a lower level of insoluble Aβ, indicating a potential role of γ-secretase palmitoylation in the modulation of Aβ deposition in the brain.

5.5. Fyn and flotillins/reggies palmitoylation and AD pathology

Many studies have suggested that Fyn and flotillins/reggies are implicated in AD pathology and their palmitoylation has also been implicated to serve a role in AD. In addition to the formation of amyloid plaques by Aβ aggregation, another neuropathological feature of AD is intracellular neurofibrillary tangles (NFTs) which are mainly composed of hyper-phosphorylated tau whose phosphorylation is caused by Fyn kinase [165–168]. Tau protein, one of microtubule-associated protein (MAP) family together with MAP2, MAP4 and others, is involved in regulation of microtubule cytoskeleton stabilization [169]. In the basal state, tau protein interacts with tubulin and promotes tubulin assembly into microtubules (Fig. 4A), which contribute to the normal morphology and structural support for neuronal cells [170]. Tubulin binding of tau is regulated by its phosphorylation state through coordinated action of kinases and phosphatases [171]. In AD, tau is not only abnormally hyper-phosphorylated and loses its tubulin binding capacity, leading to microtubule disorganization, but it is also self-polymerized, self-assembled and aggregated, resulting in the formation of the paired helical filaments (PHFs) and NFTs [172] (Fig. 4A). Tau is phosphorylated by Fyn kinase at Tyr18 (Y18), one of phosphorylation sites among 5 tyrosine residues of tau protein, and phosphorylated tau at Y18 was found in NFTs in human AD brain, suggesting a possible clinical relationship between tau phosphorylation at Y18 and AD [165,167,168] (Fig. 4B). Tau was reported to directly interact with Fyn via Fyn SH2 domains [173] or Fyn SH3 domains [165,168]. Fyn expression was reported to be elevated in AD brain [174], and it was also shown that up-regulation of Fyn affected Aβ-dependent synaptic and cognitive impairments, neuronal death, and premature mortality in APP transgenic mice, whereas down-regulation of Fyn protected against Aβ toxicity [175–177]. Therefore, Fyn has been suggested to play a role in Aβ-tau-dependent neuronal dysfunction in AD [178,179]. Fyn was revealed to be palmitoylated [180] at C3 and C6 in SH4 domain [181,182], and DHHC21 was identified as a PAT for Fyn [34]. Palmitoylation-deficient Fyn whose cysteine residues at C3 and C6 were replaced with serines (Fyn-C3S/C6S) was failed to localize to the plasma membrane in HEK293 cells and to the dendritic spines in cultured primary neurons but Fyn-C3,6S was accumulated on intracellular compartments, endosomes [181,182] (Fig. 4B), indicating that palmitoylation of Fyn is required for a proper subcellular localization and thus proper function of Fyn [181,182]. Therefore, it can be suggested that the palmitoylation of Fyn may influence the Aβ-Tau-Fyn toxic trade. By adopting the view of synaptic tau in AD [183], given that LTD-inducing NMDA receptor stimulation led to tau phosphorylation, which regulates the interaction with Fyn [184], and that tau phosphorylation is required for LTD [184,185], which could be a cellular basis for aberrant synaptic weakening and loss observed in AD [183], and that palmitoylation of the protein interacting with C-kinase (PICK1), a GluA2-interacting protein [186] is critical for cerebellar LTD induction [187], investigating palmitoylation of tau- and/or glutamate receptor-regulating factors will provide insights into synaptic roles of palmitoylation particularly in AD.

Flotillins/Reggies, originally identified as neuronal proteins upregulated during the axon regeneration after injury of the optic nerve [188,189] has also been implicated in AD pathology. Flotillins/Reggies were accumulated in AD brains [190,191] and the level of increased flotillins/reggies depended on the enhancement of Aβ deposition [192]. Many studies have suggested the putative roles of flotillins/reggies in AD as regulators for the trafficking of APP and BACE1, influencing the amyloidogenic processing of APP [193–197]. Interestingly, flotillins/reggies are palmitoylated; both flotillin-1/reggie-2 and flotillin-2/reggie-1 are palmitoylated at a conserved cysteine residue C34, while flotillin-2/reggie-1 is also myristoylated [198,199]. Palmitoylation of flotillin-2/reggie-1 was mediated by DHHC5 [84]. Palmitoylation of flotillins/reggies was revealed as a crucial process for the membrane association of flotillins/reggies. Although there have been no report showing a direct link between flotillin/reggie palmitoylation and AD, considering their putative roles in AD, it would be worthwhile to investigate a role of flotillin/reggie palmitoylation in AD pathogenesis.

5.6. Possible role of Apolipoprotein E palmitoylation on the late-onset sporadic AD?

Only less than 3% of AD cases account for FAD carrying the genetic mutations. Currently, most of the AD patients suffer from the late-onset sporadic AD (LOAD) which may not involve genetic mutations for Aβ production, implying that an increase in Aβ generation by genetic background is probably not the major pathogenic mechanism underlying LOAD [200,201], but rather a defect in Aβ clearance for blocking an increase or accumulation of toxic Aβ could underlie AD pathogenesis in LOAD [132,202,203]. Apolipoprotein E (apoE), the major apolipoprotein in the central nervous system (CNS), is one of the well-studied factors for the LOAD pathogenesis especially in the process of Aβ clearance and aggregation. Numerous studies have demonstrated the differential effect of apoE isoforms on amyloidogenesis, including the production, aggregation, and clearance of A*β in vivo* and *in vitro* [204,205]. It was reported that apoE is produced in selected classes of neurons under certain conditions, such as aging and brain injury [206–209] and plays a role in synaptogenesis, maintenance of synaptic connections [210], neurite outgrowth in an isoform-dependent manner *in vitro*, synaptic plasticity and cognitive function, including learning and memory *in vivo* [211,212]. Therefore, it is suggested that apoE is involved in synaptic dysfunction of AD even though apoE-mediated cellular mechanisms underlying AD pathogenesis are standing to be uncovered.

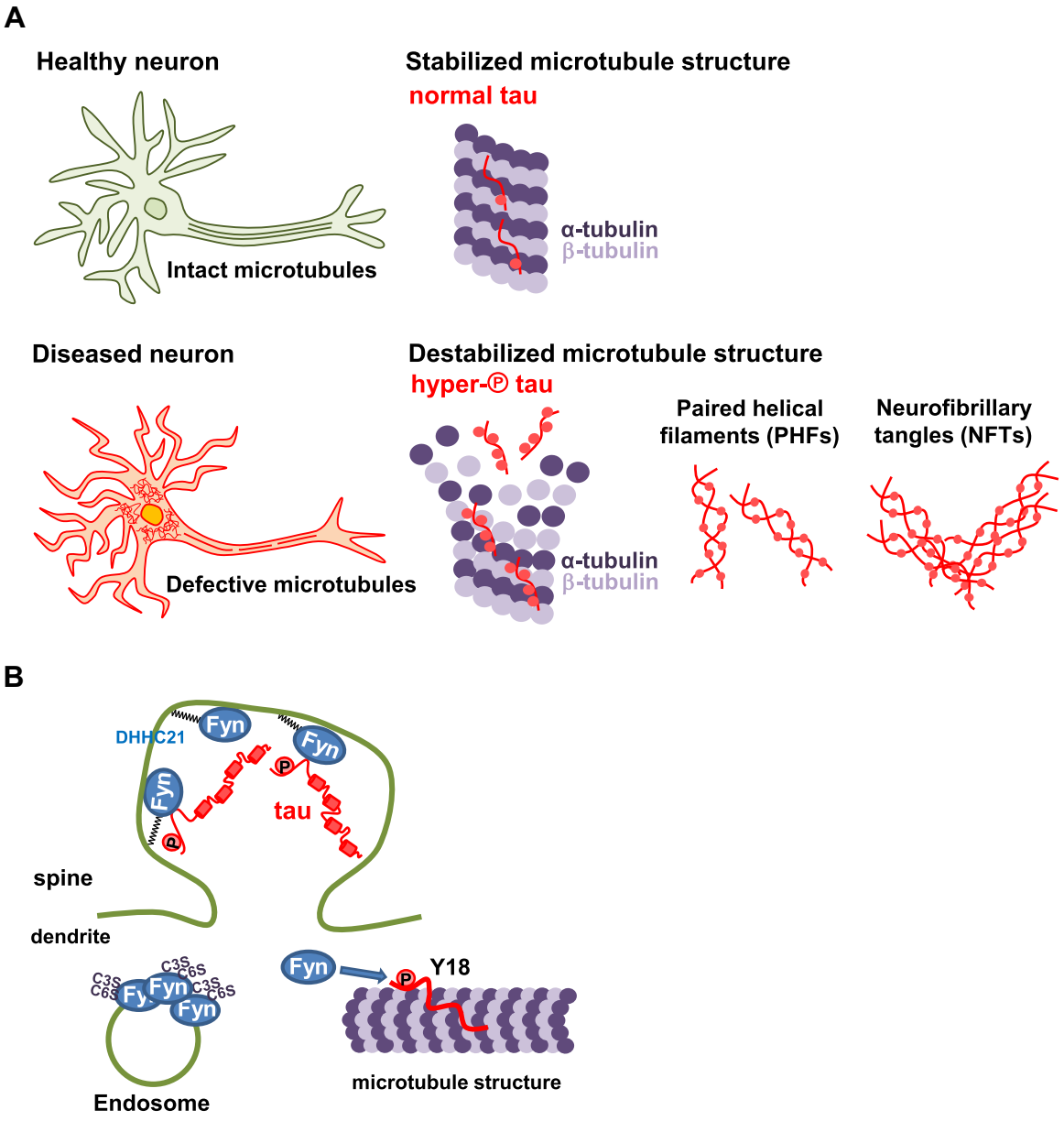

Fig. 4. Structure and pathology of tau protein and palmitoylation-related function of Fyn kinase.
In healthy neurons, tau proteins interact with tubulin, contributing to microtubule stability for supporting normal morphology and structure of cells. Phosphorylation of tau is a regulatory factor for microtubule stability. In diseased neurons, abnormal hyper-phosphorylation of tau leads to microtubule collapse and insoluble cytoplasmic tau aggregation. Aggregated and hyper-phosphorylated tau proteins twist to form paired helical filaments (PHFs), which assemble to produce neurofibrillary tangles (NFTs), a typical neuropathological feature of AD. (**B**) Fyn kinase directly interacts with tau, phosphorylates tau at Tyr18 (Y18) and facilitates trafficking of tau to dendritic spines. Fyn kinase is palmitoylated by DHHC21. Palmitoylation-deficient Fyn (Fyn-C3,6S) is accumulated on endosomes in cultured neurons. Palmitoylation of Fyn is required for its subcellular localization and thus involved in localization and phosphorylation of tau protein.

ApoE has three major isoforms, apoE2, apoE3 and apoE4. They have been considered to play differential roles in LOAD. ApoE3 is the most predominant isoform, accounting for almost 77% of the non-AD general population, while apoE2 is the most minor isoform found in 8% and apoE4 found up to 15% of the non-AD general population. However, apoE4 is more frequently found over 40% in AD patients [213], and this rate even goes up to 65% to 80% in LOAD patients. Therefore, it is likely suggested that apoE4 would be a major risk factor for LOAD [205,213–217] while the most minor isoform apoE2 exhibited a protective effect against LOAD [205,213,216,217]. Interestingly, these three isoforms of apoE proteins are only different in one or two amino acids at 112th and/or 158th residues; apoE2 has two cysteine residues, C112 and C158, apoE3 has two different residues, C112 and R158, and apoE4 has two arginines, R112 and R158. These differences can alter their folding structure and ability to bind with lipid and their receptors [218,219].

So far, there has been no report on whether apoE proteins are palmitoylated. Intriguingly, it is highly plausible that apoE2 and apoE3 might be palmitoylated at both C112 and C158 and only at C112, respectively. *In silico* screening of apoE palmitoylation using CSS palm ver.4.0 program [69] reveals that C112 and C158 of apoE2 and C112 of apoE3 were predicted to be palmitoylated with high scores whereas apoE4 was predicted to have no putative site for palmitoylation (*unpublished data in the Park laboratory*). Given that apoE4 was suggested to be a risk factor while apoE2 being suggested to serve a protective role for LOAD and also that apoE4 was predicted not to be palmitoylated but apoE2 was predicted to be

palmitoylated, it can be hypothesized that apoE2 palmitoylation at C112 and C158 might contribute to the protective role acting on the Aβ clearance process in LOAD. Manipulating ApoE2 palmitoylation would be considered as a way for therapeutic development in LOAD. It is currently still inconclusive whether palmitoylation of specific proteins alters AD pathogenesis. There is, however, no doubt in the need for further studies to clarify the specific role of palmitoylation in AD.

6. Palmitoylation in other neurodegenerative diseases

6.1. Huntington's disease

Huntington disease (HD) is a neurodegenerative disease characterized by cognitive decline, motor dysfunction, and psychiatric disturbance [220,221]. HD is caused by a mutation in the *huntingtin* gene by an expansion of CAG trinucleotide repeat to greater than 35 repeats, resulting in an abnormal huntingtin protein with a long polyglutamine, poly(Q) tail in its N-terminal region [29]. Loss of medium spiny neurons (MSNs) and loss of the striatal volume are observed as key pathological features of HD [222]. Huntingtin was shown to be highly expressed in neurons [223], and DHHC17/HIP14 that is a PAT for huntingtin was originally isolated as a huntingtin-interacting protein by Y2 H screening [40]. Its interaction with huntingtin is inversely correlated with the poly(Q) length of huntingtin, suggesting that reduced interaction of DHHC17/HIP14 with huntingtin could contribute to the pathogenesis of HD. Moreover, DHHC17/HIP14 is abundantly and widely expressed in the brain, particularly in striatal MSNs whose cell loss is a neuropathological characteristic of HD [40].

6.1.1. Huntingtin and palmitoylation

Huntingtin was reported to be palmitoylated at C214, and a mutation of huntingtin at this Cys replaced with Ser (C214S) increased NMDA-induced neuronal toxicity and inclusion formation [224]. Knockdown of DHHC17/HIP14 in cortical neuronal cultures from the YAC128 transgenic mouse model of HD, which has a full-length human *huntingtin* transgene with 128 CAG repeats [225], increased the inclusion formation of huntingtin whereas overexpression of DHHC17/HIP14 significantly reduced the huntingtin accumulation in the inclusion [224]. Palmitoylation level of huntingtin was significantly diminished in brain extracts of YAC128 mice, which could be explained by reduced palmitoylation activity of DHHC17/HIP14 most likely due to a weakened interaction between mutant huntingtin and DHHC17/HIP14 [224]. These suggest an important role for palmitoylation in HD. YAC128 mice exhibited brain weight reduction and striatal volume loss, including MSNs loss with motor and cognitive dysfunctions [225]. Similar to YAC128 mice, DHHC17/HIP14 null mice, *hip14-/-*, displayed a reduced striatal volume and behavioral deficits like HD [226]. DHHC17/HIP14 protein levels were not changed but DHHC17/HIP14 was dysfunctional in the presence of mutant huntingtin in YAC128 mice, suggesting that altered palmitoylation of huntingtin mediated by DHHC17/HIP14 may contribute to HD [226]. In addition, *hip14-/-* mice exhibited a decrease in excitatory synapses in striatum [226] and in hippocampus [227]. *Hip14-/-* mice also resulted in impaired hippocampal LTP and spatial memory [227], suggesting that loss of DHHC17/HIP14 may account for the cognitive symptoms in HD.

Huntingtin is also a substrate for DHHC13/HIP14-like (HIP14L) [76,228], which was identified by database searches for DHHC17/HIP14 homologs [40] DHHC13/HIP14L is the only PAT having a DQHC motif instead of the canonical DHHC motif [25,29,52]. While DHHC17/HIP14 has a number of substrates for palmitoylation, the specific substrates of DHHC13/HIP14L are still limited. DHHC13/HIP14L was only reported to palmitoylate GAD65 [76], huntingtin [76,229], and SNAP-25 [230]. It was recently reported that the DHHC13/HIP14L-deficient *hip14l-/-* mice exhibited the HD-like progressive neuropathological deficits, including progressive loss of striatal and cortical volume and motor impairment [230]. Palmitoylation levels of neuronal substrate SNAP-25, but not PSD-95 were diminished in *hip14l-/-* mice. In addition, DHHC13/HIP14L interaction with mutant huntingtin was reduced compared to wildtype huntingtin [230]. These findings suggest that reduced palmitoylation of neuronal substrate in *hip14l-/-* mice may contribute to the pathogenesis of HD. Taken together, dysfunction of DHHC17/HIP14 and DHHC13/HIP14L is implicated in HD.

DHHC17/HIP14 was reported to bind with the N-terminal region of huntingtin through its ankyrin domain, and the binding regions were mapped to amino acids 1–548 of huntingtin and amino acids 89–257 of DHHC17/HIP14 [76,228]. A recent study identified two potential binding domains around amino acids 224 and 427 of huntingtin for both DHHC17/HIP14 and DHHC13/HIP14 L [231]. Since huntingtin affects the palmitoylation of DHHC17/HIP14 and DHHC13/HIP14L substrates by modulating the PAT enzymatic activity [228], a further characterization on the interactions of huntingtin with DHHC17/HIP14 and/or DHHC13/HIP14L would extend the current understandings on the mechanisms underlying HD pathogenesis.

The Y2H study of DHHC17/HIP14, which is the first comprehensive work to discover interacting partners of a mammalian PAT, found that there are significant overlap between DHHC17/HIP14 interacting partners screened by Y2H and huntingtin interacting partners that are previously reported [232]. Interestingly, about half of the 36 overlapped binding partners have already been reported to be implicated in HD, providing a support for a direct link between DHHC17/HIP14 and HD. In addition, the neuronal membrane glycoprotein M6A (GPM6A) and the Sprouty domain-containing proteins SPRED1 and SPRED3 were identified as novel substrates of DHHC17/HIP14 from palmitoylated proteins among DHHC17/HIP14 Y2H binding partners, supporting that altered palmitoylation by DHHC17/HIP14 could be an important mechanism contributing to the HD pathogenesis. Further investigations on functional interactions between huntingtin and DHHC17/HIP14 or DHHC13/HIP14Lwill provide fruitful clues to understand HD pathophysiology.

6.2. Schizophrenia

Schizophrenia is a psychiatric disorder often characterized by abnormal social behavior and pervasive cognitive deficits. Decreased palmitoylation of many proteins were reported to be found in the dorsolateral prefrontal cortex from schizophrenia patients [233]. Among palmitoylating enzymes, DHHC8 has been demonstrated as a key PAT/DHHC associated with schizophrenia. The *dhhc8* gene located in the microdeletion region of chromosome 22q11 was reported to be associated with a risk of schizophrenia [234,235]. In particular, polymorphisms in the *dhhc8* gene have been reported for its association with a risk of schizophrenia [36,236] but those associations seemed to be dependent on ethnic groups, making the associations of the *dhhc8* polymorphisms and schizophrenia still controversial. There were reports showing significant association between 3 single-nucleotide polymorphisms (SNPs) in *dhhc8* gene and schizophrenia in the U.S. and South African populations [237] and in the Han Chinese population as well [238]. One of these 3 SNPs, rs175174 located in intron 4 of *dhhc8* gene, was also identified to be strongly and functionally associated with schizophrenia in American and South African patients, particularly in female patients [36]. The SNP rs175174 modulated the retention of intron 4 of *dhhc8*, which introduces

a premature stop codon *in vitro*, thereby influencing an alternative splicing of *dhhc8* and putatively leading to a truncated inactive form of DHHC8. Moreover, *dhhc8* knockout mice exhibited sexually dimorphic deficits in prepulse inhibition and reduction in locomotor activity in an open field test of spontaneous exploratory behavior under mildly stressful conditions, which is more severe in female than male mice [36]. A subsequent study demonstrated that *dhhc8*-deficient mice showed a decrease in dendritic spine density [239] and disruption of axonal growth [240]. In contrast to the studies described above, several studies have demonstrated no association between *dhhc8* gene and susceptibility to schizophrenia [236,241–246]. Some reports have demonstrated that there was no association between the SNP rs175174 and schizophrenia in a large European samples [241] and the Japanese population as well [242,243]. A recent study using meta-analytic techniques failed to find an association between the *dhhc8* gene locus and susceptibility to schizophrenia [246]. However, another report that did not find an association between *dhhc8* polymorphisms and schizophrenia in Korean population found an association with smooth pursuit eye movement (SPEM) abnormality, which is a feature of schizophrenia, suggesting that *dhhc8* gene might influence different aspects of schizophrenia [247]. An association between *dhhc8* and schizophrenia could be restricted in closely linked genetic locus based on specific ethnic groups or *dhhc8* might be indirectly implicated in schizophrenia. In a 22q11.2-deletion mouse model of schizophrenia *Df(16)A*$^{+/-}$ mice, axonal growth and branching was disrupted *in vivo* and these deficits were rescued when DHHC8 was exogenously expressed in the mice [240]. In addition, a schizophrenia-related circuit, a prefrontal cortex – hippocampus connectivity and spatial working memory were impaired in *dhhc8*-deficient mice. These data further support an association of DHHC8 with schizophrenia. It will need to further dissect the molecular mechanisms underlying palmitoylation in schizophrenia.

6.3. Intellectual disability

Intellectual disability (ID) is a developmental disorder with an onset under the age of 18 and is defined by significant limitations in cognitive and adaptive functioning such as daily living skills, social skills and communication skills [248,249]. DHHC15 [250] and DHHC9 [248,251,252] have been implicated in X-linked ID (XLID). X-inactivation and gene expression studies have revealed that the translocation breakpoint within the first exon of the *dhhc15* gene, also located on the X chromosome, disrupted the transcription of *dhhc15* gene in a female patient with severe nonsyndromic XLID, suggesting DHHC15 as a strong candidate for nonsyndromic XLID [250]. In addition, four mutations, including one frameshift, one splice-site, and two missense mutations in *dhhc9* gene at Xq26.1 were identified in 4 out of 250 families with XLID [251]. Another recent study has also identified two naturally occurring variants of *dhhc9*, encoding R148 W and P150 S from XLID patients [252]. Both mutations affected the steady state autopalmitoylation level of DHHC9 through distinct mechanisms. This altered autopalmitoylation level of DHHC9 is predicted to affect the palmitoylation of target proteins that might be involved in intellectual development [252]. By combining the value of next generation sequencing, it would be important to identify novel target proteins of DHHC9 associated with ID for providing molecular diagnosis and therapeutic treatment [249,253].

7. Perspectives

While substrate specificity of PATs/DHHCs and protein thioesterases is rather broad – some PATs/DHHCs have been reported to have more than 10 even 20 specific substrates, very little work has been investigated on how the palmitoylation or depalmitoylation of their individual substrates is individualized in terms of mechanistic regulations. Recently, the prolyl isomerase FK506-binding protein 12 (FKBP12) was reported to facilitate depalmitoylation of H-Ras [254], which may individualize and specify the regulatory mechanisms of H-Ras depalmitoylation by suggesting that H-Ras depalmitoylation is not solely dependent on protein thioesterases. Work on identifying and verifying more potential thioesterases, and further detailed and specified mechanisms dissecting the palmitoylation and depalmitoylation cycle of individual substrates will improve current understanding on the roles of palmitoylation in physiology and pathophysiology of neuronal (dys)functions.

In addition to palmitoylation, other PTMs, including phosphorylation, ubiquitination, sumoylation and nitrosylation have been demonstrated to influence synaptic function and pathophysiology of neurodegenerative diseases [255–259]. Further, crosstalk among these PTMs has also been demonstrated to contribute to fine tuning of the regulation of synaptic protein functions [27,260,261]. Knockdown of any DHHCs palmitoylating the alternatively spliced stress-regulated exon (STREX) variant of the intracellular C-terminal domain of the large conductance calcium- and voltage-activated potassium (BK) channels prevented the protein kinase A (PKA)-mediated inhibition of STREX channels [88], providing an evidence for an interplay between palmitoylation and phosphorylation to regulate STREX channels. In addition, a reciprocal control of synaptic targeting of PSD-95 was reported to be mediated by an interplay between palmitoylation and nitrosylation [260]. Furthermore, sumoylation of tau was reported to plausibly affect tau aggregation by increasing its phosphorylation and inhibiting the ubiquitination-mediated degradation of tau [261]. Given the emerging evidence on the potential crosstalk among the PTMs in precisely controlling the cellular function of proteins, which further greatly increases the functional complexity of proteins including the specificity of individual substrates of palmitoylating and depalmitoylating enzymes, unraveling the complex mechanisms involved in (de)palmitoylation-mediated control of neuronal functions would help develop broad spectra toward therapeutic development in respect to diagnosis, prevention or treatment for various neurodegenerative diseases.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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