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Altered Protein Palmitoylation as Disease Mechanism in Neurodegenerative Disorders

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Palmitoylation, a lipid-based posttranslational protein modification, plays a crucial role in regulating various aspects of neuronal function through altering protein membrane-targeting, stabilities, and protein–protein interaction profiles. Disruption of palmitoylation has recently garnered attention as disease mechanism in neurodegeneration. Many proteins implicated in neurodegenerative diseases and associated neuronal dysfunction, including but not limited to amyloid precursor protein, β-secretase (BACE1), postsynaptic density protein 95, Fyn, synaptotagmin-11, mutant huntingtin, and mutant superoxide dismutase 1, undergo palmitoylation, and recent evidence suggests that altered palmitoylation contributes to the pathological characteristics of these proteins and associated disruption of cellular processes. In addition, dysfunction of enzymes that catalyze palmitoylation and depalmitoylation has been connected to the development of neurological disorders. This review highlights some of the latest advances in our understanding of palmitoylation regulation in neurodegenerative diseases and explores potential therapeutic implications.

Key words: **palmitoylation; neurodegeneration**

Introduction

Posttranslational protein modifications essentially contribute to the complexity of the cellular proteome by providing the means for altering protein functions in multiple and diverse ways (Beltrao et al., 2013; Keenan et al., 2021). One such modification is *S*-acylation, which refers to the addition of long chain fatty acids to a target cysteine residue via a thioester bond (Deschenes et al., 1990; Mesquita et al., 2024). Because palmitate is the most abundant and commonly used lipid during *S*-acylation, this modification is most commonly referred to as *S*-palmitoylation (Magee and Courtneidge, 1985). However, other fatty acids can be incorporated and even preferred (Greaves et al., 2017; Puthenveetil et al., 2022). Attachment of palmitate is mediated by the zinc finger-containing DHHC (ZDHHC) family of palmitoyl *S*-acyltransferases (PATs; Dietrich and Ungermann, 2004; Roth et al., 2006; Korycka et al., 2012), while its removal is facilitated by serine hydrolases of the acyl protein thioesterase (APT), protein palmitoyl thioesterase (PPT), and α/β-hydrolase domain (ABHD) protein families (Camp and Hofmann, 1993; Duncan and Gilman, 1998; Lin and Conibear, 2015; Fig. 1*A*). *S*-Palmitoylation is unique in that it is the only lipid modification that is reversible, standing in contrast to *N*-myristoylation, isoprenylation, *N*-palmitoylation, and *O*-acylation (Y. Fukata and Fukata, 2010; Buszka et al., 2023). As such, *S*-palmitoylation (thereafter referred to as palmitoylation) has the power to dynamically adapt protein function in response to extracellular stimuli (Conibear and Davis, 2010; Sanders et al., 2015; Nasseri et al., 2022). As a lipid modification, palmitoylation increases the affinity of proteins for nonpolar structures such as lipid bilayers, aiding their integration into, and association with, organelle and plasma membranes (PMs; Resh, 1999, 2006a). The increase in hydrophobicity also alters protein stabilities, trafficking, and protein–protein interaction profiles (Resh, 2006a,b; Greaves and Chamberlain, 2007; Linder and Deschenes, 2007; Fig. 1*B*).

Neurons contain a large number of palmitoylated proteins (Sanders et al., 2015; Petropavlovskiy et al., 2021), suggesting a critical role of the modification in neuronal function. Indeed, palmitoylation is vital for neurodevelopment by facilitating axonal

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guidance and growth, as well as dendritic growth and differentiation (A. D. El-Husseini and Bredt, 2002; Ponimaskin et al., 2008; Y. Fukata and Fukata, 2010; Holland and Thomas, 2017; Koropouli et al., 2023). In mature neurons, it contributes to the regulation of synaptic transmission and plasticity (Y. Fukata and Fukata, 2010; Matt et al., 2019; Buszka et al., 2023), structural long-term plasticity (LTP) and spine remodeling (Albanesi et al., 2020; Ji and Skup, 2021), as well as integrity of neuronal connections (Globa and Bamji, 2017; Holland and Thomas, 2017; Fig. 1C). Maintaining a balance between protein palmitoylation and depalmitoylation is paramount for effectively controlling these processes, and disruption of protein palmitoylation is beginning to surface as a potential pathological mechanism in neurodegenerative diseases (Cho and Park, 2016; Zaręba-Kozioł et al., 2018; Ramzan et al., 2023). Indeed, key proteins involved in Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) undergo changes in palmitoylation in disease (Yanai et al., 2006; Antinone et al., 2013, 2017; Bhattacharyya et al., 2013; Dore et al., 2021; Lemarié et al., 2021; Cervilla-Martínez et al., 2022; Ho et al., 2023). In addition, aberrant activity of palmitoylating and depalmitoylating enzymes is linked to the development of childhood and adult-onset neurodegenerative diseases (Vesa et al., 1995; Mukai et al., 2008; Singaraja et al., 2011; Sutton et al., 2013; Lemire et al., 2021; W. Li et al., 2023).

In this focused review, we highlight and discuss recent studies investigating the role of palmitoylation in the onset and progression of adult neurodegenerative diseases, with a focus on AD, PD, HD, and ALS. We will also touch upon the potential therapeutic value of recent discoveries in the field.

Palmitoylation in AD

AD is a progressive neurodegenerative disease and a leading cause of morbidity and mortality in the elderly worldwide. FDA-approved therapeutics, including acetylcholesterase inhibitors, NMDA receptor antagonists, and anti-β-amyloid (Aβ) immunotherapies, slow cognitive decline in AD patients (Rösler et al., 1999; Reisberg et al., 2003; Tariot et al., 2004; Sims et al., 2023; van Dyck et al., 2023). However, these treatments do not provide a cure or stop disease development. Thus, alternatives that target a new range of therapeutic targets are urgently needed. Protein palmitoylation is beginning to surface as a significant player in AD pathology, by affecting key enzymes involved in Aβ production, like β-amyloid precursor protein (APP), β-site cleaving enzyme 1 (BACE1), and γ-secretase components nicastrin and anterior pharynx-defective 1 (APH-1), as well as effector proteins implicated in Aβ- and Tau-mediated synaptic toxicity, such as PSD95 and Fyn. A better understanding of palmitoylation in AD pathogenesis may pave the way for developing novel drugs to prevent or delay disease. In the following chapters, we will review current knowledge of how palmitoylation affects AD-related proteins and associated cellular pathways.

The role of BACE1 and γ-secretase palmitoylation in Aβ production

Palmitoylation of enzymes responsible for the amyloidogenic processing of APP critically affects Aβ accumulation and deposition in the brain, which is a main driver of disease. In healthy individuals, APP preferentially undergoes nonamyloidogenic processing at the PM by the A disintegrin and metalloprotease (ADAM) family of proteases, which releases neuroprotective soluble sAPPα and the C-terminal fragment (CTF) C83 (Nunan and Small, 2000; Hitschler and Lang, 2022). In AD development, APP processing shifts to the amyloidogenic pathway, where it is cleaved by BACE1 to generate the intracellular C-terminal domain of APP (βCTF or C99) and then by γ-secretase to give rise to Aβ (LaFerla et al., 2007; P. Z. Chia et al., 2013; Zhang and Song, 2013; Gallego Villarejo et al., 2022). Palmitoylation became a focus of investigation in amyloidogenic APP processing as BACE1, the γ-secretase subunits nicastrin and APH-1, and APP are all palmitoylated (Fig. 2A; Cheng et al., 2009; Vetrivel et al., 2009; Bhattacharyya et al., 2013; Song et al., 2022). Palmitoylation of these proteins increases their affinity for cholesterol and sphingolipid-rich microdomains, called lipid rafts (LRs; Fig. 2A; Cho and Park, 2016). Once located in LRs, BACE1 and γ-secretase activity toward APP is

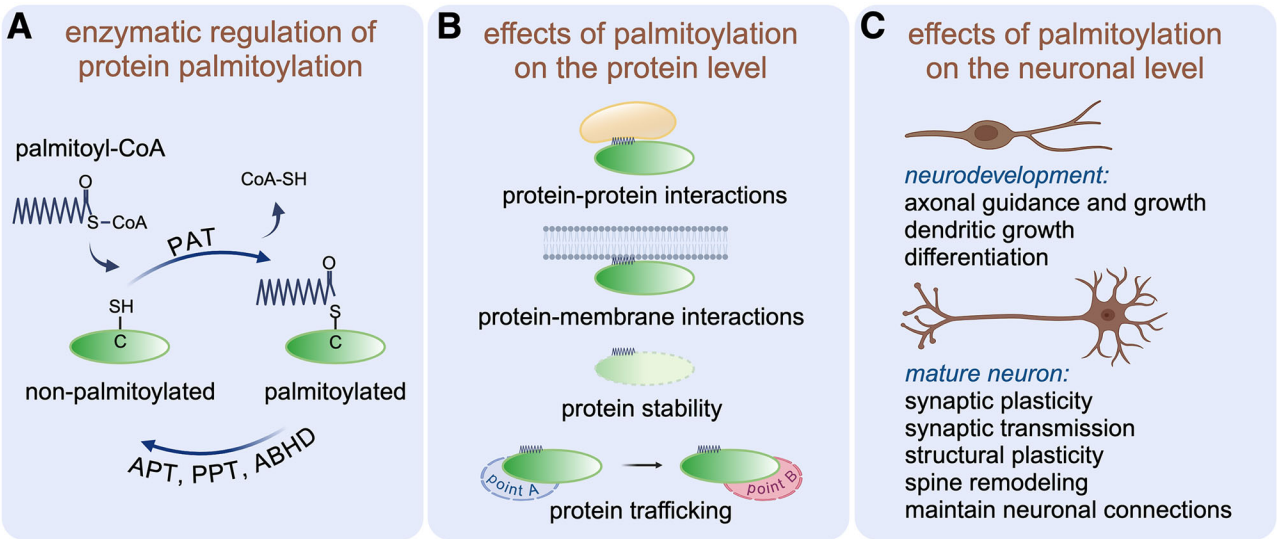

Figure 1. Mechanisms and consequences of protein palmitoylation. ***A***, Protein palmitoylation occurs through dynamic palmitoylation and depalmitoylation cycles. A PAT uses palmitoyl-CoA as a donor to transfer palmitate to the thiol group of a cysteine (C) in substrate proteins. This process is reversed by APT, PPT, as well as ABHD proteins. ***B***, Palmitoylation changes protein function by altering its affinity for membranes and other proteins, regulating its half-life and guiding its trafficking between different subcellular locations. ***C***, Palmitoylation critically influences neuronal function throughout the life span of a neuron. Created with BioRender.com.

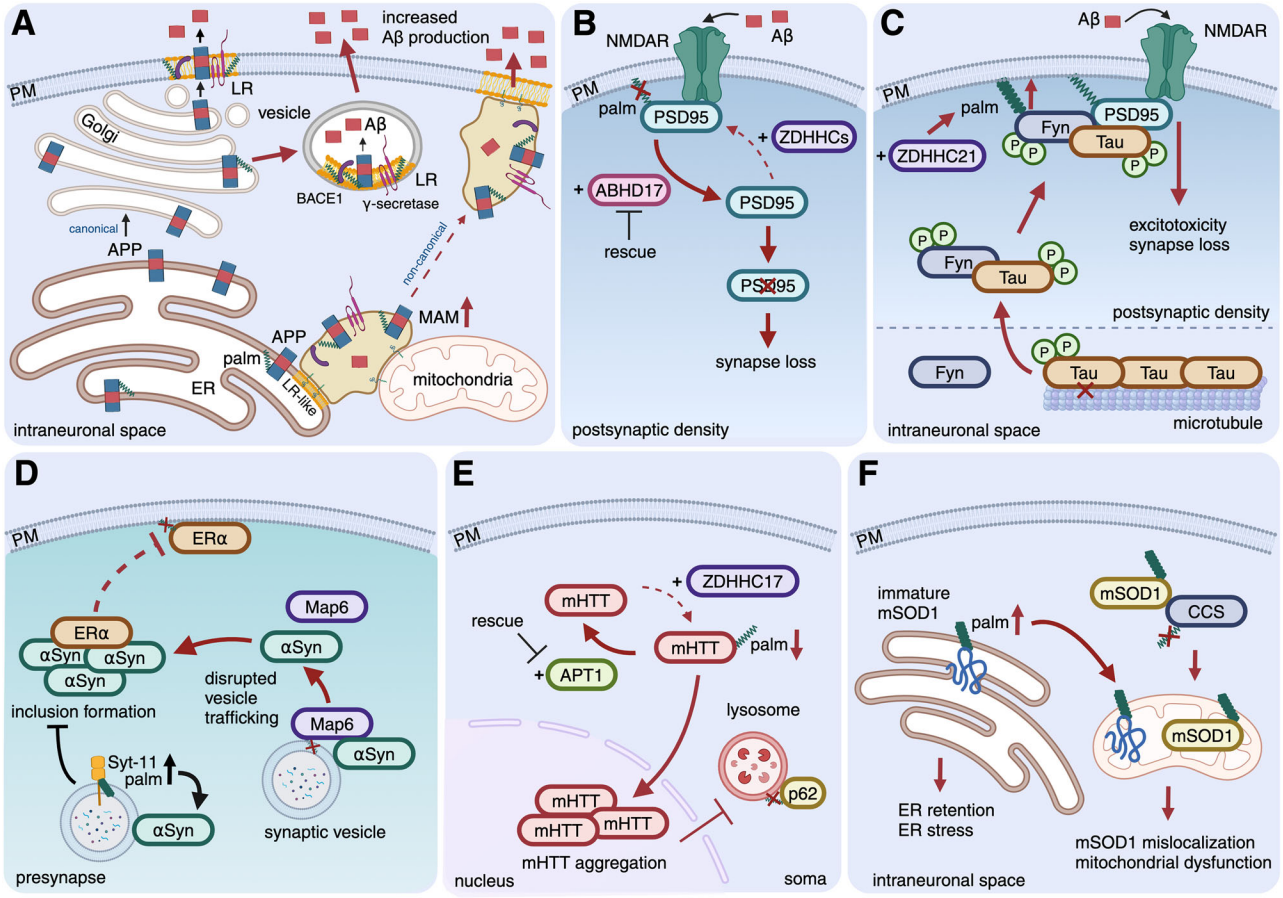

Figure 2. Palmitoylation regulates key proteins and processes involved in neurodegeneration. ***A***, APP processing and accelerated Aβ production. APP is synthesized in the ER and transported in a canonical secretory pathway via Golgi to the PM, where it is processed to form Aβ. Palmitoylation enables APP to enter endosomes, where it undergoes accelerated amyloidogenic processing in LRs due to the presence of palmitoylated BACE1 and γ-secretase. Palmitoylated APP is also enriched in LR-like MAMs that contain BACE1/γ-secretase and generate large amounts of Aβ before releasing it into the extracellular matrix. Finally, a noncanonical MAM-dependent pathway might aid in increased Aβ release via yet-unknown mechanisms. ***B***, Aβ-mediated synaptic toxicity. Aβ induces synaptic dysfunction through the NMDA receptor by mediating PSD95 depalmitoylation and subsequent loss. Inhibition of ABHD17 depalmitoylating enzymes rescues this phenotype by increasing synaptic PSD95. ***C***, Tau-mediated synaptic toxicity. Tau hyperphosphorylation causes its release from microtubules, which leads to its synaptic mislocalization. Together with Tau, Fyn translocates to the postsynaptic density, where they bind PSD95 and elicit excitotoxicity. This is exacerbated by Fyn palmitoylation by ZDHHC21, which tightens its connection with the PM and PSD95. ***D***, αSyn homeostasis. αSyn inclusions retain cytosolic ERα, which reduces levels of palmitoylated ERα at the PM. αSyn also reduces MAP6 palmitoylation, disrupting vesicle trafficking. On the other hand, increasing palmitoylation of Syt-11, a vesicle protein that can alter membrane curvature, prevents αSyn inclusion formation by promoting its binding to vesicle membranes. ***E***, mHTT aggregation. mHTT palmitoylation is decreased by ZDHHC17 inhibition and APT1 stimulation. This increases its aggregation propensity. Elevated APT1 activity may also contribute to decreased p62 palmitoylation, limiting lysosomal degradation of mHTT aggregates. Inhibition of APT1 activity rescues these phenotypes. ***F***, mSOD mislocalization. Immature mSOD1 (before disulfide bond formation) exhibits increased palmitoylation, which causes its retention in the ER, increasing ER stress. Immature palmitoylated mSOD1 also travels to mitochondria, potentially impairing mitochondrial function. In contrast to mSOD1, the chaperone CCS, required for SOD1 maturation, is less palmitoylated in disease. CCS may direct palmitoylated mSOD1 to mitochondria, again impairing function. Throughout the figure, pathogenic pathways and protein alterations are depicted in red, while modifications that protect are shown in black. Created with BioRender.com.

increased leading to enhanced secretion of the most neurotoxic Aβ species, $Aβ_{42}$ (Urano et al., 2005).

BACE1 undergoes palmitoylation at four juxtamembrane cysteine residues (Cys^{474}, Cys^{478}, Cys^{482}, and Cys^{485}; Thinakaran and Koo, 2008; Vetrivel et al., 2009). Knock-in of a palmitoylation-deficient BACE1 cysteine-to-alanine mutant resulted in a significantly reduced Aβ plaque burden and reduced deficits in spatial working memory and associative learning in 5XFAD mice, a mouse AD model (Andrew et al., 2017). However, the same mutant had no effect on the enzymatic processing of APP in vitro (Vetrivel et al., 2009). Nicastrin and APH-1 are palmitoylated at Cys^{689}, and Cys^{182} and Cys^{245}, respectively (Cheng et al., 2009). Similar to BACE1 mutants, AD transgenic mice overexpressing palmitoylation-deficient γ-secretase subunits exhibited decreased Aβ deposition compared with the ones expressing wild-type subunits (Meckler et al., 2010). Mutation of palmitoylation sites increased degradation of nicastrin and APH-1 polypeptides and reduced their association with LRs, but, again similar to BACE1 mutants, did not modulate γ-secretase processing of APP or other substrates in vitro (Cheng et al., 2009). These results indicate that palmitoylation of BACE1 and γ-secretase subunits does not alter enzymatic activity toward APP per se but may affect Aβ generation by driving changes in the complex interactions between APP, the intermediate cleavage product βCTF, BACE1, γ-secretases, and LRs. Further research is necessary to decipher how palmitoylation affects the intricate relationship between these proteins.

The role of APP palmitoylation and its localization to lipid rafts in Aβ production

APP palmitoylation critically affects Aβ production by directing APP to LRs and bringing it into close proximity to BACE1 and γ-secretase (Cho and Park, 2016). APP is palmitoylated in the

ER lumen at N-terminal Cys^{186} and Cys^{187} (amino acid numbers are based on the ubiquitous isoform APP_{756}), and palmitoylated APP is then specifically enriched in LRs (Fig. 2*A*; Bhattacharyya et al., 2013). Increasing or decreasing APP palmitoylation results in elevated or reduced Aβ production, respectively, intimately linking this modification with the extent of amyloid burden (Song et al., 2022). Palmitoylated APP cysteines reside within the copper-binding domain and are predicted to stabilize domain structure by forming disulfide bonds with Cys^{158} and Cys^{133} (Curtain et al., 2003; Barnham et al., 2003a,b). Interestingly, mutation of these cysteines increased APP palmitoylation and trafficking to LRs, while decreasing APP palmitoylation by mutating Cys^{186} and Cys^{187} caused nearly complete ER retention of APP (Bhattacharyya et al., 2013). This suggests a complex interplay between palmitoylation and disulfide linkages within APP, which determines APP ER exit and LR enrichment. Notably, APP localization to LR membranes and its cleavage by BACE1 are further determined by its dimerization status (C-D. Chen et al., 2006; Kienlen-Campard et al., 2008; Ben Khalifa et al., 2012; Isbert et al., 2012; Bhattacharyya et al., 2016).

The physical association between the ER and mitochondria, also known as LR-like mitochondria-associated membranes (MAMs) act as factories for Aβ production, as they contain APP alongside with BACE1 and γ-secretase components (Fig. 2*A*; Area-Gomez et al., 2009; Del Prete et al., 2017; W. Yu et al., 2021). The number of MAMs is increased in both fibroblasts and postmortem brains of familial and sporadic AD patients, suggesting early and sustained MAM alterations that provide a platform for accelerated APP processing (Area-Gomez et al., 2012; Schon and Area-Gomez, 2013; Leal et al., 2020). Interestingly, palmitoylation increases APP targeting to MAMs, which further enhances production of Aβ (Bhattacharyya et al., 2021). Reducing MAM levels by targeting the MAM-resident sigma-1 receptor (S1R) attenuated BACE1-dependent cleavage of palmitoylated APP, while upregulating MAMs promoted trafficking of palmitoylated APP to the cell surface, BACE1 cleavage, and Aβ generation (Bhattacharyya et al., 2021). Interestingly, regulating MAM levels specifically altered Aβ generation in neuronal processes and axons, but not in cell bodies (Bhattacharyya et al., 2021). The reason for this remains debatable. APP, BACE1, and the catalytic γ-secretase component presenilin 1 are believed to be cotransported along axons via a direct interaction with kinesin-1 (Kamal et al., 2001; Cirrito et al., 2008), suggesting amyloidogenic cleavage of APP during axonal transport that might be accelerated by MAMs. However, another study could not confirm these findings (Lazarov et al., 2005). Hence, further research is needed to clarify the mechanisms of Aβ production and transport in axons. Abnormal accumulation of APP and Aβ in axons is a consequence of the brain's response to axonal injury, such as found in traumatic brain injury (X. H. Chen et al., 2009; Johnson et al., 2013; Washington et al., 2014). Trauma-induced changes to LR domains could lead to accelerated APP processing, potentially contributing to pathology (Ehehalt et al., 2003). Whether the increase in axonal production and aggregation of Aβ after traumatic brain injury follows similar mechanisms as in AD and results in comparable long-term consequences remains to be determined. Deciphering the implications of MAM changes for AD development may lead to novel therapeutic approaches. In fact, there is precedence for MAMs to be targetable for therapy. Several pharmaceutical compounds and natural products that modulate MAM stability are undergoing preclinical and clinical studies to treat diseases such as metabolic disorders and cancer (Magalhães Rebelo et al., 2020). These may be applicable to AD as well.

Palmitoylation and impaired Ca^{2+} homeostasis in AD

A key factor of AD pathology caused by Aβ and, in turn, affecting Aβ production is the disturbance of intracellular Ca^{2+} levels (Khachaturian, 1989; Green et al., 2008). Aβ causes cytosolic Ca^{2+} overload leading to increased mitochondrial Ca^{2+} levels, which successively drive Aβ deposition and neuronal death (Calvo-Rodriguez et al., 2020). The mechanism underlying the accelerated Ca^{2+} influx into mitochondria is not clear, but there is reason to believe that palmitoylation is involved. Homeostatic Ca^{2+} levels are maintained by the sarco/ER Ca^{2+} ATPase (SERCA) isoform SERCA2b, which localizes to MAMs and pumps cytosolic Ca^{2+} into the ER (Britzolaki et al., 2018). There is evidence that SERCA2b activity is disturbed in AD and restoring SERCA activity by positive allosteric modulators offers protection against Aβ neurotoxicity and cognitive decline in an AD mouse model (Krajnak and Dahl, 2018; Dahl et al., 2023). SERCA2b activity is bidirectionally and palmitoylation-dependently regulated by calnexin and thioredoxin-related transmembrane protein (TMX1; Raturi et al., 2016; Gutiérrez et al., 2020). Both proteins undergo palmitoylation in the ER lumen, which targets them to MAMs (Lynes et al., 2012). There, palmitoylated calnexin binds to SERCA2b, which promotes Ca^{2+} flux toward the ER (Lynes et al., 2013). Palmitoylation of TMX1, on the other hand, increases its affinity for SERCA2b, which leads to dissociation of calnexin and redirection of Ca^{2+} flux into mitochondria (Gutiérrez and Simmen, 2018). Hence, the tight control of calnexin and TMX1 palmitoylation appears paramount for maintaining Ca^{2+} homeostasis, and it is reasonable to speculate that its disturbance is involved in modified SERCA activity and mitochondrial Ca^{2+} overload in AD. While this still needs to be confirmed, restoring calnexin and/or TMX1 palmitoylation might be an effective way to reinstate Ca^{2+} homeostasis in AD.

Palmitoylation of synaptic proteins and Aβ toxicity

One of the earliest pathological changes in the brains of AD patients is the loss of synapses (DeKosky and Scheff, 1990; Masliah et al., 2001). The molecular pathways preceding synaptic loss are still unclear, but mounting evidence suggests that loss of postsynaptic density protein 95 (PSD95) is one of the first events, as it is significantly depleted in the brains of AD patients and in neurons exposed to Aβ (Fig. 2*B*; Gylys et al., 2004; Almeida et al., 2005). PSD95 requires palmitoylation to remain at synapses and is undergoing continuous palmitoylation/depalmitoylation cycles that are essential for its synaptic clustering as well as that of AMPA receptors (A. E. El-Husseini et al., 2000; Bats et al., 2007; Jeyifous et al., 2016). ABHD17 enzymes, existing as isoforms a, b, and c, are known to catalyze palmitate removal from membrane-anchored proteins and were recently identified as the physiological depalmitoylating enzymes regulating PSD95 palmitoylation cycles in neurons (Yokoi et al., 2016). Palmostatin B, a chemical inhibitor of these enzymes and several other protein depalmitoylases, effectively increased PSD95 palmitoylation as well as the size of PSD95 clusters (Fig. 2*B*; Jeyifous et al., 2016). Importantly, this drug also reversed Aβ-induced synaptic depression in hippocampal slices and rescued spine density impairments (Dore et al., 2021). While these effects could be in part due to increased palmitoylation of other proteins, palmostatin B did not rescue Aβ-induced synaptic depression in slices from PSD95-KO mice, indicating a clear role of palmitoylated PSD95 in maintaining synapses in the presence of Aβ (Dore et al., 2021). PSD95 is one of the most abundant postsynaptic proteins, with ∼300 molecules present in each dendritic spine

(Sheng and Kim, 2011); therefore, it is regulated in many different ways including palmitoylation, *S*-nitrosylation, phosphorylation, ubiquitination, and protein–protein interactions (Vallejo et al., 2017). *S*-Nitrosylation, a posttranslational modification also occurring on cysteine residues, is thought to be implicated in the pathogenesis of AD (Zhao et al., 2015). Interestingly, as PSD95 interacts with neuronal nitric oxide synthase (nNOS), it can be *S*-nitrosylated on Cys^3 and Cys^5, the same residues that undergo palmitoylation (Ho et al., 2011). *S*-Nitrosylation of PSD95 inhibits its clustering as well as the one of the GluA2 AMPA receptor subunit, as it competes with its palmitoylation (Ho et al., 2011). In addition to *S*-nitrosylation, binding of calmodulin during long-term synaptic depression has been found to reduce PSD95 palmitoylation, leading to its removal from synapses (Chowdhury and Hell, 2019). Accordingly, PSD95 palmitoylation was increased during synaptic potentiation and homeostatic scaling (Shen et al., 2022). All these studies are in agreement with palmitoylated PSD95 maintaining synaptic strength and nonpalmitoylated PSD95 leading to synaptic vulnerability.

It is estimated that ∼48% of synaptic proteins undergo palmitoylation (Sanders et al., 2015; Petropavlovskiy et al., 2021); therefore numerous synaptic proteins other than PSD95 are palmitoylated as well. PSD93, a postsynaptic scaffolding protein very similar to PSD95, contains two palmitoylation sites at its N-terminus (Matt et al., 2019). Not much is known about the regulation of PSD93 palmitoylation during synaptic plasticity or neurodegeneration; however, its overexpression rescued deficits in APP/PS1 mice, an AD mouse model (L. Yu et al., 2017). SAP97, another palmitoylated postsynaptic scaffolding protein (Matt et al., 2019), was shown to promote α-secretase–mediated cleavage of APP (Marcello et al., 2007), which could be beneficial against AD. Palmitoylation of AKAP79/150, a scaffolding protein interacting with kinases and phosphatases to control AMPA receptor trafficking, is essential for LTP involving calcium-permeable AMPA receptors (Purkey et al., 2018). Interestingly, Aβ promoted the removal of these specific calcium-permeable AMPA receptors and impaired LTP by affecting local AKAP150-calcineurin signaling (Sanderson et al., 2021). All four different subunits of AMPA receptors themselves are palmitoylated at sites after transmembrane domains 2 and 4 (Matt et al., 2019), but to our knowledge, there is no information about how Aβ might affect this palmitoylation. However, it was found that homeostatic scaling by TTX application did increase GluA1 and GluA2 palmitoylation (Shen et al., 2022). The GluN2 subunits of NMDA receptors, mGluR5, and the γ2 subunit of $GABA_A$ receptors are also palmitoylated, but their palmitoylation is quite stable compared with PSD95 (Yokoi et al., 2016), suggesting less alterations in diseases like AD.

Palmitoylation and Tau toxicity

Besides Aβ accumulation, another hallmark of AD pathology is abnormally modified and aggregated microtubule-binding protein Tau (Chang et al., 2021; Samudra et al., 2023; Sexton et al., 2024). In neurons, Tau normally resides in axons but in pathological states travels to somatodendritic compartments, where it disrupts function (Hoover et al., 2010; C. Li and Götz, 2017; A. Ittner and Ittner, 2018). While there is no evidence to date that Tau itself is palmitoylated in disease, global increases in palmitate levels cause Tau mislocalization and toxic aggregation through promoting its phosphorylation and acetylation (Patil and Chan, 2005; García-Cruz and Arias, 2024). This underscores the potential of palmitate to induce Tau-associated biochemical changes similar to those observed in AD and might explain why excessive intake of saturated fatty acids increases the AD risk (Livingston et al., 2020; Fan et al., 2023).

Another link of palmitoylation to Tau toxicity involves the tyrosine kinase Fyn (Fig. 2*C*; Lee et al., 2004; Briner et al., 2020; Tang et al., 2020). Under physiological conditions, low levels of postsynaptic Fyn and Tau associate with PSD95 and the NMDA receptor, which regulates NMDA receptor-dependent synaptic plasticity (Tezuka et al., 1999; Nakazawa et al., 2001). In disease, however, Fyn enhances Tau hyperphosphorylation, and missorted Tau delivers more Fyn to the postsynapse, inducing excitotoxicity by binding to PSD95 (Fig. 2*C*; Lee et al., 2004; L. M. Ittner et al., 2010; Miyamoto et al., 2017; Park et al., 2020). Interestingly, the PSD95–NMDA receptor–Fyn–Tau axis is also heavily involved in Aβ excitotoxicity (L. M. Ittner et al., 2010; Roberson et al., 2011; Um et al., 2012) establishing a connection between Aβ toxicity, Tau pathology, and Fyn kinase activity (Haass and Mandelkow, 2010; L. M. Ittner and Götz, 2011). Fyn is palmitoylated at the N-terminus by the PAT ZDHHC21 (Koegl et al., 1994; Mill et al., 2009; Sato et al., 2009; Gottlieb-Abraham et al., 2016), which is required for its anchoring to synaptic membranes (Xia and Götz, 2014). Recent evidence suggests that ZDHHC21 activity and Fyn hyperpalmitoylation is part of AD pathology (Fig. 2*C*; W. Li et al., 2023). A gain-of-function variant, pT209S, in the ZDHHC21 gene was identified in a family with familial AD and further characterized in a mouse model where it enhanced Fyn palmitoylation and membrane association, excitotoxicity, synaptic dysfunction, and Tau pathology (W. Li et al., 2023). It is worth noting that ZDHHC21 gain-of-function also increased palmitoylation of another target, APP (Bhattacharyya et al., 2013), possibly contributing to Aβ production and further promoting AD pathology (W. Li et al., 2023). Pharmacological suppression of palmitoylation by 2-bromopalmitate (2-BP) and cerulenin mitigated the synaptic impairment in ZDHHC21 mutant neurons, suggesting that correcting the palmitoylation deficit could serve as therapeutic strategy for AD treatment (W. Li et al., 2023).

Palmitoylation in PD

PD is a devastating neurodegenerative disease that remains incurable at present. Despite advances in understanding its pathogenesis and epidemiology, the ultimate causes leading to the development of PD are unknown (Tolosa et al., 2021). The origin of PD is considered multifactorial, with environmental and genetic factors playing key roles in its pathogenesis (Tolosa et al., 2021). To date, mutations in 23 genes (PARK genes) are known to cause familial PD, accounting for 10–15% of cases. In addition to PARK genes, ∼100 genetic risk loci have been identified (Nalls et al., 2019). Here, we will review how palmitoylation affects the function of some of the proteins encoded by PD-related genes, including α-synuclein (αSyn) and DJ-1. In addition, a role of palmitoylation in dopamine (DA) regulation, which is severely impaired in PD (Ye et al., 2023), will be discussed.

The role of palmitoylation in αSyn homeostasis

PD is among the group of neurodegenerative disorders known as "synucleinopathies," which exhibit a common defining pathology: the Lewy body (LB), a cytoplasmic inclusion rich in the neuronal protein αSyn. αSyn has a central causative role in PD. Point mutations, duplication, and triplication of the SNCA gene, encoding αSyn, cause rare familial forms of PD (Polymeropoulos et al., 1997; Singleton et al., 2003; Chartier-Harlin et al., 2004). Moreover, certain single-nucleotide polymorphisms that drive

increased expression of αSyn are associated with increased risk of PD in the general population (Soldner et al., 2011). Dysregulation of αSyn causes pathogenic alterations in diverse molecular pathways, an important one being vesicle trafficking (Oliveira et al., 2021), which is also heavily regulated by palmitoylation. Here, we review recent work supporting a connection between palmitoylation and αSyn-dependent changes in vesicle trafficking.

Pathologic αSyn disrupts vesicle trafficking both in the soma and at the synapse (Nemani et al., 2010; Mazzulli et al., 2011; Chung et al., 2013; Busch et al., 2014; Román-Vendrell et al., 2021; Stojkovska et al., 2022). The mechanism by which αSyn mediates these toxic effects likely relates to its transient membrane-binding property via its amphipathic helix, which forms when in contact with curved vesicle membranes (Davidson et al., 1998; Dettmer, 2018) and is disturbed in disease (Perlmutter et al., 2009; Dettmer et al., 2017; Fonseca-Ornelas et al., 2021; Román-Vendrell et al., 2021). Interestingly, the alkyl chains of palmitoylated proteins exhibit a similar preference for curved membranes as the amphipathic helix of αSyn (Hatzakis et al., 2009). Through this, palmitoyl moieties act as both sensors and inducers of membrane curvature (Hatzakis et al., 2009), which facilitates vesicle budding and anterograde trafficking (Ernst et al., 2018), processes that are also supported by physiologic αSyn but impaired by pathologic αSyn (Cooper et al., 2006; Gitler et al., 2008). In addition, palmitoylation regulates membrane targeting of key vesicle proteins, such as SNAP25, that work in conjunction with αSyn to ensure proper synaptic vesicle dynamics and fusion (Hess et al., 1992). Again, these processes are disrupted by pathologic αSyn (Román-Vendrell et al., 2021).

Although αSyn itself is not palmitoylated (it has no cysteines), the above observations speak to a connection between palmitoylation and synucleinopathy and are consistent with reduced palmitoylation being a potential culprit. This hypothesis was tested by increasing palmitoylation through targeting the APT1 depalmitoylase in cells expressing the αSyn "3K" mutant (E35K + E46K + E61K), which is an "amplified" version of the familial E46K PD mutation that readily forms cytoplasmic inclusions in cells (Dettmer et al., 2015) and causes a robust PD-like phenotype in mice (Nuber et al., 2018). Inhibition of APT1 with the specific inhibitor ML348 (Adibekian et al., 2012) and APT1 knockdown both reduced αSyn-3K inclusions in neuroblastoma cells and rat neurons, suggesting a potential benefit (Ho et al., 2021). Furthermore, in iPSC-derived induced neurons, APT1 inhibition and knockdown reduced αSyn phosphorylation at serine 129 ($pSer^{129}$; Ho et al., 2021), a widely used marker of αSyn dyshomeostasis (Anderson et al., 2006). Importantly, these findings extended to animals. A mouse model of PD expressing transgenic αSyn-3K has been used extensively to study αSyn homeostasis and test potential therapeutics (Nuber et al., 2018, 2021; Glajch et al., 2021). In this model, oral treatment with ML348 was shown to be brain penetrant and, as in cell models, reduced levels of $pSer^{129}$ αSyn (Moors et al., 2023). Furthermore, treatment with ML348 improved performance on behavioral measures testing both PD-like motor impairments and cognitive functions (Moors et al., 2023).

So far, two distinct APT1 substrates involved in vesicle trafficking, estrogen receptor alpha (ERα), and microtubule-associated protein 6 (MAP6; Hart et al., 2007; Waites et al., 2021), were proposed to mediate these effects (Fig. 2*D*). Treatment of αSyn-3K transgenic mice with the APT1 inhibitor ML348 increased palmitoylation and PM association of ERα and alleviated the hippocampal LTP deficits apparent in symptomatic mice (Moors et al., 2023). This was partially blocked by the ERα antagonist methyl-piperidino-pyrazole, suggesting that at least part of the APT1 inhibition-dependent rescue was mediated by palmitoylated ERα. MAP6 is a bona fide substrate of APT1 as its palmitoylation was substantially increased in APT1 knock-out brains (Won and Martin, 2018). MAP6 palmitoylation was reduced in iPSC-derived neurons from patients carrying an αSyn gene triplication, possibly by increasing palmitate turnover on MAP6 (Ho et al., 2021). This suggests an αSyn-dependent MAP6 palmitoylation deficit in PD that APT1 inhibition might compensate for. Along these lines, MAP6 overexpression, like APT1 inhibition, decreased αSyn-3K inclusions (Ho et al., 2021). Together, these data support a role of palmitoylation in αSyn pathology and the vesicle trafficking deficits seen in synucleinopathies, and show that restoring palmitoylation may be used as an approach to counteract these effects. However, critical gaps remain in our knowledge of how APT1-mediated palmitoylation, αSyn pathology, and vesicular trafficking are connected. For example, we lack a comprehensive, unbiased investigation of APT1 brain substrates, which could further increase our understanding of the functional connection between APT1 and αSyn. Furthermore, how αSyn affects the palmitoyl-proteome and APT1 activity remains unknown. Finally, beyond APT1 substrates, there are likely other palmitoylated proteins which modulate αSyn homeostasis in distinct ways. For example, synaptotagmin-11, encoded by the PD risk gene SYT11, was recently shown to reduce physiologic αSyn tetramers in a palmitoylation-dependent manner (Fig. 2*D*; Ho et al., 2023). Addressing these points will be an important area of future study.

Palmitoylation of proteins encoded by other PD-related genes

Palmitoylation of proteins encoded by PARK genes and risk genes associated with PD has not been extensively investigated, but there is evidence of some PARK proteins being modified with palmitate. For example, the protein encoded by the PARK7 gene, DJ-1, is palmitoylated (Kim et al., 2013). DJ-1 binds to membrane-associated LRs in astrocytes and neurons, which requires the palmitoylation of three cysteine residues (Cys^{46}, Cys^{53}, and Cys^{106}; Kim et al., 2013). The findings in this study indicate that the association of DJ-1 with LRs is essential for LR-dependent endocytosis in astrocytes. As astrocytes support neuronal survival, the authors hypothesized that dysfunctional astrocytes, impaired in LR-dependent signaling pathways due to alterations in the palmitoylation of DJ-1, may contribute to the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc; Kim et al., 2013). Furthermore, indirect evidence using palmitoylation inhibitors in cultured cells indicates that leucine-rich repeat kinase 2 (LRRK2), encoded by PARK8, may undergo palmitoylation, potentially influencing its dimerization and function (Schapansky et al., 2014). Finally, the PD protein ubiquitin C-terminal hydrolase L1 (UCHL-1), encoded by PARK5, and the PD risk factor lysosomal acid glucosylceramidase (GBA1) were detected in the palmitoyl-proteome obtained from human cell lines (Serwa et al., 2015; Won and Martin, 2018; Zhou et al., 2019), but their palmitoylation has not been further validated.

Showing that palmitoylation alterations also occur in human PD tissue, Cervilla and colleagues identified changes in palmitoylation of 84 proteins in the cortex of PD patients compared to control subjects (Cervilla-Martínez et al., 2022). Among these, 33 proteins were more palmitoylated, and 51 were less palmitoylated in PD patients. These modifications were predicted to affect functions related to the cytoskeleton, mitochondria, fibrinogen, oxidative stress, inflammation, as well as cell survival. Notably,

when the authors analyzed the most significant biofunctions putatively influenced by these palmitoylation changes, PD molecular pathways emerged as the most impacted (Cervilla-Martínez et al., 2022). It is noteworthy that global changes in protein palmitoylation are also detected in patients with neuronal ceroid lipofuscinosis, another neurodegenerative disorder (Henderson et al., 2016). These findings suggest that altered protein palmitoylation could either play a central causative role in the pathophysiology of neurodegenerative diseases, including PD, or be a consequence of the pathological changes associated with neurodegeneration. Regardless, exploring protein palmitoylation, whether as a biomarker or a pathological mechanism, presents an intriguing avenue of research in the field of PD.

The role of palmitoylation in dopaminergic neurotransmission

PD is characterized by the loss of dopaminergic neurons from the SNpc that innervate the striatum. The neurodegenerative process leads to a DA deficit in the nigrostriatal pathway, which plays a crucial role in movement control, resulting in the main motor manifestations of PD (Ye et al., 2023). Current treatment focuses on alleviating these motor symptoms through DA replacement therapy, primarily by carbidopa/levodopa and dopaminergic agonists (Connolly and Lang, 2014). However, long-term pharmacological treatment can lead to debilitating dyskinesias in some patients (Church, 2021). Therefore, enhancing our understanding of DA regulation and signaling could help PD therapy by finding novel ways to increase DA production or release in surviving SNpc neurons. Studies have shown that the DA transporter (DAT) is palmitoylated, and defects in its palmitoylation reduce the transporter's stability and function (Foster and Vaughan, 2011; Moritz et al., 2015; Rastedt et al., 2017; Bolland et al., 2019). Additionally, palmitoylation is involved in regulating DAT subcellular localization, binding partner interactions, and dimerization (Zeppelin et al., 2021; Shetty et al., 2023). At least five PATs, ZDHHC2, 3, 8, 15, and 17, target DAT for palmitoylation in vitro (Bolland et al., 2019). Other palmitoylated proteins involved in DA signaling and/or metabolism include DA receptors 1–4 and G-protein α subunits (Linder et al., 1993; Ng et al., 1994a,b; Tsutsumi et al., 2009; Kong et al., 2011; Zhang et al., 2016; Zhang and Kim, 2016). Palmitoylation of DA receptors regulates their protein levels, trafficking, and/or signaling (Linder et al., 1993; Ng et al., 1994a,b; Kong et al., 2011; Zhang et al., 2016; Zhang and Kim, 2016), while palmitoylation of G-protein α subunits controls their association with discrete locations at the PM (Wedegaertner and Bourne, 1994; Marrari et al., 2007).

Mice deficient in the PAT ZDHHC15 (ZDHHC15-KO) exhibited reduced striatal DA content when encountering a novel environment, suggesting that ZDHHC15-mediated palmitoylation represents a novel regulatory mechanism of DA in the striatum in vivo (Mejias et al., 2021). The molecular mechanisms responsible for this phenotype are unclear, as no differences in the palmitoylation levels of known ZDHHC15 substrates, including DAT, were found in the striatum of ZDHHC15-KO mice. Psychostimulant drugs like methylphenidate and amphetamine are recognized for their ability to alter DA release and reuptake at synapses (Faraone, 2018). Administration of either of these drugs significantly increased locomotion and extracellular DA levels in the ventral striatum of ZDHHC15-KO mice compared to controls, suggesting changes in DA release and/or synaptic clearance in the ventral striatum of KO mice that are controlled by palmitoylation (Mejias et al., 2021). Further research is needed to investigate how alterations in palmitoylation affect the dopaminergic system in general and how ZDHHC15 is involved in this regulation. Since PD is characterized by a deficit of striatal DA, it would be intriguing to know whether manipulation of ZDHHC15 palmitoylation or activity could serve as a novel therapeutic target to enhance DA signaling in PD patients.

Palmitoylation in HD

HD is a progressive monogenic neurodegenerative disease caused by a dominantly inherited CAG repeat that encodes for a polyglutamine expansion in the N-terminus of the huntingtin (HTT) protein, giving rise to mutant HTT (mHTT; MacDonald et al., 1993). Partial penetrance occurs with 36–39 CAG repeats, but it is fully penetrant when the expansion reaches 40 or more repeats (Kay et al., 2016). Furthermore, CAG repeat length is inversely correlated with age at disease onset (Snell et al., 1993; Langbehn, 2022). Although HTT is ubiquitously expressed throughout the body, the striatum is predominantly degenerated in HD, but other brain regions are affected at later stages (Ghosh and Tabrizi, 2018). Wild-type HTT has emerged as an important scaffolding protein that impacts many cellular processes including vesicle trafficking, basal autophagy, and synaptic function (Rui et al., 2015; Martin and Hayden, 2017; Barron et al., 2021). mHTT loses these properties and tends to aggregate and mislocalize to intranuclear inclusion bodies (Tabrizi et al., 2020). This chapter will discuss how palmitoylation partakes in the regulation of mHTT toxicity.

The role of palmitoylation in HTT aggregation

The HTT protein is palmitoylated on Cys^{214} (Yanai et al., 2006), as well as Cys^{105}, Cys^{433}, Cys^{3134}, and Cys^{3144}, with more sites still predicted (Lemarié et al., 2023). mHTT exhibits decreased palmitoylation, which is inversely correlated to polyQ length (Lemarié et al., 2021), and increases mHTT aggregation and toxicity (Yanai et al., 2006). HTT is palmitoylated by the PATs ZDHHC17 and 13 and depalmitoylated by APT1 and 2 (Yanai et al., 2006; Singaraja et al., 2011; Lin and Conibear, 2015; Lemarié et al., 2023; Martin and Sanders, 2024). mHTT palmitoylation deficits in HD have been associated with increased APT1 and decreased ZDHHC17 activities (Fig. 2*E*; Yanai et al., 2006; Virlogeux et al., 2021). Inhibiting depalmitoylation of mHTT is protective in multiple HD models and patient cell lines (Fig. 2*E*; Lemarié et al., 2021; Virlogeux et al., 2021). The broad depalmitoylation inhibitor palmostatin B, targeting APT1, APT2, and some ABHD enzymes (Lin and Conibear, 2015), increased mHTT palmitoylation and solubility (Lemarié et al., 2021). Administration of the specific APT1 inhibitor ML348 had protective effects in the CAG140 knock-in mouse model of HD (Virlogeux et al., 2021), although HTT palmitoylation was not measured in this case. Chronic infusion of ML348 for 1 month in 7-month-old mice improved motor coordination, anxiety-, and depression-related behaviors, restored synapse number, and reduced mHTT nuclear accumulation, but did not improve exploratory behavior in the open-field test (Virlogeux et al., 2021). In human HD iPSC-derived cortical neurons, ML348 increased brain-derived neurotrophic factor (BDNF) trafficking and release at the synapse (Virlogeux et al., 2021). Beneficial effects of promoting total palmitoylation were linked to the restoration of BDNF axonal trafficking (Virlogeux et al., 2021). Protective effects were likely also mediated by increased mHTT solubility and clearance (Lemarié et al., 2021), which may be linked to increased mHTT lysosomal degradation directed by p62 palmitoylation (Fig. 2*E*). p62 (also known as

sequestosome-1, SQSTM1) is a major autophagy receptor required for targeting autophagic cargo, including aggregated proteins, to the autophagosome for degradation by the lysosome. In HD, there is an autophagosomal cargo loading defect associated with an increase in a toxic buildup of cellular waste (Martinez-Vicente et al., 2010; Walter et al., 2016). p62 was recently shown to be palmitoylated and is also substrate of APT1 (Huang et al., 2023). Subsequently, the Martin Lab found that p62 palmitoylation is significantly decreased in the brains of HD patients and in HD mouse models (Abrar et al., 2023). Therefore, ML348 may also correct p62 palmitoylation in HD, which is predicted to direct mHTT for degradation through enhanced autophagy. Of note, mutations in p62 are intimately linked to ALS and frontotemporal dementia (FTD; Van Der Zee et al., 2014). Thus, palmitoylation of p62 may provide a therapeutic link between HD, FTD, and ALS.

Palmitoylation in Amyotrophic Lateral Sclerosis

ALS is a devastating neurodegenerative disease that primarily targets motor neurons (Masrori and Van Damme, 2020). Patients typically succumb to this unrelenting disease within 3–5 years after onset, most commonly due to respiratory failure, or complications thereof caused by motor neuron degeneration. Generally speaking, ALS can be subdivided into familial (fALS) and sporadic (sALS). While the majority of ALS cases are sporadic, >30 genes have been implicated in fALS, many of which overlap with sALS (Cirulli et al., 2015; R. Chia et al., 2018). This section will review the impact of palmitoylation on the function of antioxidant Cu, Zn-superoxide dismutase 1 (SOD1), thus far the only protein reported to be modified with palmitate in ALS models (Antinone et al., 2013, 2017).

The role of palmitoylation in SOD1 function and localization

SOD1 is a ubiquitously expressed homodimeric metalloenzyme that converts superoxide to hydrogen peroxide and oxygen, and mutations in SOD1 were first linked to fALS in 1993 (Rosen et al., 1993). In vitro studies in HEK293 cells showed that SOD1 palmitoylation at Cys^{6} is more prevalent in fALS-linked SOD1 mutants A4V, G93A, and G85R (mSOD) than in wild-type SOD1 (Antinone et al., 2013). The predominant palmitoylated species was the immature form of mSOD1 (Antinone et al., 2013, 2017), which suggested that palmitoylation may target immature SOD1 to mitochondria and potentially affect mitochondrial function (Fig. 2*F*). Alternatively, palmitoylated mSOD1 might be directed to the ER where it has been found to aggregate and contribute to ER stress (Fig. 2*F*; Antinone et al., 2013). Like other enzymes linked to ALS, many SOD1 mutations maintain full enzymatic activity, suggesting that pathogenesis is not directly related to a loss-of-function of its SOD activity (Reaume et al., 1996; Antinone et al., 2013). Instead, there may be a loss-of-function or toxic gain-of-function due to mislocalization (Antinone et al., 2013; Masrori and Van Damme, 2020), which may partly be caused by palmitoylation changes.

In a follow-up study, the authors found that mSOD1 was also palmitoylated on Cys^{57} and Cys^{146}, which are involved in disulfide bond formation in mature SOD1 (Antinone et al., 2017). In human patient spinal cords, endogenous SOD1 palmitoylation was relatively low overall but detectably higher in ALS patients compared with that in non-ALS subjects (Antinone et al., 2017). The difficulty in detecting endogenous palmitoylated SOD1 may be attributed to heterodimers between SOD1 and copper chaperone of SOD1 (CCS). CCS facilitates SOD1 maturation by catalyzing copper acquisition and disulfide bond formation (Reaume et al., 1996; Antinone et al., 2017). CCS is also palmitoylated, but its levels decrease in ALS patient spinal cords compared with those in controls (Fig. 2*F*; Antinone et al., 2017). It was suggested that the palmitoylated mSOD1-CCS heterodimer may represent a long-lived maturation intermediate that is targeted to membranes (Fig. 2*F*; Antinone et al., 2017). However, the overall role of palmitoylation of mSOD1 and CCS in ALS remains unclear.

Palmitoyl-proteomic studies revealed that neurodegenerative diseases, in particular TDP43-proteinopathies such as ALS and FTD, are associated with a significant enrichment of palmitoylated proteins and that, in addition to mSOD1, more proteins encoded by ALS-linked genes are palmitoylated (Blanc et al., 2015; Sanders et al., 2015). While in need of verification, this indicates that palmitoylation may be a common mechanism to regulate localization of proteins linked to ALS. Consequently, palmitoylation may be an untapped area of research that could reveal how ALS proteins mislocalize and aggregate. As more proteins, like SQSTM1/p62 (Abrar et al., 2023; Huang et al., 2023) and myelin-associated oligodendrocytic basic protein (MOBP) (Wild et al., 2022), are confirmed, it will be important to characterize their palmitoylation in disease contexts.

Challenges and Perspectives

Accumulating evidence indicates that defects in protein palmitoylation are associated with a wide range of brain abnormalities leading to childhood- and adult-onset neurological and neurodegenerative disorders (Vesa et al., 1995; Yanai et al., 2006; Mukai et al., 2008; Singaraja et al., 2011; Antinone et al., 2013, 2017; Bhattacharyya et al., 2013; Sutton et al., 2013; Dore et al., 2021; Lemire et al., 2021; Cervilla-Martínez et al., 2022; Ho et al., 2023; Lemarié et al., 2023; W. Li et al., 2023). Thus, correction of abnormal palmitoylation may be a viable option for therapeutic intervention for these conditions. The attachment and cleavage of palmitic acid to and from target proteins is dynamically mediated by PATs and depalmitoylase (Abazari et al., 2023), which therefore present attractive targets for modifying protein palmitoylation by either pharmacological intervention or gene therapy. That this is a viable option shows the example of infantile neuronal ceroid lipofuscinosis, a devastating childhood neurodegenerative lysosomal storage disease caused by inactivating mutations in the gene encoding the depalmitoylase PPT1 (Vesa et al., 1995). Current preclinical and clinical trials suggest that either mimicking the depalmitoylation capacity of PPT1 by the depalmitoylation agent N-(tert-butyl) hydroxylamine or replacing the defective variant by gene therapy might successfully treat this condition (Sarkar et al., 2013; Rosenberg et al., 2019; Fyke et al., 2024). As described in previous chapters, altering depalmitoylase enzymatic activities also showed promising results in AD, PD, and HD preclinical models (Dettmer et al., 2015; Dore et al., 2021; Ho et al., 2021; Lemarié et al., 2021; Virlogeux et al., 2021; Moors et al., 2023). However, before we can seriously consider altering palmitoylation as a therapeutic avenue for neurodegenerative diseases, we need to further increase our understanding of how palmitoylation affects neuronal proteins in adult-onset neurodegeneration and find better ways of specifically addressing the palmitoylation deficits. Unfortunately, several factors significantly complicate research and targeting of palmitoylation for these conditions.

Despite methodological and technical advances over the last decade, the detection of protein palmitoylation remains challenging and labor-intense, relying on radiolabels, multistep click-

chemistry or biotin- and PEG-labeling methodologies that do not allow for capturing the dynamics of palmitoylation (Gao and Hannoush, 2018; Zaręba-Kozioł et al., 2018; Main and Fuller, 2022). New label-free and high temporal- and spatial-resolution imaging–based methods are necessary to investigate palmitoylation dynamics in vivo in cells or tissues. In addition, high-throughput methods that allow for unbiased discovery of palmitoylation changes in the whole-brain proteome should be further improved and employed.

The mechanism of action and substrate specificity of PATs and depalmitoylases remains poorly understood, complicating the identification and analysis of relevant proteins. PATs undergo autopalmitoylation and/or activation through palmitoylation by other PAT family members before their cognate substrate is palmitoylated, introducing an additional level of complexity (Roth et al., 2002; Jennings and Linder, 2012; Rana et al., 2018). In addition, many neuronal proteins are palmitoylated by multiple PAT members, e.g., PSD95 by ZDHHC2, 3, 8, and 15 (M. Fukata et al., 2004; Mukai et al., 2008; Noritake et al., 2009; Ho et al., 2011), or a single PAT palmitoylates many substrates (Cho and Park, 2016), making it difficult to identify PAT–substrate pairs. PAT localization to different organelles also contributes to substrate selectivity (Y. Fukata et al., 2013; Philippe and Jenkins, 2019). Finally, palmitoylation can be influenced by other PTMs, such as *S*-nitrosylation, which competes for the same cysteine residues (Zaręba-Kozioł et al., 2019), as demonstrated for PSD95 (Ho et al., 2011). This interplay between PTMs adds another layer of intricacy to the control of protein function, underscoring the importance of using advanced experimental approaches that consider these interactions.

Reflecting the complexity of the system, there is still a lack of tools and drugs that specifically modulate PAT and depalmitoylase activities and, consequently, palmitoylation of target proteins. PAT activity modification currently is almost exclusively achieved with the broad-spectrum inhibitor 2-BP. However, 2-BP is not selective for individual PATs, and off-target effects make it unsuitable as a therapeutic drug (Zheng et al., 2013; Won and Martin, 2018). In addition, it also affects lipid synthesis and metabolism, inhibits certain depalmitoylases, and shows cytotoxic effects, raising concerns about its use in studying palmitoylation (Mikic et al., 2006; Lanyon-Hogg et al., 2017; Abrami et al., 2021). Recently, an improved version of 2-BP, cyanomyracrylamide, was developed that does not exhibit some of the weaknesses of 2-BP (Azizi et al., 2021). However, it still lacks specificity for a specific PAT. Depalmitoylase inhibitors have a better specificity profile and therefore show higher promise as therapeutic drugs. For example, palmostatin B inhibits both APT1 and 2, while ML348 is specific for APT1 and ML349 for APT2 (Adibekian et al., 2012; Lin and Conibear, 2015; Won et al., 2016). GNS561 is a selective PPT1 inhibitor used in cancer treatment (Brun et al., 2022). However, while it is able to cross the blood–brain barrier (Brun et al., 2022), its efficacy in changing the brain palmitoyl-proteome has not been determined. Further development of highly selective drugs that regulate the palmitoylation/depalmitoylation cycle of specific proteins, particularly in the brain, will accelerate progress toward potential therapies for neurodegenerative diseases.

Finally, research over the past years has made it clear that neurodegeneration exhibits sex and gender differences in disease prevalence and progression (Young et al., 2023). Interestingly, there is also a notable sex difference in brain palmitoylation, which causes differential responses to stress and anxiety in males and females (Hohoff et al., 2019; Meitzen et al., 2019; Kerkenberg et al., 2021; Zaręba-Kozioł et al., 2021). In particular, the PAT ZDHHC7 was demonstrated to palmitoylate brain substrates in a sex-specific manner (Zaręba-Kozioł et al., 2021). Further identification of the intracellular mechanisms regulating palmitoylation in both sexes will be critical for the development of sex-specific therapies for neurodegenerative disorders.

In conclusion, palmitoylation is a unique lipid-based protein modification with steadily increasing links to neurodegenerative conditions, including AD, PD, HD, and ALS. If we can address the current obstacles hindering the effective study and manipulation of palmitoylation, its targeting will increase our understanding of the pathophysiology of these diseases and may be used as an innovative approach to achieve therapeutic goals.

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