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Protein palmitoylation in the development and plasticity of neuronal connections

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Protein palmitoylation, or the reversible addition of the fatty acid, palmitate, onto substrate proteins, can impact the structure and stability of proteins as well as regulate protein–protein interactions and the trafficking and localization of proteins to cell membranes. This posttranslational modification is mediated by palmitoyl-acyltransferases, consisting of a family of 23 zDHHC proteins in mammals. This review focuses on the subcellular distribution of zDHHC proteins within the neuron and the regulation of zDHHC trafficking and function by synaptic activity. We review recent studies identifying actin binding proteins, cell adhesion molecules and synaptic scaffolding proteins as targets of palmitoylation, and examine the implications of activity-mediated palmitoylation in the establishment and plasticity of neuronal connections.

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Introduction

Protein palmitoylation is the most common form of protein *S*-acylation in eukaryotic cells and involves the reversible addition of the fatty acid, palmitate, to cysteine residues of the substrate protein. This lipid modification is mediated by a family of multi-pass transmembrane proteins containing a conserved aspartate-histidine-histidine-cysteine (DHHC) motif required for its palmitoyl-acyltransferase (PAT) activity [1,2]. The DHHC catalytic motif is located within a cysteine-rich, zinc finger-like domain, resulting in the current, standard 'zDHHC' nomenclature. It is important to note that DHHC and zDHHC nomenclatures are not interchangeable, and that some clone numbers initially collected in Fukata *et al.* [3] using the 'DHHC' nomenclature are different from the 'zDHHC' nomenclature. For clarity, the 'zDHHC' nomenclature will be used in this review. To date, 23 mammalian zDHHC proteins have been identified with the majority of them being validated as having PAT function in yeast [4] and in mammalian cells [3]. As palmitoylation is a reversible modification, the enzymes responsible for depalmitoylation are also of great interest to researchers. All palmitoyl-protein thioesterases (PPTs) identified to date contain α/β-hydrolase domains (ABHD proteins) [5]; however, the search for other families of enzymes with PPT activity continues.

Palmitoylation/depalmitoylation cycles vary greatly between substrates [6•,7••,8••,9–11,12••,13]. Rapid palmitate turnover is likely responsible for regulating local, dynamic cellular events such as activity-mediated protein trafficking in neurons [6•,7••,8••,9,11,12••], whereas slower palmitate turnover has been observed in the long-term static targeting of proteins to cell membranes [10,13]. It stands to reason that PATs and PPTs that rapidly palmitoylate/depalmitoylate proteins are localized in close proximity to their substrates including specific subcellular regions within axons and dendrites. In contrast, PATs that mediate the long-term static targeting of proteins to cell membranes are typically localized to the somatic golgi [10,13–15].

Detailed discussion of the palmitoylation of glutamate receptors [16] neuronal kinases [17], and presynaptic vesicle machinery [18] has been reviewed elsewhere. Here we review recent studies identifying actin binding proteins, cell adhesion molecules and synaptic scaffolding proteins as targets of palmitoylation, and discuss how activity-mediated palmitoylation of these substrates can regulate the establishment and plasticity of neuronal connections.

Subcellular localization of zDHHC proteins in neurons

According to the Allen Brain Atlas almost half of all zDHHCs are detectable in the brain [19] (Table 1). Although some PATs, including zDHHCs 5, 9 and 17, are ubiquitously expressed in the brain, a subset of PATs exhibit highly specific expression patterns including high expression of zDHHCs 2 and 7 in CA1 hippocampal pyramidal neurons, and strong expression of zDHHCs 5 and 7 in cerebellar Purkinje cells. Work from the Barres lab has examined zDHHC mRNAs in specific cell types derived from mouse cortical samples, providing a deeper understanding of zDHHC expression in the brain [20] (Table 1).

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Table 1

Localization, known substrates and disease associations of zDHHCs in the brain

zDHHC	Brain expression pattern[a]	Cell type[b]	Subcellular localization[c]	Substrates[d]	Disease associations[e]
zDHHC1	**Medium:** CA1 hippocampus [56]	**Medium:** cortical astrocytes, cortical neurons, stellate/basket cells, corticostriatal neurons **Low:** cortical oligodendrocytes, cortical microglia	**Yeast:** ER **Neurons:** dendrites, early endosomes when overexpressed [24]	Neurochondrin [24]	
zDHHC2	**High:** cortex, CA1 hippocampus [57] **Medium:** hypothalamus, olfactory bulb, pallidum **Low:** striatum	**High:** cortical neurons, cortical oligodendrocyte precursor cells, cortical newly formed oligodendrocytes **Medium:** cortical astrocytes, cortical myelinating oligodendrocytes, cerebellar granule cells, striatal cholinergic neurons, cortical olig2+ oligodendrocytes **Low:** cerebellar olig2+ oligodendrocytes, motor neurons	**Yeast:** ER/Golgi **Neurons:** dendrites; activity dependent movement from shaft to spine after activity blockade [8••,25]	PSD95, SNAP25, SNAP23, eNOS, Fyn, NDE1, NDEL1, CD151, CKAP4, ABCA1, GAP43, Tetraspanins CD9/ CD151, CKAP4/p63	
zDHHC3 (GODZ)		**Medium:** cortical oligodendrocyte precursor cells, cortical endothelial cells **Low:** cortical astrocytes, cortical neurons, cortical newly forming oligodendrocytes, cortical myelinating oligodendrocytes, cortical microglia, cerebellar granule cells, Drd1 medium spiny neurons	**Yeast:** Golgi **Neurons:** somatic golgi [9,25]	PSD95, SNAP25, SNAP23, Gαs, Gαq, Gαi2, CSP, $GABA_A\gamma2$, eNOS, GluA1/2, GAD65, STREX, Fyn, BACE1, NDE1, NDEL1, NCAM140f, CaMKIγ, NR2A/B, Neurochondrin [24]	
zDHHC4		**Medium:** cortiacal neurons, cortical astrocytes, cortical oligodendrocytes, cortical microglia, cortical endothelial cells **Low:** Drd2 medium spiny neurons, striatal cholinergic neurons, motor neurons	**Yeast:** Golgi	BACE1	
zDHHC5	***Ubiquitous Expression.*** **High:** cortex, olfactory bulb, hippocampus, pallidum, thalamus, hypothalamus, pons, medulla, cerebellum (specifically Purkinje cell layer) **Medium:** striatum, midbrain.	**High:** Corticostriatal neurons **Medium:** cortical neurons, cortical oligodendrocyte precursor cells, cortical microglia, cortical endothelial cells **Low:** cortical astrocytes, cortical newly formed oligodendrocytes, cortical myelinating oligodendrocytes, Purkinje cells, stellate/basket cells	**Yeast:** Plasma Membrane **Neurons:** dendrites, excitatory and inhibitory synapses. Activity-dependent movement from PM to recycling endosomes [7••] but others found stronger localization in dendritic shaft [9]	STREX, flotillin-2 [58], GRIP1 [9], δ-catenin [6•], somatostatin receptor 5 [59]	Schizophrenia [51]
zDHHC6	**Low:** cortex, olfactory bulb	**Medium:** cortical oligodendrocyte precursor cells, cortical endothelial cells **Low:** cortical neurons, cortical astrocytes, cortical newly formed oligodendrocytes, cortical myelinating oligodendrocytes, cortical microglia, Drd2 medium spiny neurons, striatal cholinergic neurons, forebrain cholinergic neurons, corticospinal neurons, corticostriatal neurons	**Yeast:** ER	Calnexin [60], Inositol 1,4,5-triphosphate receptor [61]	

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