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SUMO and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and is the most common cause of dementia in the elderly. Histopathologically, AD features insoluble aggregates of two proteins in the brain, amyloid-β (Aβ) and the microtubule associated protein tau, both of which have been linked to the *s*mall *u*biquitin-like *mo*difier (SUMO). A large body of research has elucidated many of the molecular and cellular pathways that underlie AD, including those involving the abnormal Aβ and tau aggregates. However, a full understanding of the etiology and pathogenesis of the disease has remained elusive. Consequently, there are currently no effective therapeutic options that can modify the disease progression and slow or stop the decline of cognitive functioning. As part of the effort to address this lacking, there needs a better understanding of the signaling pathways that become impaired under AD pathology, including the regulatory mechanisms that normally control those networks. One such mechanism involves SUMOylation, which is a post-translational modification (PTM) that is involved in regulating many aspects of cell biology and has also been found to have several critical neuron-specific roles. Early studies have indicated that the SUMO system is likely altered with AD-type pathology, which may impact Aβ levels and tau aggregation. Although still a relatively unexplored topic, SUMOylation will likely emerge as a significant factor in AD pathogenesis in ways which may be somewhat analogous to other regulatory PTMs such as phosphorylation. Thus, in addition to the upstream effects on tau and Aβ processing, there may also be downstream effects mediated by Aβ aggregates or other AD-related factors on SUMO-regulated signaling pathways. Multiple proteins that have functions relevant to AD pathology have been identified as SUMO substrates, including those involved in synaptic physiology, mitochondrial dynamics and inflammatory signaling. Ongoing studies will determine how these SUMO-regulated functions in neurons and glial cells may be impacted by Aβ and AD pathology. Here, we present a review of the current literature on the involvement of SUMO in AD, as well as an overview of the SUMOylated proteins and pathways that are potentially dysregulated with AD pathogenesis.

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Keywords

SUMO; Alzheimer's disease; amyloid; tau; plaques; tangles; neurodegeneration; synaptic plasticity; neurobiology

Alzheimer's Disease

Over one hundred years ago, a German doctor named Alois Alzheimer presented a clinical case detailing a particular patient's cognitive decline, neuropsychological symptoms and peculiar post-mortem brain histopathology (Moller and Graeber 1998). Today, the disease that carries that doctor's name is the most common type of dementia worldwide, affecting more than 35 million people (Mayeux and Stern 2012). The major risk factor for Alzheimer's disease (AD) is advanced age. In the United States, AD is currently the 6th leading cause of death and, due in part to demographic changes, is poised to become one of the major unmet medical needs in the foreseeable future (Alzheimer's 2012).

Alzheimer's disease is a neurodegenerative disorder characterized by the progressive loss of neurons, deposits of insoluble protein and clinical dementia. Sporadic AD may have a number of interrelated causes stemming from genetic predisposition and the impact of environmental factors that trigger other cellular events in the brain. Irrespective of the particular nature of the initiating factor(s), two hallmark histopathological features are the accumulation of amyloid plaques and neurofibrillary tangles (NFTs) (Fig. 1). The plaques contain insoluble extracellular deposits of amyloid-beta (Aβ) protein while NFTs are intracellular structures composed of aggregates of the microtubule-binding protein tau (Holtzman et al. 2011a; Ballard et al. 2011; Serrano-Pozo et al. 2011; Mandelkow and Mandelkow 2012). The combination of these two abnormal aggregation processes leads to extensive neuronal degeneration and cell death – by the end-stages of the disease, there is widespread neuronal loss that is manifested as gross cerebral atrophy in multiple regions of the brain, including the temporal, parietal and frontal lobes (Thompson et al. 2003). On neurochemical and ultrastructural levels, numerous studies have found that neuronal deterioration is the most severe in the hippocampus (Arendt 2009). Cell death is prominent in this region; by disease end-stage, as much as 60–70% of the neurons are lost in parts of the hippocampus, with NFTs in many of the remaining cells (West et al. 1994). It is this neuronal degeneration, in the hippocampus and other cortical regions, that ultimately results in the primary clinical manifestations of AD – cognitive decline, dementia and behavioral changes.

These pathological features have been extensively investigated for their relationships with various post-translational modifications. In particular, the ubiquitin proteasome system (UPS) and, more recently, connections to autophagy have been in focus (Lee et al. 2013). Post-translational conjugation by *s*mall *u*biquitin-like *mo*difiers (SUMO) and the contributions of SUMO-regulated pathways to AD pathology and neuronal physiology have been less widely investigated. However, the involvement of SUMOylation in these fields has been gaining increasing traction in the past several years.

Amyloid-β

Amyloid-β (Aβ) is a small ~4 kDa peptide that was initially identified as the major constituent of the amyloid plaques (Masters et al. 1985). Decades of research have now implicated Aβ as the primary molecular culprit in AD pathogenesis, in what is classically known as the "amyloid cascade hypothesis" (Haass and Selkoe 2007; Holtzman et al. 2011b) (Fig. 1). Aβ is produced through sequential enzymatic cleavages of the amyloid precursor protein (APP). APP is a type I transmembrane protein that contains α-, β- and γ-

secretase cleavage sites. Processing at the α-secretase site releases a large portion of the ectodomain and precludes the formation of Aβ since the cleavage occurs within the Aβ sequence. Alternatively, APP can be cleaved at the β- secretase site which, together with an intramembrane γ-secretase cleavage, produces Aβ peptides (Fig. 2).

In neurons, the primary β-secretase is β-site APP cleaving enzyme 1 (BACE1), a transmembrane aspartyl protease that generates the N terminus of Aβ. The γ-secretase complex is comprised of four subunits: presenilin 1 or 2 (PS1/PS2), nicastrin, PEN-2 and APH-1 (De Strooper et al. 2012). There are multiple γ-cleavage site possibilities, which result in the production of Aβ peptides with varying lengths (usually 38–43 amino acids). Approximately 90% of secreted Aβ is 40 amino acids long ($A\beta_{40}$). However, there is also a smaller proportion of 42 residue-long Aβ peptides ($A\beta_{42}$) that make up <10% of the total Aβ pool. In a series of studies, $A\beta_{42}$ was found to have a much higher propensity for aggregation compared to the shorter peptides, leading to a focus on $A\beta_{42}$ as the primary amyloidogenic species in AD (Burdick et al. 1992; Hilbich et al. 1991; Jarrett et al. 1993; Jarrett and Lansbury 1993).

Thus, although Aβ is initially produced as a single monomeric peptide, Aβ peptides, and especially $A\beta_{42}$, have the propensity to aggregate into oligomeric species. A large amount of research now indicates that these soluble Aβ oligomers are the primary molecular culprits involved in AD pathogenesis (Selkoe 2008; Benilova et al. 2012; Haass and Selkoe 2007; Ballard et al. 2011; Holtzman et al. 2011b). These aggregates can be formed from synthetic Aβ as well as natural Aβ secreted by cultured cells (Masters and Selkoe 2012). In addition, soluble Aβ oligomers can be directly extracted from AD patient brains and cerebrospinal fluid (CSF); these natural human Aβ oligomers have been found to have potent neurotoxic and inhibitory effects on synaptic plasticity and cognition (Shankar et al. 2008; S. Li et al. 2009; Jin et al. 2011). In contrast to amyloid plaques, which do not correlate well with cognitive decline, soluble Aβ species are significantly correlated with disease symptoms and severity (McDonald et al. 2010; McLean et al. 1999).

Synaptic Pathology in AD

Ultimately, Alzheimer's disease is a disorder of cognitive dysfunction and by extension, synaptic failure. The degeneration of dendritic arbors observed in AD was first posited in 1975 to be of clinical significance in addition to the overall loss of neurons (Scheibel et al. 1975). In the following decades, multiple studies have confirmed that synapse loss is indeed a major structural correlate of cognitive decline and likely underlies the progressive dementia of AD (DeKosky and Scheff 1990; Terry et al. 1991). Synaptic deterioration occurs early in the disease, well before the formation of amyloid plaques and neuron loss (Davies et al. 1987; Masliah et al. 2001; Selkoe 2002). This degeneration is evident on both ultrastructural and neurochemical levels – abnormal spine morphology, decreased spine densities and decreased levels of synaptic proteins are prominent characteristics of AD brain. Overall, the medial temporal lobe, which includes the hippocampus and entorhinal cortex, is the most severely affected by synaptic deterioration; this spatial pattern matches the progressive distribution of NFT pathology, another strong correlate of cognitive dysfunction (Arendt 2009). Studies have shown that even at the earliest stages before probable AD diagnosis, there is already substantial synapse loss which worsens with disease progression (Scheff et al. 2006; Masliah et al. 1994; Scheff et al. 2007).

Although amyloid plaques are a histopathological hallmark of AD, there is minimal correlation between plaque numbers and cognitive status (Terry et al. 1991; McLean et al. 1999). As previously mentioned, the strongest correlation with AD-related dementia and its early clinical presentation is the degree of synapse loss, which is a measure that has been

linked to Aβ toxicity (Shankar et al. 2007; Lacor et al. 2007; Hsieh et al. 2006). A prevailing hypothesis based on a large number of studies implicates soluble oligomers of Aβ as the primary cytotoxic species in AD, and indeed, these aggregates have been shown to have many detrimental effects at the synapse (Haass and Selkoe 2007; Mucke and Selkoe 2012). Several studies have observed that soluble Aβ oligomers can preferentially bind to or cluster at synapses, with one study observing that >90% of Aβ oligomer binding in neurons occurs at dendritic spines at sites positive for PSD-95, a marker for post-synaptic compartments (Lacor et al. 2004). On a structural level, Aβ oligomers have been shown to cause changes in spine morphology and decreases in spine density (Lacor et al. 2007; Selkoe 2008). However, the identity of the Aβ binding receptor(s)/partner(s) that mediate these synaptic effects remains unclear and controversial. Several receptors have been implicated in binding or interacting with Aβ, including the metabotropic glutamate receptor 5 (mGluR5) (Renner et al. 2010), the receptor for advanced glycation end products (RAGE) (Yan et al. 1996; Sturchler et al. 2008), the α7 nicotinic acetylcholine receptor (α7-nAChR) (Wang et al. 2000; Dougherty et al. 2003), receptor tyrosine kinase EphB2 (Cisse et al. 2011) and the cellular prion protein (PrP^C) (Lauren et al. 2009). In general, each of these proposed cell surface proteins have been shown to interact with and/or exhibit direct binding affinity for Aβ, which in turn can mediate pathogenic downstream signaling events (Larson and Lesne 2012; Mucke and Selkoe 2012).

Whatever the initial signaling receptor(s) may be, the pathological downstream effects of Aβ oligomers on synaptic physiology are well-studied. The numerous detrimental effects observed in these studies include internalization of glutamate receptors, altered neurotransmitter release and uptake and deficits in synaptic plasticity (Li et al. 2009; Haass and Selkoe 2007; Holtzman et al. 2011b; Mucke and Selkoe 2012). The latter effect has been particularly well-documented by studies demonstrating the inhibition of long term potentiation (LTP) and facilitation of long term depression (LTD) by Aβ (Selkoe 2008; Li et al. 2009; Shankar et al. 2008; Walsh et al. 2002). The functional consequences of this Aβ-induced synaptic dysfunction is evident in the learning and memory deficits of various rodent AD models, including acute intracerebral Aβ injections and transgenic mice overexpressing amyloid precursor protein (APP). In a compelling study, passive immunization with an Aβ antibody rapidly reversed memory impairments in a transgenic APP mouse model without affecting the overall Aβ burden in the brain (Dodart et al. 2002). Although the translatability of this finding into humans remains to be fully determined (Nistico et al. 2012), these results emphasize the acute toxicity of soluble Aβ species on synaptic functioning as well as the value of therapeutic approaches that may prevent such damage.

Tau and Neurofibrillary Tangles

Tau is a microtubule associated protein (MAP) involved in the regulation of microtubule stability and axonal development (Mandelkow and Mandelkow 2012). As with the Parkinson's disease (PD) related -synuclein, tau is a natively unfolded protein – this family of proteins display extended conformations *in vitro* with little ordered secondary structure (Schweers et al. 1994; Weinreb et al. 1996). Purified tau (endogenous and recombinant) is also highly soluble and resistant to heat denaturation, characteristics that are indicative of this group of proteins. Human tau is present in multiple isoforms as a result of post-transcriptional splicing, with a particular feature being the ratio of microtubule binding repeats within the C-terminus (Wang et al. 2013; Mandelkow and Mandelkow 2012). The major tau isoforms contain either four (4R) or three (3R) repeats which are the functional points of interaction with microtubules (Fig. 2).

Tau is highly expressed in the brain and is associated with several neurodegenerative disorders including Alzheimer's disease, frontotemporal dementia (FTD), Pick's disease (PiD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) – collectively, these diseases are referred to as tauopathies. As with other amyloidogenic proteins, tau undergoes a pathological transition from random coil to a -pleated sheet conformation that is accompanied by extensive aggregation and fibril formation (David et al. 2002). In AD, tau aggregates, which form highly ordered fibrils with regular periodic twisting, have been termed paired helical filaments. Between the various tauopathies, there are differences in the isoform composition of tau aggregates. In AD, both 3R- and 4R-tau splice isoforms are observed in NFTs (Goedert et al. 1992). In contrast, deposits in parasupranuclear palsy (PSP) are exclusively 4R-tau while Pick's disease deposits are made up of only 3R-tau isoforms (Buee and Delacourte 1999). Investigations into the structural characteristics of 3R and 4R tau suggest that there may be unique differences in their aggregation and fibrillogenesis pathways (Siddiqua et al. 2012). In all of these tauopathies, including AD, the accumulation of these fibrous structures within neurons is considered to be one of the key factors in cell death and dysfunction.

Post-translational modifications have been shown to affect tau structure and function as well as contribute to protein aggregation in the disease process. Tau is a phosphoprotein with multiple tightly regulated Ser/Thr and Tyr phosphorylation sites. In AD, hyperphosphorylation of paired helical filaments is a common feature (Wang et al. 2013). In addition, tau can also be ubiquitinated and is degraded by the proteasome through ubiquitin-independent (David et al. 2002) and –dependent pathways (Shimura et al. 2004). Similar events are observed for -synuclein, another natively unfolded protein. Alzheimer's NFTs are strongly immunoreactive for ubiquitin (Mori et al. 1987; Perry et al. 1987), and tau is also a substrate for the ubiquitin E3 ligase TRAF6 (Babu et al. 2005). The consequences of tau ubiquitination are not currently known and could merely reflect the inability of cells to effectively degrade the protein, which leads to aggregation and tangle formation. Alternatively, ubiquitin modification may contribute to the misfolding and subsequent aggregation involved in AD pathology. Given the overlap of the ubiquitination and SUMOylation pathways, investigations have been conducted to determine what role SUMO may play in Alzheimer's disease and related tauopathies.

As detailed above, although a large amount of research in the past few decades have elucidated many pathological mechanisms involved in Alzheimer's disease (Querfurth and LaFerla 2010; Holtzman et al. 2011b), there is still much that is unknown including basic questions such as: what initiates the disease, are the underlying mechanisms fundamentally different from normal aging, and can the disease process be stopped or reversed? Unfortunately, the answers remain unclear; and while there are currently no effective medications for modifying disease progression, a number of possible therapeutic targets are currently being investigated (Citron 2010; Lane et al. 2012). Genetic studies initially identified several loci in APP and the presenilins that are involved in early-onset familial AD (FAD), which have provided clues on the key factors involved in AD (Selkoe 1996; Holtzman et al. 2011b; Bateman et al. 2011; Tanzi 2012). Although FAD represents only a small proportion of the disease, there is a very high degree of phenotypic similarity between FAD and sporadic late-onset AD (LOAD), suggesting that mechanistic information obtained about FAD would also be directly relevant for LOAD (Selkoe 2001). Overall, AD is highly heritable (~70% heritability), and recent genome wide association studies (GWAS) have identified a collection of additional genes which are more broadly linked to sporadic LOAD (Naj et al. 2011; Hollingworth et al. 2011; Tanzi 2012). Although the genetics are complex and remain to be fully elucidated, further investigation of these genes and their associated cellular pathways will likely point to new targets for the treatment of AD.

SUMO and Alzheimer's Disease

Given the wide variety of proteins which are SUMOylated or predicted to be SUMOylated in neurons, it is not surprising that dysregulation of this post-translational modification has been found to be involved in multiple neurological diseases including Alzheimer's (Wilkinson et al. 2010; Dorval and Fraser 2007; Sarge and Park-Sarge 2011).

Evidence from genetic studies support this hypothesis. A genome-wide association study found a link between variations in a SUMO-related gene and sporadic late-onset AD (Grupe et al. 2007). A single nucleotide polymorphism (SNP) on chromosome 6 (rs6907175) that maps to a homolog of the SUMO-activating enzyme subunit 2 (SAE2) was found to be significantly associated with AD in multiple independent sample sets. This SNP was later verified as significant in another genetics study on sporadic AD (Corneveaux et al. 2010). How this SAE2 homolog SNP impacts AD pathogenesis is unclear; in a study that correlated cerebrospinal fluid Aβ levels with known AD-relevant SNPs, the SAE2 homolog SNP was not observed to significantly impact overall Aβ levels or the $A\beta_{42}$:$A\beta_{40}$ ratio (Kauwe et al. 2009).

Another SUMO enzyme, the protease SENP3, was identified as having altered expression in microarray analyses of the inferior parietal lobes of sporadic AD patients (Weeraratna et al. 2007). There was a significant downregulation of SENP3 expression with AD; this alteration was confirmed by real-time RT-PCR, which found that AD tissue had on average approximately half of the SENP3 expression of controls. The SUMO conjugating enzyme Ubc9 is the third SUMOylation protein that has been linked to AD. An analysis of genomic DNA from patients with late-onset AD discovered a SNP (rs761059) in intron 7 of the Ubc9 gene (*UBE2I*) that was significantly associated with the disease (Ahn et al., 2009). In addition, when stratified by gender, two additional *UBE2I* SNPs (rs8052688, rs8063) were significantly associated with mild cognitive impairment (MCI) in women. These studies indicate that alterations in SUMOylation are likely involved in AD, although the underlying mechanisms remain to be elucidated.

Immunohistology findings also support SUMO dysregulation. By immunohistochemistry, SUMO labeling was readily detected post-mortem in brain sections from AD patients and non-demented controls (Li et al. 2003). In particular, there was strong labeling of hippocampal neurons, which constitute a cell population that is particularly vulnerable in AD. Preliminary results indicate that the pattern of SUMO localization may be altered in AD, with a more limited somal distribution compared to somal and nuclear staining in non-demented controls (Li et al. 2003). Further studies, immunohistological and biochemical, are warranted to better analyze the changes in SUMOylated proteins and SUMO enzymes that may occur with AD.

SUMO and Tau

Alzheimer's disease, as previously discussed, is characterized by the aberrant aggregation of Aβ and tau proteins, both of which have neurotoxic properties in the oligomerized forms. Interestingly, SUMOylation of both tau and the Aβ precursor protein have been reported. In HEK293 mammalian cell line cultures, overexpressed tau can be SUMOylated, primarily at one consensus site (K340) located within the fourth microtubule binding repeat (Fig. 2) and almost exclusively by SUMO1 (Dorval and Fraser 2006). Pharmacological inhibition of the proteasomal system with MG132 decreased SUMO1-tau conjugates and increased ubiquitinated tau, suggesting that the two PTMs may be competing for the same lysine residue. Furthermore, tau SUMOylation also has a phosphorylation dependence, since inhibition of phosphatases by okadaic acid increased SUMO1-tau levels. A microtubule de-polymerizer, colchicine, that increases the levels of free tau was also able to significantly

elevate tau SUMOylation. It appears that free soluble tau is the preferred target subset, with possible cross-talk interactions with ubiquitination and phosphorylation.

Supporting these findings is another study which demonstrated SUMO1 immunoreactivity in phospho-tau aggregates in the Tg2576 APP overexpressing transgenic mouse model (Takahashi et al. 2008). The colocalization was observed in degenerating neurites around neuritic amyloid plaques in the cortex of aged mice. Interestingly, this colocalization of SUMO and tau was not observed in the JNPL3 tau transgenic mice, which overexpress human four-repeat tau with a pathogenic mutation (P301L) and also develop large numbers of hyperphosphorylated tau aggregates. This suggests that amyloid pathology may be involved in regulating tau SUMOylation.

How these results translate to human AD remains unclear. While pathological aggregates in other neurodegenerative diseases have been observed to be SUMO-positive, tau aggregates in post-mortem AD brain tissue do not exhibit elevated SUMO1 by immunohistochemistry (Pountney et al. 2003). These results have been reported as reproducible by another group (Takahashi et al. 2008). One possible explanation is that proteasome impairments, which occur with both aging and neurodegenerative disease, may lead to downregulation of SUMO-tau (Dorval and Fraser 2006). As discussed above, this is supported by *in vitro* data showing that acute proteasome inhibition leads to decreased SUMOylation and increased ubiquitination of tau (Dorval and Fraser 2006). Indeed, in studies with post-mortem AD tissue, hyperphosphorylated tau aggregates are also prominently ubiquitinated (Pountney et al. 2003; Takahashi et al. 2008). The findings to date indicate a connection between tau and SUMOylation, particularly by SUMO1, but the physiological and functional consequences of this tau modification is an area in need of further investigation.

SUMO and APP Processing

Amyloid precursor protein (APP), from which Aβ peptides are derived, has also been reported to be a SUMOylated substrate. In a proteomic screen for SUMO1-modified human protein substrates, APP was identified (Gocke et al. 2005). The *in vitro* efficiency of SUMO conjugation to APP was found to be a relatively high 34%; the authors did find that *in vivo* SUMOylation efficiency was generally much lower than *in vitro* efficiency, although the specific percentage for APP was not investigated. *In vivo* SUMOylation of APP was later reported by another study that detected SUMO-APP conjugates in transfected HeLa cell cultures as well as in mouse brain tissue (Zhang and Sarge 2008). In the cell cultures, APP was observed to be SUMOylated at two consensus motif lysine residues (K595, K587; Fig. 2). SUMOylation by either SUMO1 or SUMO2 was associated with decreased levels of high molecular weight Aβ species that likely represent Aβ aggregates. Conjugation-deficient mutations of one or both of the lysines (K587R, K595R) in APP resulted in increased levels of Aβ aggregates. These results were paralleled by those from the overexpression of Ubc9, the SUMO E2 ligase; increasing SUMOylation via Ubc9 overexpression led to a decrease in Aβ aggregates.

However, questions have been raised as to how a lumenal domain of APP could be SUMOylated since this is considered to be a primarily cytoplasmic event. To partly address this issue, this study also looked at the cellular distribution of Ubc9, in order to elucidate where APP may undergo SUMOylation. Ubc9 protein was observed in the ER compartment, which is consistent with previous studies that found non-nuclear expression patterns suggestive of ER localization (Lee et al. 1998; Rodriguez et al. 2001). More specifically, the authors posited that Ubc9 is present in the lumenal compartment of the ER since Ubc9 was detected inside sealed vesicles in a brain microsome assay. Since the N-terminus of APP that contains the β-secretase site is located in the ER lumen during trafficking, the localization of

some Ubc9 to this compartment could provide the opportunity for APP SUMOylation. This can be a contentious issue, since Ubc9 has mostly been described as a nuclear and cytosolic protein and, besides glycosylation, post-translational modifications have not been traditionally viewed as occurring in the ER lumen. However, recent studies demonstrating the acetylation of BACE lysine residues in the ER lumen (Pehar and Puglielli 2013; Costantini et al. 2007) support the notion that SUMOylation may also be possible in the ER.

The two reportedly SUMOylatable lysine residues of APP are located next to the β-secretase cleavage site (between residues M596 and D597). Therefore, SUMO conjugations at these lysines have the potential to affect the processing of APP, possibly via steric hindrance. Intriguingly, one of the lysines is also the site of a well-characterized APP mutation (K595N) that was initially discovered in a Swedish family with autosomal dominant early-onset AD. It is tempting to speculate that the pathogenicity of the mutant APP may involve altered SUMOylation (Sarge and Park-Sarge 2011). However, it remains to be determined if this mutation affects the SUMOylation of APP *in vivo* and if so, whether the increased Aβ levels associated with this mutation result from altered SUMOylation. In addition, another group previously reported that no SUMO-APP conjugates were detected using another cell line (HEK293) (Y. Li et al. 2003), so the ability of APP to be SUMOylated and the conditions under which such SUMOylation occurs remain to be validated.

SUMO and Amyloid-β

There have been multiple studies on the upstream effects of SUMO on APP processing and Aβ levels, although the issue remains unclear due to conflicting results. In the previously-discussed study, APP SUMOylation decreased levels of Aβ aggregates (Zhang and Sarge 2008). This finding is supported by another study, performed with HEK293 cell cultures, reporting that overexpression of SUMO2 greatly reduced Aβ production (Li et al. 2003). On the other hand, inhibiting endogenous SUMO2 SUMOylation with a conjugation-deficient mutant (G93A) significantly increased Aβ levels. However, contrary to the data of Zhang and Sarge, these effects were not due to direct SUMO conjugation of APP – the authors noted that they did not observe SUMOylation of either APP or the β-secretase BACE in their analyses. In this particular study, the SUMO-regulated Aβ reduction effect appeared to be at least partially due to a shunting of APP processing from the β-secretase cleavage pathway to the α-secretase pathway, since an α-secretase cleavage product exhibited increases with SUMO2 overexpression. Interestingly, a SUMO2 (K11R) mutant that cannot form polymeric SUMO chains had the opposite effects on Aβ levels. This indicates that it is important to consider SUMOylation beyond a binary on-off paradigm – the paralog, number and arrangement of SUMO proteins are all likely significant factors in the regulation of APP processing.

Other studies have reported conflicting results on the direction of changes in Aβ levels upon SUMO manipulations. One of those studies, performed in HEK293 cell cultures, found that SUMO3 overexpression significantly increased secretion of $A\beta_{40}$ and $A\beta_{42}$ peptides as well as APP levels (Dorval et al. 2007). These were paralogspecific effects not observed with SUMO1 or SUMO2 overexpression. Furthermore, the modulatory effects were found to be independent of covalent SUMOylation, as mutants deficient for conjugation or polySUMO chain formation provided similar results. It was also observed that levels of BACE, the APP β-secretase, were specifically increased by SUMO3 overexpression, which together with higher APP levels could explain the elevated Aβ secretion. Another point of difference between this study and the previous one is APP metabolism. While Li *et al.* found that SUMO overexpression did not affect APP half-life, Dorval *et al.* observed that SUMO3 overexpression significantly increased APP half-life. Given the conflicting observations, it is currently unclear if SUMO can affect the turnover kinetics of APP.

Somewhat surprisingly, inhibition of SUMOylation via knockdown of SUMO1 or SUMO2/3 did not affect either APP or Aβ levels (Dorval et al. 2007). The results from this study suggest that endogenous SUMOylation is not required but could have indirect, non-covalent modulatory effects on APP processing. The ability of SUMO to non-covalently regulate cellular processes has been previously observed in other studies on different protein targets, including dynamin (Mishra et al. 2004) and parkin (Um and Chung 2006). SUMO-interacting motifs (SIMs), which are sequences that can interact non-covalently with SUMO, likely underlie these conjugation-independent effects.

These results are generally supported by another study reporting that overexpression of any of the SUMO paralogs increased APP expression and $A\beta_{40}$ levels in the H4 neuroglioma cell line, independent of covalent SUMO conjugation and dependent on BACE1 (Yun et al. 2012). SUMO was found to upregulate BACE1 protein levels via non-covalent interactions with a di-leucine motif and is a likely mechanism for the observed Aβ increases.

Overall, due to the conflicting results from the various studies, the topic of SUMOylation in APP processing is currently murky and controversial. Although the available evidence does suggest that SUMO can affect Aβ levels, it is unclear in what direction, by which mechanism(s), and whether APP SUMOylation is a factor in amyloid processing. The majority of the experiments in the previously-discussed studies utilized transfection-based overexpression of tagged constructs in immortalized cell line cultures; although this can be a valuable technique in elucidating cellular mechanisms, it does have inherent limitations which may partially explain the conflicting results. It is also important to note that almost nothing is known about these potential regulatory effects in neurons and in brain tissue – it will be important to address these questions in future studies.

Aβ-Mediated Effects on SUMOylation

Besides the upstream effects of SUMO on APP processing and Aβ levels, Aβ peptides could also directly affect SUMOylation in downstream signaling pathways that impact synaptic physiology and/or disease pathogenesis (Fig. 3). With high concentrations of oligomeric assemblies, Aβ is well-established as a neurotoxin with many deleterious effects on synaptic function (Holtzman et al. 2011b; Haass and Selkoe 2007; Mucke and Selkoe 2012). Given SUMO's currently known (and expanding) role in neuronal functioning and synaptic signaling, it is probable that Aβ-induced pathology could alter neuronal SUMO regulation. In addition, it is likely that multiple SUMO components and/or substrates are affected by pathological Aβ conditions, given the widespread roles of SUMOylation in basic cell and neuron-specific functioning.

One way to investigate the potential *in vivo* effects of Aβ on SUMO is to analyze transgenic mouse models of AD which overexpress APP and consequently have highly-elevated levels of Aβ peptides. One study using aged APP/PS1 double transgenic mice found that the levels of free, unconjugated SUMO1 protein were elevated compared to wild-type mice (Yun et al. 2012). In addition, immunohistochemical analyses demonstrated enhanced SUMO1 immunoreactivity along with partial colocalization with amyloid plaques in aged transgenic mice. While these results suggest that SUMO1 expression can be altered by Aβ pathology, this study did not address potential changes in the levels of SUMOylated conjugates in the brain. Another study investigated this possibility, using Tg2576 APP overexpressing mice, and did not detect changes in global SUMO1 or SUMO2/3 conjugation levels (McMillan et al. 2011). In contrast to the previously-mentioned study, no changes in the levels of unconjugated SUMO proteins were reported. However, it was observed that some individual SUMO2/3 conjugate bands in western blots were altered. Specifically, two high molecular weight SUMO2/3 conjugates were significantly decreased in transgenic cortical tissue. The

full extent to which the high molecular weight SUMO conjugates (100–250+ kDa) are altered in the various brain regions of AD mouse models, including the hippocampus, was not fully examined; however, previous studies have indicated that these conjugates tend to be the most labile to regulatory changes (Johnson and Gupta 2001; Saitoh and Hinchey 2000; Tatham et al. 2008).

Since sporadic AD may ultimately be one end of the spectrum of cognitive aging, it could also be useful to examine mouse models of old age for changes in SUMOylation. One study that has done so with aged (25 months old) wild-type mice observed a significant increase in free unconjugated SUMO2/3 levels in the hippocampus (Yang et al. 2012). Interestingly, this is similar to the increased free SUMO1 in one of the above-discussed studies using AD transgenic mice (Yun et al. 2012). In addition, the free SUMO2/3 pool was inversely correlated with performance in a radial arm water maze behavioral task, which is a measure of hippocampal-dependent spatial memory. However, actual SUMO conjugation levels were not shown or discussed in this study; based on the results from McMillan *et al.*, it is possible and even likely that SUMOylation is altered with cognitive aging. As a possible explanation for the increased pools of free SUMO with aging and APP overexpression, there may be corresponding decreases in SUMO conjugation and therefore reduced levels of high molecular weight conjugates. This could potentially occur via enhanced deSUMOylation or reduced SUMOylation.

Changes in the expression of the SUMO components may account for alterations in SUMOylation capacity. In the aged APP overexpressing mice, protein levels of Ubc9 and SENP1 were reported to be unchanged (McMillan et al. 2011). However, in a study with semi-aged wild-type mice (15 months old), significant decreases in both Ubc9 and SUMO1 mRNA levels were demonstrated (Akar and Feinstein 2009). The SUMO1 decrease is in contrast to later studies showing increased SUMO1 and SUMO2/3 protein levels in APP overexpressing and aged mice, respectively (Yang et al. 2012; Yun et al. 2012). Further studies are required to investigate these unresolved issues and fully elucidate the *in vivo* changes in SUMOylation regulation/capacity with aging and AD pathology.

In addition to animal models, the direct effects of Aβ on SUMO needs to be addressed using other systems, since APP overexpressing models result in the production of multiple cleavage products besides Aβ peptides. One study so far has tested the effect of exogenous Aβ on SUMOylation (Yun et al. 2012). It was observed that applying high concentrations of $A\beta_{40}$ peptides to cell cultures increased SUMO1 protein levels in primary cortical neurons and SUMO1 conjugation levels in a cell line culture. However, $A\beta_{40}$ peptides do not readily oligomerize (Stine et al. 2003) so it remains unclear how AD pathology-relevant $A\beta_{42}$ oligomers might affect SUMOylation levels in neuronal cell types.

Potential Downstream Dysfunction of SUMO-Regulated Pathways

As for the identities and functions of the SUMO conjugates affected by high Aβ or other AD-related pathology, the topic remains unexplored. Based on recent findings, there are several potential candidates, the SUMOylation of which may be impacted in AD. One example is mitochondrial functioning and dynamics. In AD as well as many other neurodegenerative diseases, mitochondrial impairment and oxidative stress are prominent features (Hirai et al. 2001; Lin and Beal 2006; Reddy and Beal 2008). More specifically, mitochondrial dynamics including fission and fusion are impaired in AD (X. Wang et al. 2009; Chen and Chan 2009; Manczak et al. 2011). Interestingly, in recent years, SUMOylation has emerged as an important regulator of mitochondrial dynamics, along with other post-translational modifications (Harder et al. 2004; Braschi et al. 2009; Zunino et al. 2007; Cerveny et al. 2007). In particular, the GTPase dynamin related protein (DRP1),

which is required for mitochondrial fission, was identified as a SUMO conjugation substrate that can be modified by all SUMO paralogs at multiple non-consensus sites (Harder et al. 2004; Figueroa-Romero et al. 2009). SUMOylation of DRP1 protects the protein from degradation and localizes DRP1 to its basal cytosolic compartment. Intriguingly, in a post-mortem analysis, DRP1 levels were observed to be significantly reduced in AD brain, which likely contributes to the abnormal mitochondrial morphology and distribution observed with AD (Wang et al. 2009). Furthermore, this study also demonstrated that $A\beta_{42}$ oligomers can directly cause deficits in mitochondrial dynamics, along with synapse loss. However, increasing expression of DRP1 blocks this process, suggesting that the reduced DRP1 observed in AD brain is pathogenic. Although not yet directly demonstrated, it is plausible that SUMO regulation of DRP1 stability and localization is involved in this aspect of Aβ-induced pathology. Such a finding would likely be applicable to other neurodegenerative diseases besides AD, since dysfunction of mitochondrial dynamics figures prominently in several diseases including Parkinson's and Huntington's (Chen and Chan 2009).

In addition, DRP1 SUMOylation has recently been shown to be involved in cell death following ischemic stress in cultured neurons (Guo et al. 2013). deSUMOylation mediated by SENP3, which undergoes degradation with oxygen/glucose deprivation, is required for initiating mitochondrial fragmentation and apoptosis. Drawing a link to AD, SENP3 was one of the SUMO enzymes previously detected as downregulated in AD brain tissue (Weeraratna et al. 2007). Thus, it is possible that metabolic and/or cerebrovascular changes in AD can lead to a decrease in SENP3 expression, which in turn could cause dysregulation of DRP1 SUMOylation and mitochondrial dysfunction in AD pathology.

Since AD is a disease primarily of synaptic and cognitive dysfunction, proteins involved in synaptic morphology, transmission and plasticity that are also SUMOylated would be particularly interesting targets to investigate. Although still a relatively new field, a number of such proteins have been identified. Among the ones characterized in neurons and/or brain tissue are the myocyte enhancer factor 2 (MEF2) transcription factor (Shalizi et al. 2006), the kainate receptor subunit GluR6 (Martin et al. 2007), the RNA-binding protein La (van Niekerk et al. 2007), the cannabinoid receptor type 1 (CB1) (Gowran et al. 2009), the immediate early gene Arc (Craig et al. 2012) and the calcium/calmodulin-dependent serine protein kinase (CASK) (Chao et al. 2008). SUMOylation of these proteins was found to regulate a variety of neuron-specific functions, including postsynaptic differentiation (MEF2), receptor endocytosis (GluR6), axonal transport (La), homeostatic synaptic scaling (Arc), and spine morphogenesis (CASK). Whether these proteins and their SUMO-regulated neuronal functions are affected by Aβ oligomers or other AD-related pathology are open questions for future studies (Fig. 3).

In addition, several other proteins that are known to be involved in neuronal and synaptic signaling have been identified as SUMO conjugation targets in non-neuronal cell types. For example, the cAMP responsive element binding protein (CREB) was found to be SUMOylated at two lysine residues under hypoxic conditions in nonneuronal cell cultures; CREB SUMOylation stabilized the protein and promoted nuclear localization (Comerford et al. 2003). Since CREB is well-established as a central transcription factor in the induction of synaptic plasticity and memory, it is feasible that dysregulated CREB SUMOylation may be involved in AD as a factor contributing to impaired synaptic and cognitive function. In addition to CREB, other SUMOylated proteins that have important roles in neuronal physiology have also been identified in non-neuronal cells, including glycogen synthase kinase 3 β (Eun Jeoung et al. 2008), axin (Rui et al. 2002), protein tyrosine phosphatase 1B (Dadke et al. 2007), GLUT1 and GLUT4 glucose transporters (Giorgino et al. 2000), and K2P1 potassium channels (Rajan et al. 2005). It remains to be determined if these proteins

are indeed SUMOylated in the brain and furthermore, whether such SUMOylation is affected with AD.

At the synapse, it is likely that both the pre- and post-synaptic compartments contain SUMOylated proteins that are affected by AD pathology. As described above, known and potential SUMOylated targets can be found in both compartments. In addition, the requisite SUMO enzymatic machinery is also present throughout neurons and can undergo activity-dependent redistribution (Martin et al. 2007; Loriol et al. 2013). There is spatial overlap and therefore, potential interactions with Aβ-induced toxicity and dysfunction, which also occurs throughout neurons, including axonal terminals and dendritic processes (Palop and Mucke 2010; Wang et al. 2004; Lacor et al. 2007; Selkoe 2008). Post-synaptically, for example, Aβ has been shown to perturb receptor trafficking and spine density/morphology (Snyder et al. 2005; Hsieh et al. 2006; Shankar et al. 2007; Wei et al. 2010). It is therefore feasible that the SUMOylation of proteins involved in such functions, such as MEF2 and GluR6, may become dysregulated with AD. Pre-synaptically, Aβ has also been shown to induce a multitude of signaling effects and impairments (Palop and Mucke 2010; Moreno et al. 2009; Abramov et al. 2009; Preda et al. 2008; Mura et al. 2010; Grilli et al. 2010; Khan et al. 2010). Since pre-synaptic SUMOylation has been shown to modulate synaptosomal glutamate release and calcium influx (Feligioni et al. 2009), both of which are also processes impacted by Aβ, there may be potential SUMO-related pathology in these and other signaling functions in the pre-synaptic compartment with AD. Overall, given the widespread role of SUMOylation in a multitude of signaling networks, there are likely numerous SUMO targets present at both the pre- and post-synaptic compartments as well as downstream in the cytoplasm and nucleus of the neuron. The potential impact of pathological Aβ and/or tau aggregates on these SUMO-regulated functions could contribute significantly to the observed synaptic pathology of Alzheimer's.

SUMO and Glial Cells

Another significant point to note is that besides neurons, glial cells are also intricately involved in AD pathology (Wyss-Coray and Rogers 2012). Although not much is known about the roles of SUMOylation in regulating this involvement, there is evidence that glial SUMOylation can impact cellular processes that are relevant under pathological conditions. In AD, astrocytes undergo reactive gliosis which is accompanied by inflammatory signaling and morphological changes involving increases in glial fibrillary protein (GFAP). A recent study found that $A\beta_{42}$ exposure can decrease the levels of Ubc9 and SUMO1 conjugates in primary astrocyte cultures, concomitant with reactive astrogliosis (Hoppe et al. 2013). Overexpression of SUMO1, but not a conjugation-deficient SUMO1, was found to prevent GFAP upregulation and morphological reactivity. Curcumin, a compound found in turmeric curry spice, was previously reported to have anti-amyloidogenic effects and ameliorate pathology in an AD mouse model (Lim et al. 2001; Ono et al. 2004; Yang et al. 2005). When applied to the astrocyte cultures, curcumin prevented the Aβ-induced decrease in SUMOylation, indicating that glial SUMO pathways may be involved in the therapeutic benefits.

Another study has implicated SUMO in inflammatory signaling mediated by astrocytes (Akar and Feinstein 2009). In these glia cells, nitric oxide synthase 2 (NOS2) is induced by inflammatory stimuli (Galea et al. 1992; Hewett et al. 1993; Lee et al. 1993) and has been implicated in the pathogenesis of multiple neurological disorders including multiple sclerosis (Bo et al. 1994), ischemia (Endoh et al. 1994) and AD (Wallace et al. 1997; Heneka et al. 2001; Hu et al. 1998; Akama and Van Eldik 2000). In particular, Aβ can directly activate astrocytes and stimulate NOS2 expression via cytokine signaling (Hu et al. 1998; Akama and Van Eldik 2000). SUMO may be involved in this Aβ-mediated NOS2

induction – SUMO1 has been demonstrated to regulate NOS2 expression in activated astrocytes (Akar and Feinstein 2009). In this study, a strongly inflammatory stimulus, lipopolysaccharide, was found to decrease levels of SUMO1, Ubc9 and SENP1 in primary astrocyte cultures. Overexpression of these SUMO components was able to reduce NOS2 promoter activation, possibly involving SUMOylation of the C/EBPβ transcription factor. This study highlights the role of SUMO in regulating astrocyte function and indicates that targeting glial SUMOylation may have anti-inflammatory therapeutic benefits.

In general, astrocytes have multiple functions both in pathology, including cytokine production and Aβ degradation, and normal physiology, including the regulation of synaptic transmission and plasticity. If and how SUMOylation is involved in these functions are issues that require further studies.

Another glial cell type, microglia, is also intimately involved in AD pathology. As the resident macrophages of the central nervous system, microglia have been implicated in the inflammatory and oxidative stress components of multiple neurological diseases including AD (Wyss-Coray and Rogers 2012). In addition, microglia have the ability to phagocytose Aβ, including fibrillar Aβ in amyloid plaques, and are thus potentially important elements in controlling Aβ elimination. Although not yet demonstrated, probable links can be drawn between microglial functioning in AD and SUMOylation. For example, in macrophage cells such as microglia, peroxisome proliferator-activated receptor-γ (PPARγ) and liver X receptors (LXRs) are transcription factors involved in regulating inflammatory signaling. Significantly, in cultured macrophages, PPARγ and LXR have been found to be SUMOylated, which regulates the transrepression of inflammatory response genes (Pascual et al. 2005; Ghisletti et al. 2007). Although not yet directly shown in microglia, it is probable that such SUMO regulation of inflammatory signaling occurs in the brain as well. This could have important implications for AD therapeutic strategies, since PPARγ and LXR activation have been demonstrated in many studies to ameliorate pathophysiology, decrease soluble and insoluble Aβ levels, decrease glial inflammation and improve cognitive function in AD mouse models (Heneka et al. 2005; Koldamova et al. 2005; Riddell et al. 2007; Zelcer et al. 2007; Donkin et al. 2010; Fitz et al. 2010; Toledo and Inestrosa 2010; Mandrekar-Colucci et al. 2012). Mechanistically, the Aβ-reducing effects are at least partially due to PPARγ and LXR-mediated regulation of brain levels of apolipoprotein E (apoE), which is produced mainly by astrocytes, promotes the degradation of Aβ, and is also the top genetic risk factor for sporadic late-onset AD (Corder et al. 1993; Jiang et al. 2008; Kim et al. 2009).

The potential roles of SUMOylation in glia-mediated processes are open questions that will likely emerge as an important aspect of AD pathobiology. As significant cellular components in AD as well as other neurological diseases, the functions of SUMOylation in astrocytes and microglia warrant additional study and could potentially have significant impact on future AD therapeutic developments.

Conclusions

Overall, the data so far suggest that there is potentially widespread dysregulation of SUMOylation under Aβ-induced pathology, and that such dysregulation may involve changes in the SUMO components or downstream SUMO conjugates (Fig. 3). Many important issues remain to be investigated, including whether altered SUMOylation is involved in the synaptic and cognitive dysfunction that characterize AD. This is a likely hypothesis, since among the SUMO substrates that have been identified so far are proteins involved in synaptic signaling and plasticity. Questions that remain be addressed include: 1) how are the SUMO components and SUMOylation processes altered by Aβ, 2) how do any

such changes affect downstream neuronal signaling pathways involving SUMOylated proteins, 3) what is the impact of any Aβ-induced SUMOylation changes on the functional output of synaptic physiology and behavior, and 4) what are the functional consequences of tau SUMOylation? In addition, the questions of whether and how SUMO exerts upstream effects on APP processing, Aβ levels and tau aggregation are not currently resolved and will require further studies to validate in neurons and in the brain.

One particular area that needs to be addressed is *in vivo* modeling of neurological diseases in combination with SUMOylation. There are a large number of transgenic mouse models for AD that replicate amyloid and tangle pathology and which can be examined with respect to changes in SUMO-related pathways and conjugation targets. However, there has been little in the way of SUMO transgenic model development to investigate neurological diseases as well as the impact of SUMOylation on normal brain function and development. Recently, there was a report of a knock-in mouse model expressing a tagged version of SUMO1 (Tirard et al. 2012). However, in neurons, the SUMO1 conjugates in this mouse model were only detected in the nucleus and annulate lamellae, which is in contrast to previous studies identifying a number of SUMO1-conjugated proteins in the cytosolic compartment. A number of tagged SUMO1 conjugates were identified by proteomic analyses but most of the previously identified neuronal SUMO substrates were not detected, including well-established ones such as MEF2A. Further development and analysis of SUMO mouse models is necessary, along with combinations with existing transgenic and knockout models of neurodegenerative diseases such as AD and PD. Such multiple transgenic mice will likely provide valuable information on the intersections between the various pathways.

The involvement of SUMOylation in Alzheimer's disease is a relatively new topic, one with many interesting possibilities and unanswered questions that could have significant clinical implications. There is currently an increasing focus on and discovery of neuronal and synaptic SUMO substrates – and AD, as a disease of synaptic failure, most likely impacts many aspects of the PTM-based regulation of such proteins. Phosphorylation, ubiquitination and acetylation are PTMs currently known to be affected in AD pathology and are consequently the subject of various drug discovery efforts. Similarly, SUMOylation is also emerging as a central PTM, the targeting of which could become a future therapeutic strategy for AD as well as other neurological diseases.

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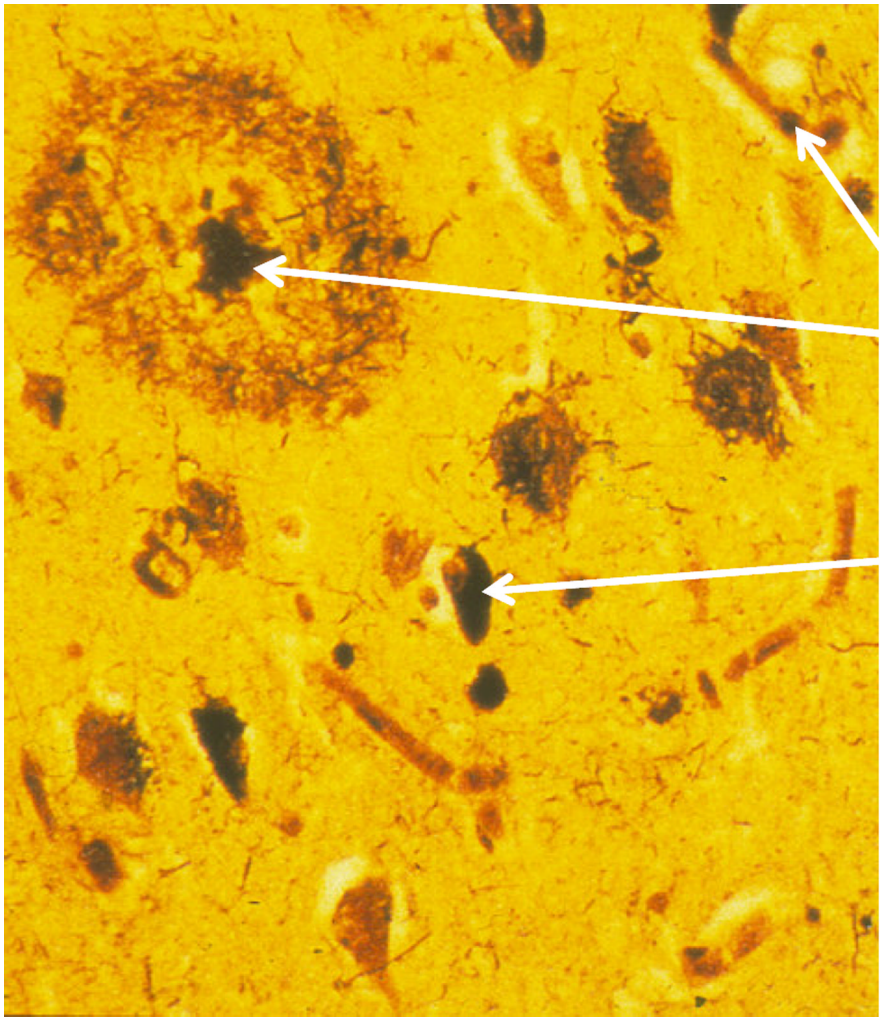


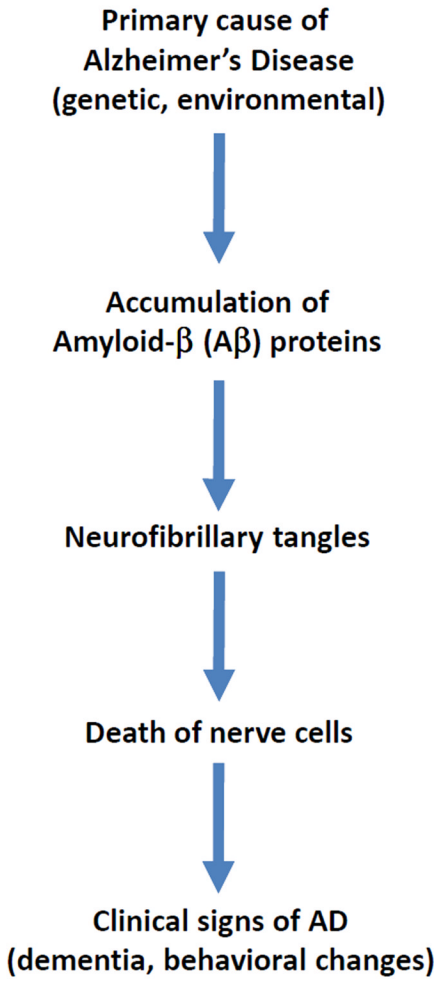
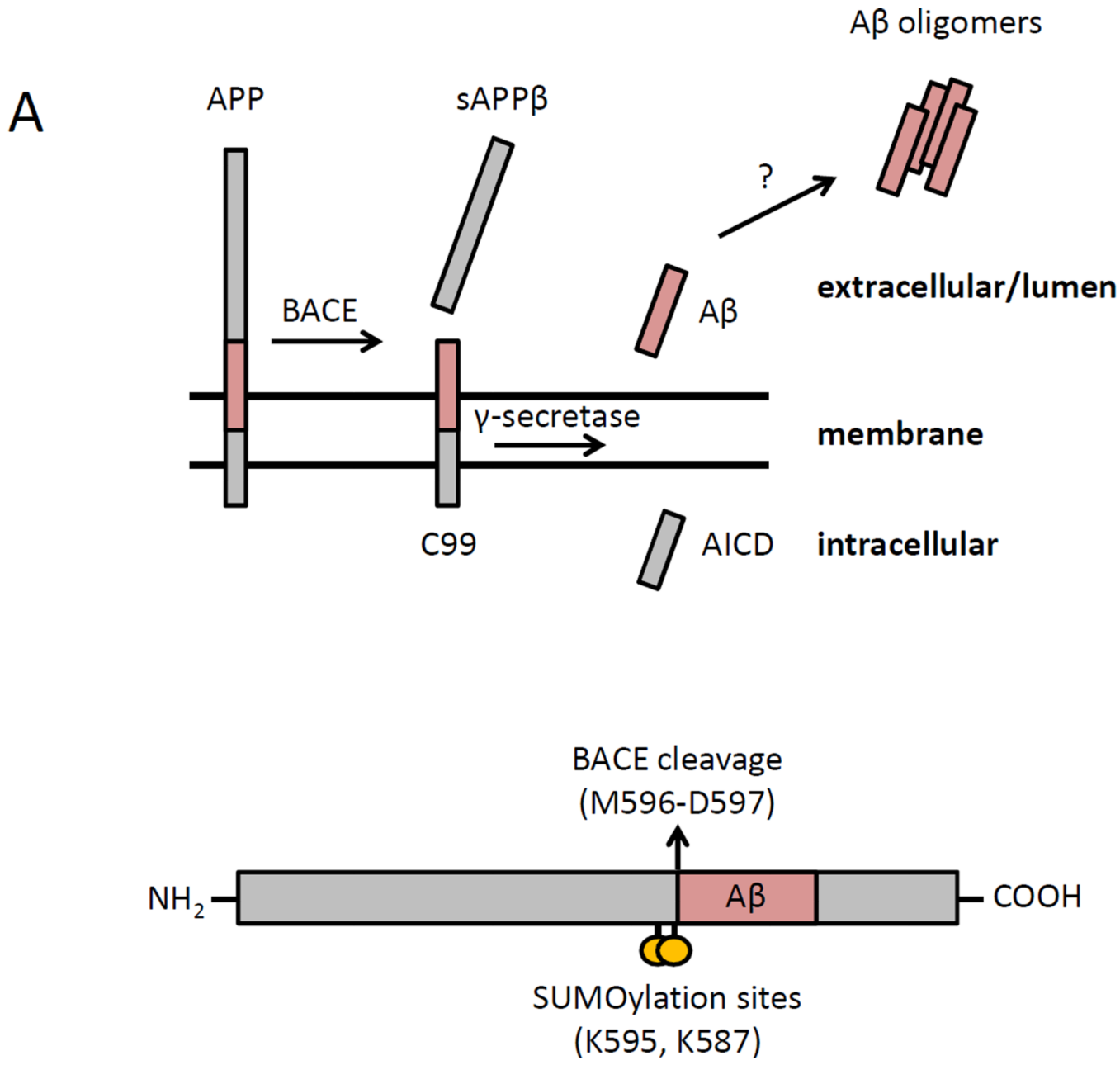


Figure 1. Alzheimer's disease pathology

Initiating factors, likely comprising multiple genetic and environmental components, result in a build-up of amyloid-β aggregates. These Aβ aggregates include soluble neurotoxic oligomers and insoluble amyloid plaques. With neuronal damage, microtubule associated protein tau becomes hyperphosphorylated and aggregates into intracellular structures termed neurofibrillary tangles. The subsequent neurodegenerative cell death features prominently in AD and accounts for the clinical symptoms of cognitive decline, dementia and behavioral changes.



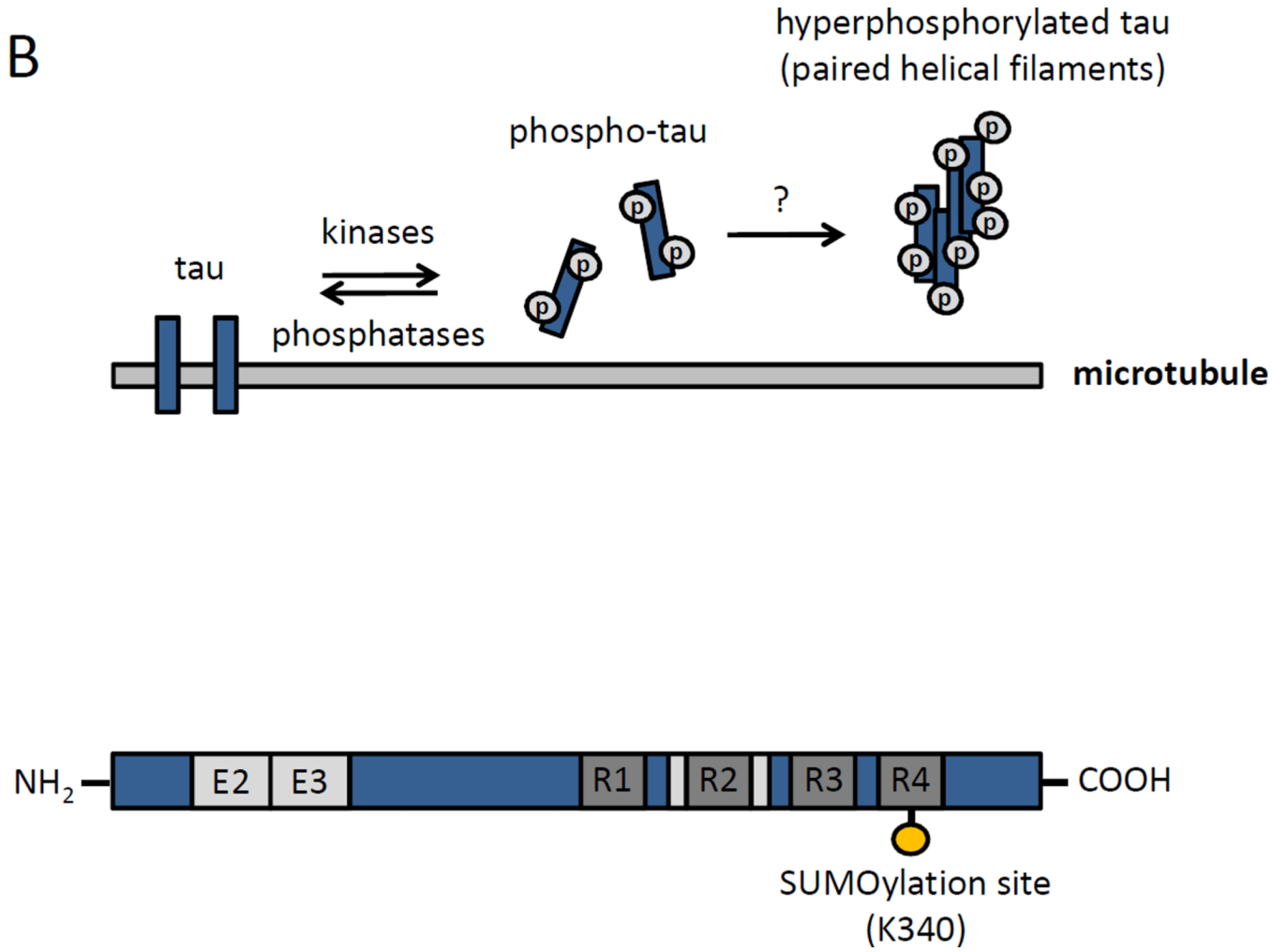
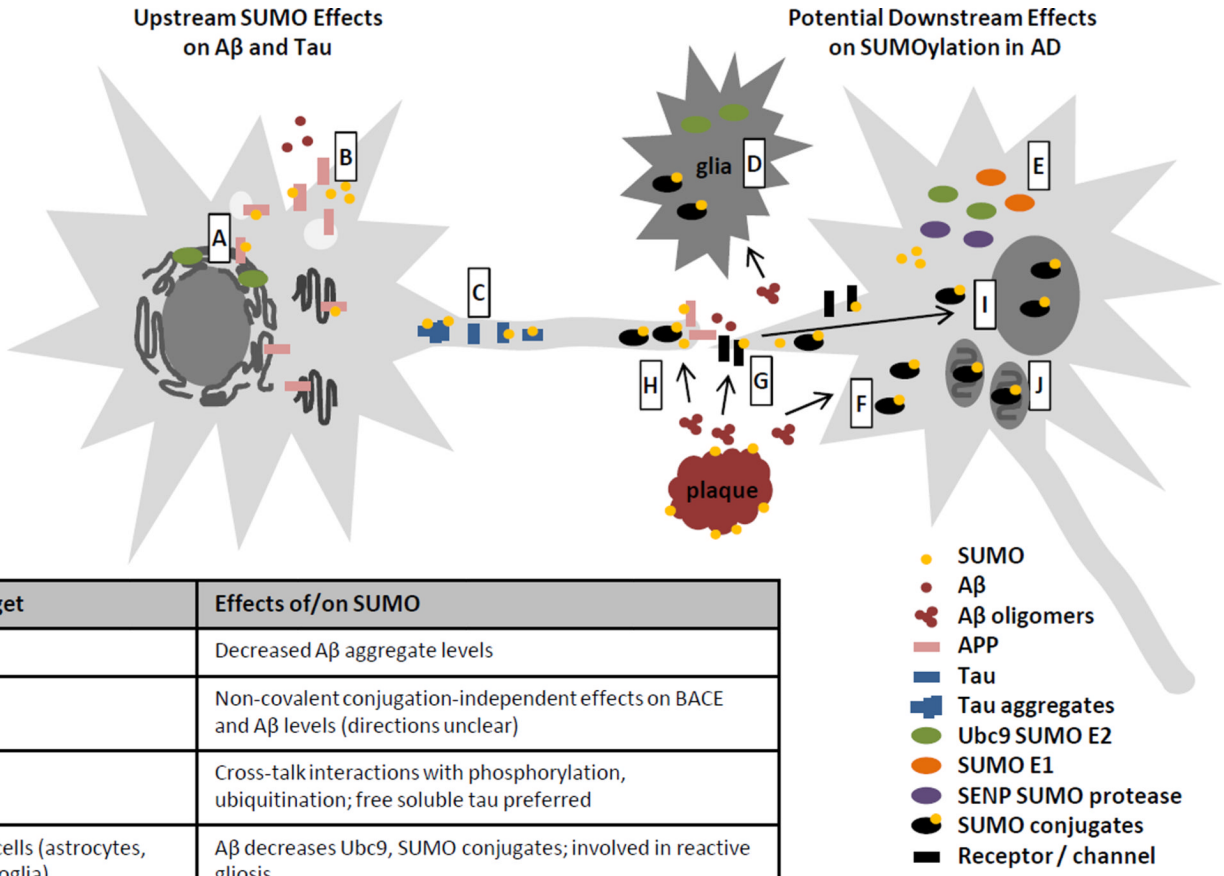


Figure 2. Amyloid-β and tau processing

(A) Amyloid precursor protein (APP) undergoes sequential proteolytic cleavages to produce Aβ peptides. The β-site APP cleaving enzyme (BACE) releases a large soluble N-terminal domain (sAPPβ). Intramembrane cleavage by the γ-secretase complex releases Aβ peptides of varying lengths (usually 39–43 amino acids) and a C-terminal APP intracellular domain (AICD) involved in transcriptional regulation. Aβ peptides can aggregate into soluble oligomers of varying sizes (e.g. dimer, trimer, dodecamer, etc.). Aggregation can further proceed into fibrils that can deposit as amyloid plaques. There are two postulated SUMOylation sites in APP (K595, K587) located near the BACE cleavage site. **(B)** Tau proteins dynamically bind to and stabilize microtubules, a function that is regulated by phosphorylation. Pathogenic dysregulation of this process can lead to tau hyperphosphorylation and aggregation into paired helical filaments. These structures can further aggregate to form the neurofibrillary tangles that characterize many neurodegenerative diseases including AD. The major tau isoforms include either three or four microtubule binding repeats (R1–R4) and also the E2 and/or E3 exons. There is a potential SUMOylation site in the R4 domain (K340).



	Target	Effects of/on SUMO
A	APP	Decreased Aβ aggregate levels
B	Aβ	Non-covalent conjugation-independent effects on BACE and Aβ levels (directions unclear)
C	tau	Cross-talk interactions with phosphorylation, ubiquitination; free soluble tau preferred
D	glia cells (astrocytes, microglia)	Aβ decreases Ubc9, SUMO conjugates; involved in reactive gliosis
E	SUMO enzymes	Potential alterations in SUMO enzymatic machinery with AD and by high Aβ
F	SUMO conjugates	Decrease in some conjugates in an AD mouse model; unknown effects in human AD
G	Post-synaptic compartment	Potential effects on receptors (e.g. GluR6, CB1) and ion channels (e.g. K2P1); spine morphology
H	Pre-synaptic compartment	Potential effects on presynaptic function (e.g. calcium influx, neurotransmitter release)
I	synaptic plasticity signaling molecules	Potential effects on downstream plasticity-related signaling proteins (e.g. Arc, CREB)
J	mitochondria	Potential effects on mitochondrial proteins (e.g. DRP1) and dynamics

Figure 3. Overview schematic of SUMO involvement in Alzheimer's disease

(Left side) SUMO can regulate upstream APP processing and tau dynamics. A – Direct SUMOylation of APP can decrease levels of Aβ aggregates. B – SUMO may exert conjugation-independent effects on Aβ and BACE levels, although the directions of the effects are currently unclear. C – Tau SUMOylation, preferentially of free soluble tau, has cross-talk interactions with phosphorylation and ubiquitination. **(Right side)** Aβ aggregates and AD pathology have observed and hypothesized downstream effects on multiple pathways. D – Aβ exposure can decrease SUMOylation in astrocytes. There may also be effects on SUMO-regulated inflammatory signaling by astrocytes and microglia. E – Genetic and biochemical studies indicate potential changes in the SUMO component

enzymes with AD. There may also be alterations with aging and Aβ exposure. F – Aβ may alter overall SUMOylation capacity/regulation to generally affect SUMO conjugate levels. Some high molecular weight conjugates have been observed to be decreased in an AD mouse model. G – Aβ exposure may alter post-synaptic functioning by perturbing the conjugation of known SUMOylated proteins with roles in spine morphology/development and synaptic signaling. H – Aβ could also impact the SUMOylation of presynaptic proteins, with potential effects on calcium influx and neurotransmitter release. I – Downstream signaling proteins involved in synaptic plasticity may have altered SUMOylation, along with the known Aβ-induced impairments in these signaling pathways. J – Mitochondrial dynamics (e.g. fission) may be altered from dysregulated SUMOylation of mitochondrial proteins known to be SUMOylated, such as DRP1.