

SUMOylation in Neurodegenerative Diseases

Andrea Princz^a Nektarios Tavernarakis^{a, b}

^aInstitute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Department of Basic Sciences, Faculty of Medicine, University of Crete, Heraklion, Greece; ^bDepartment of Basic Sciences, Faculty of Medicine, University of Crete, Heraklion, Greece

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Abstract

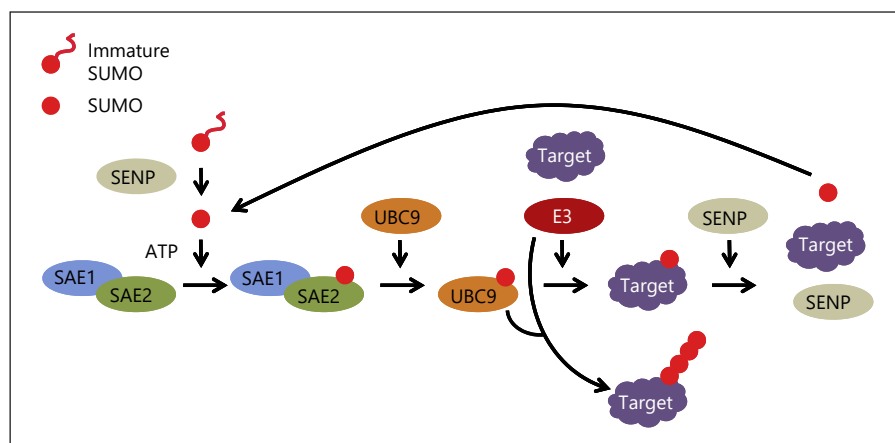
Posttranslational modifications are ubiquitous regulators of cellular processes. The regulatory role of SUMOylation, the attachment of a small ubiquitin-related modifier to a target protein, has been implicated in fundamental processes like cell division, DNA damage repair, mitochondrial homeostasis, and stress responses. Recently, it is gaining more attention in drug discovery as well. As life expectancy keeps rising, more individuals are at risk for developing age-associated diseases. This not only makes a person's life uncomfortable, but it also places an economic burden on society. Therefore, finding treatments for age-related diseases is an important issue. Understanding the basic mechanisms in the cell under normal and disease conditions is fundamental for drug discovery. There is an increasing number of reports showing that the ageing process could be influenced by SUMOylation. Similarly, SUMOylation is essential for proper neuronal function. In this review we summarize the latest results regarding the connection between SUMOylation and neurodegenerative diseases. We highlight the significance of specific SUMO target proteins and the importance of SUMO isoform specificity.

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Introduction

Posttranslational modifications are key regulators of cellular processes under normal, stress and disease conditions. These modifications provide the means to a fast and generally reversible response to an external or internal stimulus. This feature is especially important for healthy neuronal function and synaptic transmission. Proper neuronal function relies on and requires actions to be carried out within milliseconds; a time which is insufficient for transcription and translation of a new protein. Instead, an already synthesized protein can be activated, inhibited or change subcellular localization with the use of posttranslational modifications, like phosphorylation, acetylation, ubiquitination or SUMOylation. The attachment of a small ubiquitin-related modifier (SUMO), to a target protein happens through an evolutionarily conserved series of enzymatic reactions (Fig. 1) [1, 2]. Invertebrates have only one SUMO protein, while the human genome encodes 4 SUMO paralogues [3]. The newly synthesized SUMO proteins are inactive; they require a proteolytic cleavage by a SUMO protease (sentrin-specific proteases, SENPs) to expose their C-terminal di-glycine motif through which they can interact with the enzymatic machinery and the target protein. First, the mature SUMO binds to the heterodimer E1 activating enzyme (consisting of SAE1 and SAE2) in an ATP-de-

Fig. 1. SUMOylation pathway. The immature SUMO protein is cleaved by a SUMO protease (SENP), producing the mature SUMO capable of entering the SUMOylation cycle. The E1 enzyme, which is a heterodimer consisting of SAE1 and SAE2, will activate SUMO through an ATP-dependent reaction and transfer it to the E2 enzyme UBC9. UBC9, together with the E3 ligase, will attach SUMO to the target protein. A protein can be mono- or polySUMOylated, and the process is reversible: a SENP will cleave SUMO from the target protein and the components can enter into a new SUMOylation cycle.



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pendent manner. Then, through a transesterification reaction SUMO is transferred to the E2 conjugating enzyme, UBC9. There is only one E1 and E2 enzyme identified to date in the SUMOylation pathway. UBC9 is able to conjugate SUMO to some target proteins *in vitro*; however, *in vivo* the involvement of an E3 SUMO ligase provides a faster reaction and specificity. SUMO, similar to ubiquitin, can also form chains in an isoform-specific manner: SUMO2 and 3 possess an internal lysine that can act as a SUMO acceptor site while SUMO1 does not have this feature; therefore, it can serve as a chain terminator. SUMOylation is a reversible and often very transient modification; SUMO proteases cleave the SUMO moiety from the target protein after it has carried out its function and the components can re-enter the SUMOylation cycle (Fig. 1) [3]. There are 6 SENPs identified to date (SEN1–3 and SEN5–7) and recently, 3 additional SUMO proteases were described: deSUMOylating isopeptidase 1 and 2 (DeSI 1 and 2) [4] and ubiquitin-specific protease-like 1 (USPL1) [5]. The subcellular localization of these enzymes provides a layer of specificity. The target protein usually contains a SUMO consensus site: ψ KXD/E, where ψ is a large hydrophobic amino acid, K is the target lysine, X is any amino acid and D/E is aspartate or glutamate. Nevertheless, SUMOylation can take place on non-canonical, extended sites [6]. Moreover, SUMO can influence protein-protein interactions not just by covalent attachment but through non-covalent interactions between SUMO and SUMO interaction motifs (SIMs) [7]. Whole protein complexes can assemble this way, like in the case of PML nuclear body formation [8] and DNA damage response [9]. The importance of protein complexes and their manipulation for therapeutic purposes are becoming increasingly apparent. Protein modification by SUMO mostly influences the localization, activity and interac-

tion partners of the target proteins. These functions are analogous to the non-proteolytic functions of ubiquitination. SUMO can also compete with ubiquitin for the same lysine residue and therefore protect the protein from degradation [10]. On the other hand, SUMO chains (but not single SUMO moieties) can be recognized by SUMO-targeted ubiquitin ligases (STUbLs), marking the protein for degradation by the ubiquitin-proteasomal system [11].

SUMO1–3 are expressed ubiquitously and are widely studied; however, we have limited information about SUMO4 whose expression is specific to the kidney, spleen, lymph nodes [12] and placenta [13]. SUMO1 shares only ~50% sequence identity with SUMO2 and SUMO3, while the latter 2 are biochemically indistinguishable; they differ in only 3 amino acids in the N termini of the proteins, hence they are referred to as SUMO2/3. The group of target proteins is different for SUMO1 and SUMO2/3, although there are proteins which can be modified by both isoforms. Moreover, under normal conditions, most of SUMO1 is conjugated to target proteins and there are free pools of SUMO2/3 available for attachment upon stress signals [6]. Stress insults, for example, heat shock or ischemia, result in accumulation of SUMO2/3-modified proteins in the cell, which has a cytoprotective role probably through the enhanced solubility of target proteins [6]. Under normal, unstressed conditions, protein SUMOylation regulates vital cellular processes, like genome stability, transcription, translation or protein stability [14]. Furthermore, in concert with ubiquitin, SUMO is also essential for the maintenance of protein homeostasis (proteostasis) under normal and stress conditions [15]. It is also important to note that SUMO-targeted ubiquitination can play a role in changing the subcellular localization of a protein next to its degradation and ubiquitin can also be removed by specific ubiquitin proteases, prevent-

ing proteasomal degradation and fine-tuning the regulation of target proteins [15]. Although early studies mostly focused on nuclear processes regulated by SUMO (e.g., transcription, DNA damage repair, chromatin organization), there is growing evidence demonstrating the role of SUMOylation outside of the nucleus [16]. In this review we summarize the latest advances in our understanding of SUMOylation during age-related diseases. We focus on the 3 most common neurodegenerative disorders (Alzheimer's, Parkinson's and Huntington's disease) which have been linked to the process of SUMOylation. Other age-related diseases (cancer and cardiovascular diseases) and their connection to SUMOylation have been discussed elsewhere [17, 18].

SUMOylation during Ageing

Considering that SUMOylation has been implicated in nearly all cellular processes, the question arises about the specific role of SUMOylation during senescence and physiological ageing [19–21]. An earlier study reported an increase of SUMO2/3 in mouse hippocampus and prefrontal cortex which resulted in better memory performance [22]. It is important to note that the authors measured unconjugated SUMO2/3, which could indicate a higher turnover rate of the SUMO2/3-modified proteins along with its increased expression. It has also been proposed that SUMO2/3 plays a neuroprotective role under ischemic stress [23]. It is compelling to hypothesize the same role of the protein during ageing, which could in turn lead to the preservation of memory of these older mice. Recently, it has been shown that in cortical lysates of wild-type mice, the amount of SUMO2/3-conjugated proteins is increasing until 10 months of age, while in synaptosomes it starts to decrease after 6 months of age [24]. Interestingly, total SUMO1-modified protein levels show an increase in cortical lysates until 6 months, while in synaptosomes their level continues to rise until 18 months of age [24]. Another study reported that SUMO1-conjugated protein levels increase in the cortices but not hippocampi of mice during ageing [25]. These data not only indicate the important function of SUMOylation in brain development but also in neuronal function during ageing. They also demonstrate the different stoichiometry of SUMO1 and SUMO2/3, which implies their divergent functions. Although it has been shown that SUMO1 knock-out mice are viable, SUMO2/3 is able to compensate for the lack of SUMO1 [26], while SUMO2 knock-out mice die early in development [27]. The importance

of SUMO in neuronal function was also shown in an overexpression study: neuron-specific SUMO1 overexpression caused impaired synaptic activity and dendritic spine density which resulted in learning and memory deficits [28]. Moreover, mice lacking SUMO1–3 in neurons demonstrate reduced recovery capacity from transient ischemia compared to wild type [29]. However, it is still an open question whether the decrease of SUMOylated proteins in older animals could be the cause or the consequence of age-related neurodegeneration.

SUMOylation in Neuronal Function

SUMOylation is indispensable for proper neuronal function starting from the developing brain. Taking into account the nature of synaptic transmission, it is imperative that the cell is able to respond to extrinsic and intrinsic signals in a fast and tightly regulated manner. Protein modification by SUMO is an excellent candidate to fine-tune synaptic function because of its transient quality. The role of SUMOylation in healthy neuronal and synaptic activity has been widely reviewed elsewhere [30, 31]. However, detecting and validating SUMOylation specifically at synapses is still challenging due to the lack of reliable antibodies and models which generated a debate in the field [32]. Nevertheless, identifying new SUMO targets is important and advances in this area of research can help our understanding of neuronal functions in healthy and disease conditions. In this review we will focus only on SUMOylation under pathological conditions.

SUMOylation in Disease

Alzheimer's Disease

The most common neurodegenerative disorder which leads to memory loss is Alzheimer's disease (AD). The patients accumulate in their brains amyloid- β ($A\beta$) plaques and neurofibrillary tangles which consist of the hyperphosphorylated form of tau protein. The formation of these protein aggregates leads to synapse and neuron loss which is the underlying cause of memory impairment [33]. Currently, there is no cure for AD, making it even more important to understand the basic mechanisms leading to the aetiology of the disease and to exploit this information in the development of therapies.

$A\beta$ is generated from the amyloid precursor protein (APP) by cleavage of β - and γ -secretases. The small, 4-kDa $A\beta$ plays a role in synaptic physiology and plastic-

ity [33]. APP has been reported as a SUMO substrate. Early studies examining the consequences of APP SUMOylation yielded diverse results. SUMO3 overexpression in human embryonic kidney 293T cells decreased the levels of A β plaques. However, this effect was lost when a mutant form of SUMO3, which was incapable of chain formation, was overexpressed in 293T and human neuroblastoma cells [34]. Conversely, another report showed that overexpression of SUMO3 led to the increase of A β and this result was independent of its SUMO chain-forming ability. Moreover, the elevated levels of SUMO3 specifically triggered the upregulation of the APP processing enzyme, β -secretase (BACE) [35]. Therefore, there is a need to clarify the precise consequence of SUMO3 attachment to APP under relevant disease conditions, like in cultured neuronal cells or in AD models. Looking at the effect of SUMO1 overexpression, it has been observed to reduce the production of A β in HeLa cells. The authors hypothesized that the attachment of SUMO1 to APP interfered with the cleavage site of BACE [36]. On the contrary, a recent study showed a positive correlation between SUMOylation and the development of aggregates in an AD mouse model. The expression of SUMO1 was upregulated, along with BACE-1, which led to an increase in A β accumulation [37]. In line with these results, another group demonstrated the accumulation of SUMO1 in another AD mouse model at 3 and 6 months of age, compared to wild type. Interestingly, there was no change in the modification rate by SUMO2 until 17 months of age, where a significant decrease was detectable [38]. One reason behind these contradictory results could be the use of different model systems and pushing them with overexpression, which could yield results that are not present under physiological conditions. Therefore, it is very important to determine strict conditions when one wishes to study the role of a transient modification, like SUMOylation in disease models.

More recent studies have been carried out with the use of AD mouse models, making the results more reliable. It has been shown that A β is able to induce the SUMOylation of HDAC1 by PIAS1. This leads to the activation of CREB (cAMP response element binding protein). The introduction of a constantly SUMOylated HDAC1 to the hippocampus of an AD mouse model decreases the amount of A β plaques and neuronal cell death. In turn, the memory impairment of these animals is augmented [39]. This study demonstrates that depending on the target molecule, increased SUMOylation can have beneficial effects under disease conditions and raises the importance of targeting the SUMOylated status of specific proteins to

tackle AD. A recent study examined the reason behind the increased A β plaque formation in a SUMO1-overexpressing AD mouse model. The authors found that instead of acting on the production of APP, the clearance of plaques is compromised through a decrease in microglia numbers upon SUMO1 overexpression [40]. Considering the reversible nature of SUMOylation, it has been reported that SENP1 and SENP2 are both able to deconjugate SUMO from APP. Interestingly, in an AD mouse model, the females were more aggressively affected by the disease, which can be the result of a female-specific, age-related increase in SENP1 expression. The authors argue that SUMOylation of APP prevents the cleavage of the protein by BACE; therefore, removing the modification allows for the processing of APP and generation of A β [41]. Although this is an intriguing finding, the conclusions are based on an earlier study that has been carried out in HeLa cells [36]; thus, the underlying cause for their observation might be a different, yet to be uncovered, one. Nevertheless, it highlights the gender-related differences in disease aetiology and suggests the need for a gender-specific treatment. Another study underlined the significance of SUMOylation at specific subcellular localizations. Increased SUMO-1ylation levels in synaptosomes led to impaired neurotransmitter release in an AD mouse model. Decreasing the rate of SUMOylation at the level of synapse resulted in improved synaptic function [42]. Yet another report showed no difference in the amount of SUMO1-modified proteins in the brains of an AD mouse model. Moreover, the authors noted that in the neurons of these mice, SUMO1-conjugated proteins are mainly nuclear and do not localize to amyloid plaques [25]. All these results stress the importance of studying the consequences of SUMOylation in neurons in a target-specific and subcellular localization-specific manner.

In healthy neurons, tau is bound to microtubules and its function is to stabilize them; however, under disease conditions the protein forms neurofibrillary tangles [33]. It is important to note here that the classic dogma about tau function is changing. The new studies which are investigating the role of tau are performed in neurons and the conditions are closer to the *in vivo* state. In this case tau seems not to stabilize the microtubules, but on the contrary, tau can inhibit other stabilizing proteins to bind to the labile domain of microtubules. This is crucial when a therapy targets the microtubule stabilizing function of tau [43]. Nevertheless, when tau is hyperphosphorylated, it detaches from the microtubules and accumulates in neurofibrillary tangles [33]. Tau contains 2 consensus SUMOylation sites and it has been shown that the major

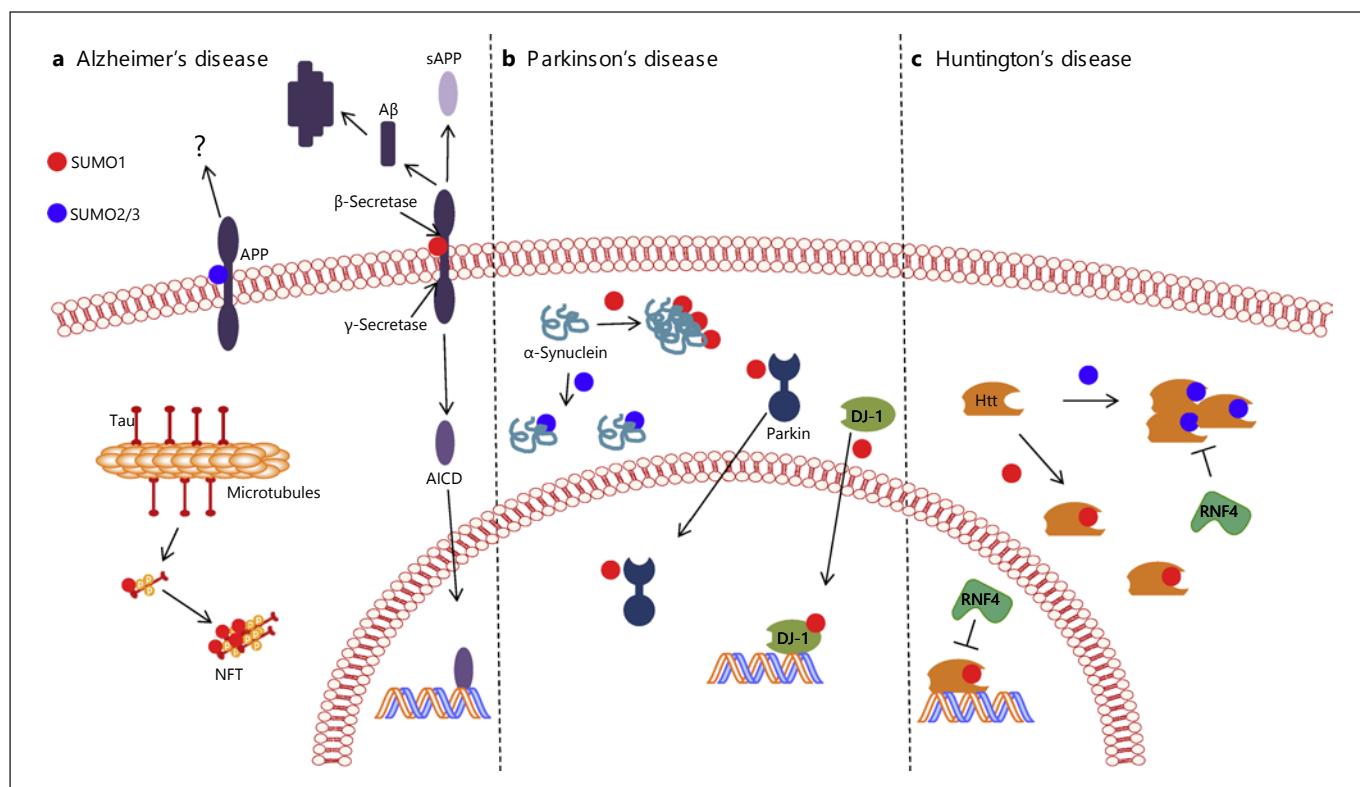


Fig. 2. Overview of SUMOylation in neurodegenerative diseases. **a** Alzheimer's disease. Under disease conditions, the amyloid precursor protein (APP) is processed by a β - and γ -secretase and this will result in the production of 3 peptides: sAPP (soluble amino terminal ectodomain of APP), AICD (APP intracellular domain) and the aggregation-prone A β (amyloid- β). SUMO1 attachment to APP causes an increase in the formation of A β plaques through a mechanism that is still not fully understood. Moreover, the consequences of SUMO2/3 modification of APP require further research as well. When tau is hyperphosphorylated, it is no longer associated with the microtubules and it can undergo SUMO1 modification. The aggregation of these modified tau proteins will lead to the formation of neurofibrillary tangles (NFT). **b** Parkinson's disease. α -Synuclein can be a substrate for SUMO1 and

SUMO2/3. While the attachment of SUMO2/3 will increase the solubility of α -synuclein, SUMO1 makes the protein aggregation prone. The chaperone and transcriptional co-activator DJ-1 requires SUMOylation to carry out its function. Interestingly, the E3 ubiquitin ligase parkin is not modified by SUMO1 but they interact non-covalently. This interaction promotes the nuclear translocation of parkin and increases its E3 ligase activity which results in its auto-ubiquitination and degradation. **c** Huntington's disease. The SUMO2/3-modified Huntingtin (Htt) protein forms aggregates in neurons; however, this form is less toxic. On the other hand, SUMO1 attachment to Htt increases its solubility and toxicity. The SUMO-targeted ubiquitin ligase RNF4 can clear the Htt aggregates from the cell and augment the detrimental transcriptional changes caused by a nuclear fraction of Htt.

SUMO acceptor site is K340. Moreover, SUMO targets the non-microtubule bound form of the protein and the same residue can also be modified by ubiquitin. Therefore, the attachment of SUMO inhibits the proteasomal degradation of tau [44]. SUMO was also found to co-localize with phosphorylated tau aggregates in an AD mouse model [45] and in AD patients [46]. In addition, the latter study also demonstrated that SUMO modification of tau triggered its hyperphosphorylation. Moreover, phosphorylation of tau induced SUMOylation and inhibited ubiquitination and consequently proteasomal degra-

tion [46]. Taken together, the inhibition of SUMO modification and promotion of ubiquitination of tau could be a promising therapeutic approach, and this would bypass the now-questioned original function of tau in neurons. The effects of SUMOylation in AD are summarized in Figure 2a.

Parkinson's Disease

Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta.

This area of the brain controls voluntary movements; hence, the localized progressive loss of neurons leads to resting tremor, impaired balance, muscle rigidity and difficulties in speech and writing. Interestingly, only ~5% of the reported PD cases have genetic origin and the reasons behind the sporadic cases are still not fully understood. One characteristic of the disease on the cellular level is the existence of Lewy bodies (LBs) which are large, insoluble protein aggregates. The most prominent component of the LBs is α -synuclein, but they also stain positive for ubiquitin as well as SUMO1, raising the possible involvement of SUMOylation in this condition [47].

α -Synuclein is a small (14 kDa) presynaptic protein and mutations in its gene have been linked to the familial cases of PD. Through its association with SNARE (soluble N-ethylmaleimide-sensitive factor activating protein receptor) proteins at the presynaptic site, α -synuclein can play a role in the regulation of neurotransmitter release and synaptic plasticity [48]. Under normal conditions, α -synuclein can be found in an unfolded form in the cytoplasm or bound to synaptic vesicles in an α -helical form [49]. In pathological conditions, α -synuclein takes up another conformation and first forms intermediate oligomers which can assemble to large protein aggregates. The oligomers behave as prion strains and have the ability to spread across various brain regions and serve as conformational templates for the monomeric form of α -synuclein to form aggregates in a disease-specific way [49]. α -Synuclein can be modified by SUMO1 and SUMO2, and the consequences of the attachment of each isoform have been shown to be different. The most important lysine residues for SUMO2 modification are K96 and K102. Conjugation of SUMO2 to α -synuclein on these sites increases the solubility of the protein [50]. On the other hand, a different study demonstrated that attachment of SUMO1 to α -synuclein promotes its aggregation [51]. This observation could provide an explanation as to why only SUMO1, but not SUMO2, was found to be present in LBs. Additionally, when the proteasomal system is compromised, SUMO-modified α -synuclein forms aggregates, but this process does not interfere with the ubiquitination of the protein [52]. This finding was challenged by a new study which reported that SUMOylation counteracts α -synuclein ubiquitination and this could result in aggregate formation of the protein instead of its degradation [53]. Interestingly, next to modulating the aggregation properties of α -synuclein, SUMOylation can also influence the extracellular vesicular release of α -synuclein. This is achieved through the endosomal sorting complex required for transport (ESCRT); SUMO is present at

ESCRT formation sites, interacts with phosphoinositols and initiates the extracellular release of α -synuclein [54]. In summary, SUMO1 modification of α -synuclein can be responsible for its aggregation and spreading across the brain, contributing to disease development. Finding an approach which blocks SUMO1 attachment to α -synuclein or promotes SUMO2 modification in contrast to SUMO1 could be a possible treatment option to consider in the future.

In familial cases of PD, the most frequently mutated gene is PARK2, which encodes the parkin E3 ubiquitin ligase. Next to α -synuclein, parkin has also been found in LBs in patients. So far, there is no direct evidence linking SUMO and parkin in the development of the disease; however, SUMO1 can interact non-covalently with parkin. The E3 ligase activity of parkin is boosted upon interaction with SUMO1 and a small fraction of parkin is translocated to the nucleus. Moreover, it has been shown that one of the targets of parkin ubiquitination is a SUMO E3 ligase, RanBP2 [55]. Therefore, perturbations in parkin activity could lead to improper SUMOylation of specific proteins which in turn could aggravate the development of the disease.

DJ-1 is a transcriptional co-activator and under oxidative stress it acts as a molecular chaperone. Mutations in the PARK7 gene, which encodes DJ-1, have been associated with 1–2% of early-onset PD cases. It is expressed ubiquitously in the brain, both in neurons and in glial cells, and it is mainly localized in the cytoplasm, nucleus and at mitochondria. Additionally, DJ-1 can be found both at pre- and postsynaptic terminals [56]. It has been shown that DJ-1 needs to be SUMOylated upon UV irradiation in order to translocate to the nucleus and carry out its cytoprotective function. Importantly, mutating the main SUMO acceptor site in the protein K130 leads to the aggregation of DJ-1 in the cell, coupled with increased sensitivity to UV irradiation [57]. Thus, promoting the SUMOylation of DJ-1 could be a way to alleviate disease conditions. The consequences of SUMOylation in PD are summarized in Figure 2b.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disease characterized by progressive motor function decline, and psychiatric and cognitive impairment. It is caused by a dominant mutation in the gene encoding huntingtin (Htt). HD is categorized as a polyglutamine (polyQ) disorder because the disease-causing mutation affects the CAG (glutamine coding) repeats at the N terminus of the protein: instead of 23 residues, the mutant form contains

Table 1. Key proteins regulated by SUMOylation in neurodegenerative diseases

Name	Function	Reference
APP	SUMO1 modification of the protein increases amyloid- β plaque formation The consequences of SUMO3 attachment are still not clear; amyloid- β plaques have been shown to increase and decrease as well	37, 38 34, 35
Tau	SUMOylation of tau increases its aggregation and inhibits the proteasomal degradation of the protein	44, 46
α -Synuclein	Attachment of SUMO1 makes α -synuclein aggregation prone and inhibits its degradation SUMO2 modification of α -synuclein increases its solubility; hence Lewy bodies are not positive for SUMO2, only for SUMO1	51, 53 50
Parkin	The non-covalent interaction with SUMO1 enhances the E3 ligase activity of the protein	55
DJ-1	SUMOylation of DJ-1 is required for its full activation upon UV stress	57
Huntingtin	Modification by SUMO1 renders the protein more soluble and more cytotoxic The aggregation of huntingtin is increased upon SUMO2 attachment and in this state the protein is less toxic	59–61 60

40 or more and this leads to misfolding of Htt. The length of the expansion correlates with the onset of HD; more polyQ repeats induce earlier development of the disorder. The phenotype of HD does not simply arise from the accumulation of misfolded mutant Htt; the protein acquires toxic gain of function roles in the cell, and this triggers neuronal death which mainly localizes in the striatum [58].

Htt is a large, 348-kDa protein and can be found in the cytoplasm and nucleus of neurons. Its role has been shown in vesicular transport, transcription and RNA trafficking. Htt is a target protein for many posttranslational modifiers, including ubiquitin and SUMO. These 2 small proteins attach to the same lysine residue which creates a competition for the modification of the protein. While SUMOylation of Htt makes the protein more soluble [59], it also exacerbates the disease phenotype and the cytotoxicity of the protein [60, 61]. On the other hand, ubiquitination of Htt promotes its degradation and protects the neurons from cell death in *Drosophila* [59]. These results further strengthen the notion that the pathogenesis of HD cannot be mainly attributed to protein aggregation but to cytotoxic functions of the mutated protein. Interestingly, when modified by SUMO2, Htt becomes aggregation prone in HeLa cells and this modification was also observed in insoluble fractions of the striata of HD patients [60]. It would be important to further analyse the consequences of SUMO2 attachment to Htt in neuronal cells and in HD models. Based on this information a treat-

ment could be developed which could favour either ubiquitination or SUMO2 modification of Htt instead of SUMO1. More recently, another layer of Htt regulation has been described. The STUbL RNF4 has been found to target Htt in yeast and various human cell lines. Overexpression of RNF4 protected against Htt aggregates and augmented the transcriptional changes observed in HD by acting directly on the chromatin-associated Htt [62]. This finding could give the opportunity to design an effective treatment against this neurodegenerative disease, since the RNF4-dependent degradation of Htt would be SUMO isoform insensitive. These findings are depicted in Figure 2c.

Concluding Remarks

The importance of SUMOylation in neurodegenerative and other age-related diseases has become increasingly apparent. Table 1 summarizes the key SUMO target proteins which are discussed in this review. As our knowledge improves about the basic mechanisms behind age-related pathologies, we can develop more specific and efficient treatments. The development of new therapies has the potential to increase the health span of the population thereby improving personal well-being. Targeting SUMOylation on a cellular or specific protein level is a novel and promising approach to tackle diverse disorders. It has been shown that increasing SUMOylation of

SERCA2a (sarcoplasmic reticulum calcium ATPase) with a small molecule can augment the contractile profile of cultured cardiomyocytes and improve heart function in mice with heart failure [63]. Another study demonstrated that downregulation of general SUMOylation with a selective E1 enzyme inhibitor decreased the proliferation of various cancer cell lines [64]. A recent report showed that targeting SUMOylation is a treatment option in gut inflammation as well [65]. It has recently been reported that instead of interfering with SUMO conjugation, we have the opportunity to interrupt the non-covalent interactions between SUMO-modified and SIM-containing proteins. This can be achieved by the generation of synthetic proteins and this method can be applied to other protein-protein interactions as well [66]. These examples demonstrate that it is not only feasible, but also efficient to target

SUMOylation in different diseases, paving the road towards SUMO-specific treatments for neurodegenerative disorders.

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