Review

Influence of Sox protein SUMOylation on neural development and regeneration

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Abstract

SRY-related HMG-box (Sox) transcription factors are known to regulate central nervous system development and are involved in several neurological diseases. Post-translational modification of Sox proteins is known to alter their functions in the central nervous system. Among the different types of post-translational modification, small ubiquitin-like modifier (SUMO) modification of Sox proteins has been shown to modify their transcriptional activity. Here, we review the mechanisms of three Sox proteins in neuronal development and disease, along with their transcriptional changes under SUMOylation. Across three species, lysine is the conserved residue for SUMOylation. In *Drosophila*, SUMOylation of SoxN plays a repressive role in transcriptional activity, which impairs central nervous system development. However, deSUMOylation of SoxE and Sox11 plays neuroprotective roles, which promote neural crest precursor formation in *Xenopus* and retinal ganglion cell differentiation as well as axon regeneration in the rodent. We further discuss a potential translational therapy by SUMO site modification using AAV gene transduction and Clustered regularly interspaced short palindromic repeats-Cas9 technology. Understanding the underlying mechanisms of Sox SUMOylation, especially in the rodent system, may provide a therapeutic strategy to address issues associated with neuronal development and neurodegeneration.

Key Words: axon regeneration; neural development; neurological disorder; neuroprotection; post-translational modification; small ubiquitin-like modifier; Sox transcription factor; SUMOylation

Introduction

Post-translational modification (PTM) is the process of covalent addition of a molecular group to proteins, leading to changes in protein subcellular localization, function and stability (Gupta et al., 2021), of which the small protein, small ubiquitin-like modifier (SUMO), is one example (Chang and Yeh, 2020). In *Drosophila*, only one SUMO has been found (smt3) (Urena et al., 2016) whereas four types of SUMOs (SUMO1/2/3/4) have been identified in humans (Sarge and Park-Sarge, 2011). Unlike the process of ubiqitination leading to protein degradation (Schmidt et al., 2021), SUMOylation, a PTM which attaches SUMO to a lysine residue of protein, does not lead to protein degradation (Savare et al., 2005), and is broadly studied in plants (Augustine and Vierstra, 2018), fruit flies (Nie et al., 2009; Koltun et al., 2017) and frogs (Bertke et al., 2019). There are three enzymatic activities that contribute to the SUMOylation process including E1 SUMO1 activating enzyme subunit 1/2 (Lois and Lima, 2005), E2 ubiquitin conjugating enzyme (Reverter and Lima, 2005), and E3 ligases such as RNA binding protein 2 and protein inhibitor of activated STAT1 (PIAS1) (Morozko et al., 2021). These E3 ligases mainly target the SUMO acceptor lysine within a ΨKXE motif (Ψ is any hydrophobic amino acid and X is any amino acid). In humans, many reports of SUMOylation focus on roles in cancer biology (Seeler and Dejean, 2017) involving transcription factor signal transduction, protein localization and downstream epigenetic regulation of transcription. In the eye, five SUMOylation enzymes have been observed in ocular tissues (Nie et al., 2018). PIAS3-dependent SUMOylation was reported to affect mouse photoreceptor differentiation by modifying Cone enriched transcription factors (TFs) (Onishi et al., 2010), and rod specific TFs (Onishi et al., 2009). Another study reported that PIAS3-independent SUMOylation of neural retina leucine zipper (NRL) is required for rod photoreceptor development and that NRL^{K20R} reduces transcriptional activation of rod specific TF nuclear receptor subfamily 2 group E member 3 (Roger et al., 2010). Being a reversible modification, SUMO can be deconjugated by SUMO isopeptidases and proteases such as sentrin-specific protease (SENP) (Chen et al., 2021). A study showed that seven SENPs were observed in retinal, corneal and lens tissues (Xiang et al., 2018), suggesting that the balance between SUMOylation and deSUMOylation plays important roles in regulating signal transduction and cellular physiology. In this mini-review, we explored the function of SUMOylation, focusing on Sox transcription factors in central nervous system (CNS) development, and its potential role as a therapeutic target to treat neurodegeneration.

Search Strategy and Selection Criteria

We performed a literature search on PubMed and Google Scholar until March 2021 published in English. The key words/terms were neural regeneration, neural development, neurological disorder, Sox transcription factor, SUMOylation.

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Signaling Pathways of SUMOylation

SUMOylation is known to interact with three major pathways: Ras/mitogen-activated protein kinase (Ras/MAPK), Jun N-terminal kinase (JNK) and Hedgehog (Hh) pathways (Yau et al., 2020). Ras/MAPK is a key signal for cell proliferation and differentiation (Jafry and Sidbury, 2020). In cancer cells, SUMOylated growth factor receptor-bound protein 2 has been reported to promote oncogenic features, while genetic deletion of growth factor receptor-bound protein 2 decreased transplanted cells' motility and proliferation in a tumor engraftment model by suppressing Ras/MAPK pathways (Qu et al., 2014). JNK, one member of the MAPK superfamily of proteins, is involved in many cellular processes, especially in apoptosis (Hammouda et al., 2020). As a key regulator in cellular physiology, JNK signaling is also regulated by SUMO (Schneider Aguirre and Karpen, 2013). In *Drosophila*, SUMO attaches to homeodomain-interacting protein kinase (Hipk) on lysine 25 in the wing disc, promoting Hipk translocation into the nucleus (Hofmann et al., 2005). Genetic deletion of SUMO in the wing disc leads to apoptosis, which is reversible if JNK signaling is reduced (Huang et al., 2011). In addition, JNK-mediated tumor necrosis factor alpha secretion enhances SUMOylation of retinoid X receptor and this cellular response can be blocked by JNK inhibition (Schneider Aguirre and Karpen, 2013). Hh signaling regulates animal development, and many human developmental diseases, such as Pallister-Hall syndrome, are associated with misregulation of the Hh signaling pathway (Briscoe and Therond, 2013). In *Drosophila*, several studies have revealed that SUMOylation of Smoothened (Smo) leads to its cell-surface accumulation and elevation of Hh pathway activity (Ma et al., 2016; Zheng and Shabek, 2017). This relationship between SUMO and Hh is conserved in mammals, in which Sonic hedgehog stimulates SUMOylation of mammalian Smo (mSmo), further regulating its ciliary localization and Sonic hedgehog pathway activity (Ma et al., 2016).

Mechanisms of SUMOylation in Neurodegenerative Diseases

In addition to cell differentiation, apoptosis and development, SUMOylation is reported to be involved in neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease (HD) (Chen et al., 2021), which are regulated by mitochondria-mediated responses (He et al., 2020). In PD, growing evidence shows that α-synuclein has a causative role in disease pathology (Wakabayashi et al., 2007) and that SUMO-mediated mechanisms regulate α-synuclein aggregation and degradation (Eckermann, 2013; Rott et al., 2017), which is thought to be involved in disease onset. Amyloid-beta (Aβ) and microtubule-associated protein Tau aggregation is the major pathological hallmark of AD. It was reported that SUMO1 promotes Aβ production (Cho et al., 2015). Similarly, Tau hyper-phosphorylation enhances its SUMOylation, which decreases its solubility, promoting protein aggregation (Luo et al., 2014). These studies suggest that SUMOylation of Aβ and Tau leads to pathogenic protein aggregation, resulting in AD progression. HD is the result of an abnormal Huntingtin (HTT) protein accumulation due to a polyQ stretch located in the N-terminal domain of the protein, which leads to neuronal toxicity (Steffan et al., 2004). SUMOylation of htt competes for the same residues of ubiquitination, preventing ubiquitin-induced degradation, leading to htt aggregation (Ehrnhoefer et al., 2011). Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is associated with superoxide dismutase 1 (SOD-1) mutations (Johnson and Giulivi, 2005). A study showed that SUMO-3 conjugation enhances SOD-1 protein stability and promotes intracellular aggregate formation, suggesting an underlying mechanism relevant to the pathogenesis of ALS (Niikura et al., 2014).

SUMOylation of Sox family proteins

The SRY-related HMG-box (Sox) superfamily includes nine family members (Guth and Wegner, 2008) and potential SUMOylation sites (ΨKXE motif) have been predicted in several Sox proteins in human and *Drosophila* (Savare et al., 2005). Among subfamilies, SoxC TFs, Sox4, Sox11 and Sox12, are involved in embryonic development, tumorigenesis and skeletogenesis (Penzo-Mendez, 2010; Lefebvre and Bhattaram, 2016). In eye development, SoxC TFs are required for retinal ganglion cell (RGC) differentiation (Chang et al., 2017; Chang and Hertz, 2017; Kuwajima et al., 2017) as deletion of Sox4/Sox11 establishes optic nerve defeat, leading to vision loss (Chang et al., 2017). In RGC progeny, Sox11 is SUMOylated at K91 and expressed mainly in the cytoplasm while deSUMOylated Sox11 ($Sox11^{K91R}$) is mostly in the nucleus, and blocking Sox11 SUMOylation enhances RGC differentiation (Chang and Hertz, 2017). In addition, exogenous overexpression of a non-SUMOylatable Sox11 mutant ($Sox11^{K91A}$) promotes more axon regeneration *in vivo* but reduces $spp1^{+}$ and $opn4^{+}$ gene expression in early postnatal primary RGC cultures (Chang et al., 2021). In addition, SoxC TFs also affect Muller glia development (Chang et al., 2017), a process which may similarly depend on protein SUMOylation. Although another lysine residue (K240) was predicted as a SUMO site in Sox11 (Savare et al., 2005), the physiological influence of its modification remains unclear. The above findings indicate that SUMOylation mediates the transcriptional activity of Sox11 in retinal cell development, RGC survival and axon regeneration (**Figure 1**). Notably, Sox11 regulation has opposing effects on RGC survival and regeneration. However, the underlying regulatory mechanisms with respect to SUMOylation of Sox11 on axon regeneration and RGC survival, especially the relative ligase(s), remain open for study.

SoxE (Sox8, 9 and 10) subfamily proteins have been characterized as transcriptional activators. In *Xenopus*, Sox8 regulates the onset of expression of Sox9, which further regulates Sox10 expression during neural crest development (O'Donnell et al., 2006). Deletion of Sox8 leads to defects of neural crest precursor formation (O'Donnell et al., 2006), while Sox9 deletion also leads to a failure of inner ear formation in *Xenopus* (Saint-Germain et al., 2004). Like SoxC proteins, SoxE proteins also contain many predicted SUMO sites in humans (Savare et al., 2005). In *Xenopus*, lysine residues 61 and 365 (K61, 365) were shown as SUMOylated sites of Sox9 (Taylor and Labonne, 2005). Compared to wildtype Sox9, overexpression of $Sox9^{K61,365R}$ (unSUMOylated) leads to more neural crest precursors formation but inhibits inner ear development (Taylor and Labonne, 2005). Similar study of TF manipulation in rodents showed that a Sox10 (another SoxE TF) mutation leads to deafness (Brizzolara et al., 2004). A later study reported that $Sox9^{K61,365R}$ interacts with CBP/p300 to initiate transcriptional activity, and that SUMOylated Sox9 fails to bind to CBP/p300 but recruits groucho-related gene 4 (Grg4) as a corepressor to the transcriptional binding site, which promotes melanocyte formation but inhibits neural differentiation (Lee et al., 2012). This study reveals a novel mechanism for SUMO-mediated recruitment of coregulatory factors (**Figure 2**). However, how Sox9 SUMOylation plays a positive role in inner ear development but a negative role in neural crest formation remains unclear. One possible mechanism could be that SUMO-modified Sox9 represses expression of genes involved in neural crest formation as well as genes that block inner ear development. Further investigations are needed to study the downstream signaling underlying this regulatory mechanism.

Sox-Neuro (SoxN), encoded by Sox3 in humans, belongs to the SoxB1 subfamily. SoxN was identified in *Drosophila* to function as a developmental regulator (Cremazy et al.,

2000). Mutation of SoxN leads to severe impairments in *Drosophila* CNS development, especially in neuroblast formation (Overton et al., 2002). Like most of the Sox proteins, SoxN contains a SUMO motif (ΨKXE) at lysine 439 (K439) in *Drosophila*, which is conserved at K375 in human Sox3 (Savare et al., 2005). Since SUMOylation is functionally conserved in vertebrates and invertebrates, SoxN was able to be SUMO modified in transfected human HeLa cells with both SUMO1 and SUMO2 (Savare et al., 2005). To study the effect of SUMOylation function on SoxN *in vivo*, $SoxN^{K439R}$ was overexpressed in larval imaginal discs during development. Since overexpression of $SoxN^{K439R}$ globally in *Drosophila* was lethal, eye-specific overexpression was conducted, which enhances transcriptional activity (**Figure 3**), leading to severe impairments of CNS development in *Drosophila* such as headless (Savare et al., 2005). These studies indicate that SUMOylation of SoxN in *Drosophila* is required for CNS development. In human and mouse, many Sox families show identical genomic organization including Sox3 (Schepers et al., 2002). In human, Sox3 is implicated in mental retardation (Laumonnier et al., 2002) and in mouse, Sox3 is required during the formation of the hypothalamus-pituitary axis (Rizzoti et al., 2004). We therefore speculate that SUMOylation of Sox3 might also be important for neural development in mammals and it would be an interesting area for future study.

Conclusions and Perspectives

This mini review describes the essential roles of Sox protein SUMOylation in neural development and regeneration in invertebrates and vertebrates (**Table 1**). SUMOylatoin is a conserved PTM across species, which increases protein functional diversity without requiring additional specific genomic elements for each protein. However, much is still unexplored about SUMOylation. For example, in the eye, neuronal regeneration, which spontaneously occurs in fish and frogs but not mammals, can be controlled by SUMOylation of Sox11 (Fischer and Bongini, 2010), suggesting a comparative difference in SUMOylation dynamics in development and disease. Over the past decade, RNA sequencing (RNA-seq) technology facilitates transcriptome-wide analysis, which is capable of examining gene sliced transcripts, PTMs and single-nucleotide polymorphisms (Stark et al., 2019). A previous RNA-Seq study revealed that SUMOylation of Sox11 regulates RGC survival and axon regeneration by activating different signaling pathways (Chang et al., 2021). Using such a technology would provide a deeper understanding of SUMO regulatory mechanism in neural development and neurological disease.

Across different species, SUMOylation of SoxN (*Drosophila*) shows neural protection in CNS development, whereas deSUMOylation of SoxC (murine) and SoxE (*Xenopus*) can promote axon regeneration and neural crest formation, respectively. It seems, at least in our reviewed cases, deSUMOylation plays a greater role in neural protection. In addition, another study showed that SUMO-specific protease 1 (SENP1) protects neurons from apoptosis during transient brain ischemia in a mouse model, which supports our hypothesis that deSUMOylation plays a neuroprotective role (Zhang et al., 2016). In regard to genetic neurological disorders, aberrant SUMOylation leads to PD, AD and HD (Chen et al., 2021). Pharmacologic inhibition of E3 ligase might be a potential therapeutic target for those diseases.

Table 1 | **SUMOylated Sox proteins that influence neural physiology**

Gene	Species	Group	SUMO site	Physiologic impacts of SUMOylation	Reference
SoxN	Drosophila	B1	K439	Central nervous system development	Savare et al., 2005
Sox9	*Xenopus*	E	K61, 365	Neural crest precursor formation	Taylor et al., 2005
Sox11	Mouse	C	K91	Retinal ganglion cell differentiation and axon regeneration	Chang et al., 2017, 2021

SUMO: Small ubiquitin-like modifier.

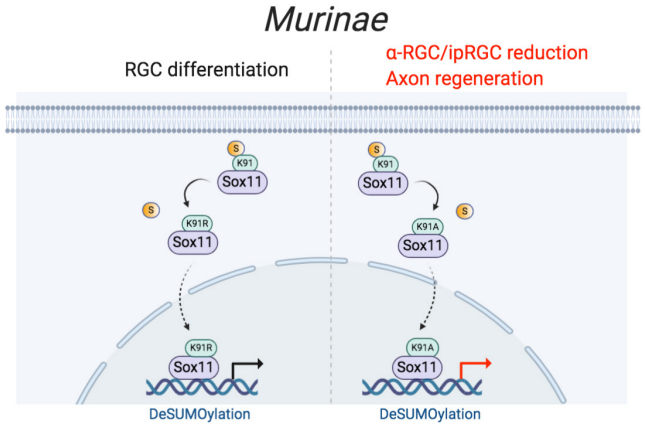

Figure 1 | **DeSUMOylation of Sox11 by lysine 91 (K91) mutation promotes RGC differentiation and axon regeneration but reduces α-RGC and ipRGC expression in *Murinae*.**
ipRGC: Intrinsically photosensitive retinal ganglion cell; Sox: SRY-related HMG-box; SUMO: small ubiquitin-like modifier. Created with BioRender.com.

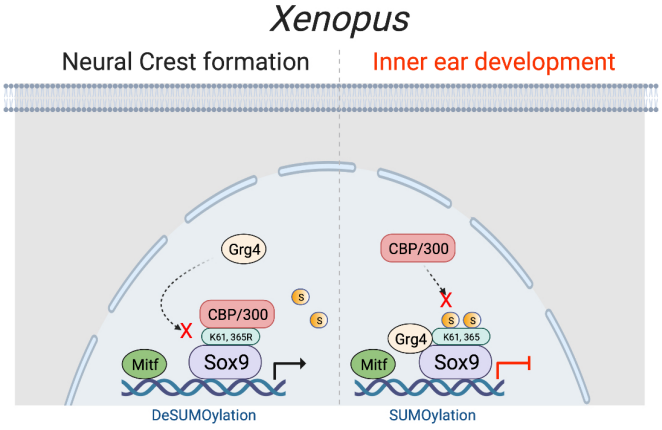

Figure 2 | **SUMOylation of Sox9 on lysine 61 and 365 (K61, 365) represses transcriptional activity by recruiting repressor Grg4 to form an inhibitory complex, which suppresses neural crest formation but promotes inner ear development in *Xenopus*.**
Grg4: Groucho-related gene 4; Sox: SRY-related HMG-box; SUMO: small ubiquitin-like modifier. Created with BioRender.com.

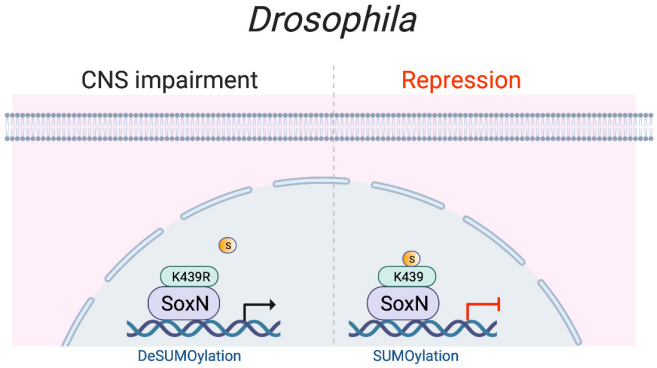

Figure 3 | **SUMOylation of SoxN on lysine 439 (K439) suppresses transcriptional activity, which prevents CNS from impairment in *Drosophila*.**
CNS: Central nervous system; Sox: SRY-related HMG-box; SUMO: small ubiquitin-like modifier. Created with BioRender.com.

In contrast, SUMOylation could play a protective role in pathogenesis. For example, vascular endothelial cell growth factor receptor 2 SUMOylation by deleting SENP1 alleviates vascular endothelial cell growth factor-induced angiogenesis in the retina (Zhou et al., 2018), suggesting that enhancing SUMOylation could be a therapeutic strategy for diabetic retinopathy. In addition, SUMOylation of SoxN is important for CNS development in *Drosophila*. Since Sox3 is involved in mental retardation, investigation of the SUMO site of Sox3 in the human genome can help us to understand the molecular mechanism of Sox3 in such neural diseases. Using SENP inhibitors as a treatment for promoting Sox3 SUMOylation could be a therapeutic strategy targeting Sox3-mediated disease.

Manipulation of signaling pathways might provide another therapeutic strategy. For example, extracellular signal-regulated kinase (ERK) phosphorylation was found to be increased in human cerebral cavernous malformation lesions (Wustehube et al., 2010). PIAS3-mediated nNOS SUMOylation was required for ERK1/2 activation in hippocampal neurons (Du et al., 2020), suggesting a possibility that blockade of PIAS3 can alleviate cerebral cavernous malformation degree by suppressing ERK signaling. In the eye, N-retinylidene-N-retinylethanolamine, a oxidative stress inducer leading to mitochondrial DNA mutation (Donato et al., 2020), is accumulated in retinal pigment epithelium tissue, which causes degeneration (Adler et al., 2015) and neovascularization (Scimone et al., 2020). Since mitochondrial SUMOylations are found frequently in many diseases, it would be an interesting research direction to investigate whether N-retinylidene-N-retinylethanolamine-mediated degeneration is also regulated by SUMOylation.

In regard to gene therapy, overexpression of a SUMO site mutant gene was applied to PRE65-mice by subretinal AAV2 injection, showing a restorative phenotype (Maurya et al., 2019). Growing evidence on intravitreal AAV injection shows the therapeutic benefits of promoting axon regeneration by knocking down Krüppel-like transcription factor 9 (Moore et al., 2009) or overexpressing a non-SUMOylatable Sox11 mutant (Sox11^{K91A}) (Chang et al., 2021). Clustered regularly interspaced short palindromic repeats (CRISPR) technology can specifically modify, delete or correct precise regions of DNA, which is thought to be a potential method to treat genetic diseases. Many successful animal studies used CRISPR/Cas9 to treat retinitis pigmentosa (Arno et al., 2016) and choroid neovascularization (Huang et al., 2017). Targeting SUMO sites using CRISPR/Cas9 to modify SUMO-binding residues might also carry therapeutic benefit to genetic neurological disorders, which is still an unmet need for future exploration.

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