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Senataxin: A Putative RNA: DNA Helicase Mutated in ALS4— Emerging Mechanisms of Genome Stability in Motor Neurons

Arijit Dutta, Robert Hromas and Patrick Sung

Abstract

Amyotrophic lateral sclerosis type 4 (ALS4) is a rare, autosomal dominant childhood- or adolescent-onset motor neuron disease caused by genetic defects in senataxin (SETX), a putative RNA–DNA helicase. Studies on the yeast SETX ortholog Sen1 revealed its role in small RNA termination pathways. It has been postulated that ALS4-associated neuronal pathologies could stem from defects in RNA metabolism and altered gene expression. Importantly, SETX prevents the accumulation of R-loops, which are potentially pathogenic RNA–DNA hybrids that stem from perturbations in transcription. SETX also interacts with the tumor suppressor BRCA1 that helps promote DNA double-strand break repair by homologous recombination. As such, SETX could contribute toward the removal of harmful R-loops and DSBs in postmitotic neurons. This chapter will visit the plausible mechanistic role of SETX in R-loop removal and DNA break repair that could prevent the activation of apoptotic cell death in neurons and pathological manifestation of ALS4.

Keywords: spinal muscular atrophy, SETX, transcription, R-loop, DNA double-strand break, homologous recombination, nonhomologous DNA end joining

1. Introduction

Amyotrophic lateral sclerosis (ALS) type 4 is a rare form of distal spinal muscular atrophy (SMA) with onset at age 25 years or younger. The disease first manifests itself with weakness of ankles and wrists and gradually paralyzes the limbs due to severe muscle wasting. However, unlike classical ALS, the respiratory and bulbar muscles, sensory abilities, and cognitive functions are largely preserved in ALS4 patients. Hence, ALS4 patients, while having to endure severe disabilities, could expect an otherwise normal life expectancy with proper medical attention.

In 1998, the joint effort of Phillip Chance and David Cornblath described the Mattingly disease, a hereditary peripheral neuropathy as ALS type 4 (ALS4) [1]. The Mattingly disease was first seen among the descendants of a seventeenth-century English colonist, Thomas Mattingly from Maryland. With collaborations of the Mattingly clan, the work of Chance and Cornblath led to the identification of the disease gene locus located at chromosome 9q34 [1]. The causative gene was

identified to be *Senataxin* (SETX), which is a large protein with features that typify RNA–DNA helicases [2]. Three distinct mutations in SETX were found in pedigree analysis of ALS4 patients. Some later studies also reported sporadic mutations in SETX [3, 4], which are summarized in **Table 1**. It should be noted that the other three forms of juvenile ALS (JALS) stem from mutations in different genes, namely, *ALS2* (ALS2), *SPG11* (ALS5), and *SIGMAR1* (ALS16).

Pathological studies of ALS4 have been hampered because of the rarity of the disease, with only about a dozen of diagnosed families around the world. Chen et al. [2] detected degeneration of anterior horn cells in spinal cords and cortico-spinal tracts in postmortem tissues from two aged individuals of pedigree K7000. Specifically, even though sensory abilities were not significantly affected in these individuals, a significant loss of dorsal root ganglia and posterior columns was detected, along with marked axonal degeneration of motor and sensory roots and peripheral nerves.

In another study, cytosolic mislocalization of the transactive response DNA-binding protein (TDP-43) was observed in spinal cord motor neurons in postmortem tissues from all the ALS4 patients examined [8]. TDP-43 is an RNA metabolism factor and is a well-documented biomarker that forms toxic protein aggregates in multiple neurodegenerative diseases including ALS [9, 10]. Recapitulation of TDP-43 histopathology in motor neurons of mice carrying ALS4 mutations led the authors to imply that dysfunction of SETX converges on TDP-43 pathology causing an ALS-type motor neurodegeneration [8], although the mechanism was not identified.

SETX has also been found mutated in another neurodegenerative disorder termed ataxia with oculomotor apraxia type 2 (AOA2) [11]. However, in this case, disease is caused by missense mutations leading to premature termination of the SETX mRNA transcript. AOA2 patients suffer from progressive cerebellar ataxia with peripheral neuropathy, cerebellar atrophy, and occasional oculomotor apraxia. However, unlike in ALS4, the motor neuron functions are largely preserved in AOA2 patients [12]. It has been suggested that distinct pathologies of AOA2 and ALS4 stem from unique alterations in expression of genes regulated via SETX in neuronal cells [13].

In spite of the seminal discovery of SETX mutations as being the root cause of ALS4, the etiopathogenesis of this disease remains largely unknown. In this

Mutation	Amino acid substitution	Family history	Origin	References
c.8C → T	T3I	Positive	Austria	Chen et al. [2]
c.1166T → C	L389S	Positive Positive	United States Italy	Rabin et al. [5] Chen et al. [2] Avemaria et al. [6]
c.2672T → T	V891A	Positive	Germany	Rudnik-Schoneborn et al. [7]
c.4660T → G	C1554G	Negative	United States	Hirano et al. [3]
c.6085C → G	K2029Q	Negative	United States	Hirano et al. [3]
c.6407G → A	R2136H	Positive	Belgium	Chen et al. 2004 [2]
c.6406C → T	R2136C	Negative	Japan	Saiga T et al., 2012 [4]
c.7640T → C	I2547T	Negative	United States	Hirano et al. [3]

Table 1.
ALS4-associated mutations in SETX.

chapter we will consider the properties of SETX and its role in the maintenance of genomic stability that are likely germane for the health of motor neurons and ALS4 pathology.

2. Senataxin at the crossroads of RNA metabolism and genomic stability

Studies on SETX predate its ALS4 association. SETX is the likely ortholog of a budding yeast protein, splicing endonuclease 1 (Sen1), so named because of its suspected role in the endonucleolytic processing of tRNA during its splicing and maturation [14]. However, because Sen1 lacks endonuclease activity, it likely functions as a non-catalytic effecter of the nucleolytic entity within the splicing machinery [15]. Sen1 possesses sequence motifs characteristic of superfamily 1 (SF1B) nucleic acid helicases [16]. Consistent with this, Sen1 possesses a helicase activity capable of unwinding RNA-DNA hybrids [17–19]. Like other SF1B helicases, Sen1 translocates on nucleic acid strands in the $5' \rightarrow 3'$ direction [20].

SETX is of low abundance (<500 molecules/cell) predominantly a nuclear protein with some studies reporting its presence in the nucleolus [21, 22]. SETX interacts with RNA polymerase II (pol II) and helps ensure correct termination of transcription and, as such, is important for the processing of noncoding RNAs (ncRNAs) and mRNAs [23, 24]. Importantly, recent studies suggest a role of SETX in maintaining genomic stability across highly transcribed genomic regions via resolution of RNA–DNA hybrids called R-loops, which arise as a consequence of RNA pol II stalling or perturbations of a transcription-coupled process such as mRNA splicing [25]. Moreover, SETX could also clear RNA–DNA hybrids at genomic breaks and promote DNA repair via homologous recombination (HR) [26]. We will explore the various functions of SETX/Sen1 and possible mechanisms by which SETX mutations give rise to ALS4.

2.1 Biochemical and structural features of SETX

SETX is a large protein of 2677 amino acid residues (303 kDa) and, like yeast Sen1, harbors SF1B-type helicase motifs (**Figure 1A**). It should be noted that even though Sen1 is known to unwind RNA-DNA hybrids [14, 15], such an activity has not yet been demonstrated for SETX. However, ALS4-associated missense mutations (K2029Q, R2136H, and I2547T) are all located in the putative C-terminal helicase domain of SETX (**Figure 1A**). Both SETX and Sen1 have an N-terminal domain that undergoes SUMO modification (**Figure 1A**) and that mediates protein–protein interactions with factors that function in RNA metabolism [27]. SETX likely forms a homodimer via the N-terminal domain, but the hereditary ALS4 mutations do not appear to affect protein dimerization [28].

2.1.1 SETX has a large intrinsically disordered region (IDR)

In silico analysis suggests that there is a large IDR in SETX that spans more than 1000 amino acid residues, a structural feature that is absent in the yeast ortholog Sen1. This putative IDR could confer to SETX the ability to interact with different protein partners, to bind nucleic acids [29]. IDRs in nucleic acid-binding proteins are often subject to post-translational modifications and could undergo phase separation, a molecular phenomenon of rearrangement of molecules in a homogenous solution into distinctly concentrated regions of space called condensates [30–33]. However, unrestrained phase separation causes protein aggregation that is observed with FUS [34] and TDP-43 [35], two extensively studied factors associated with
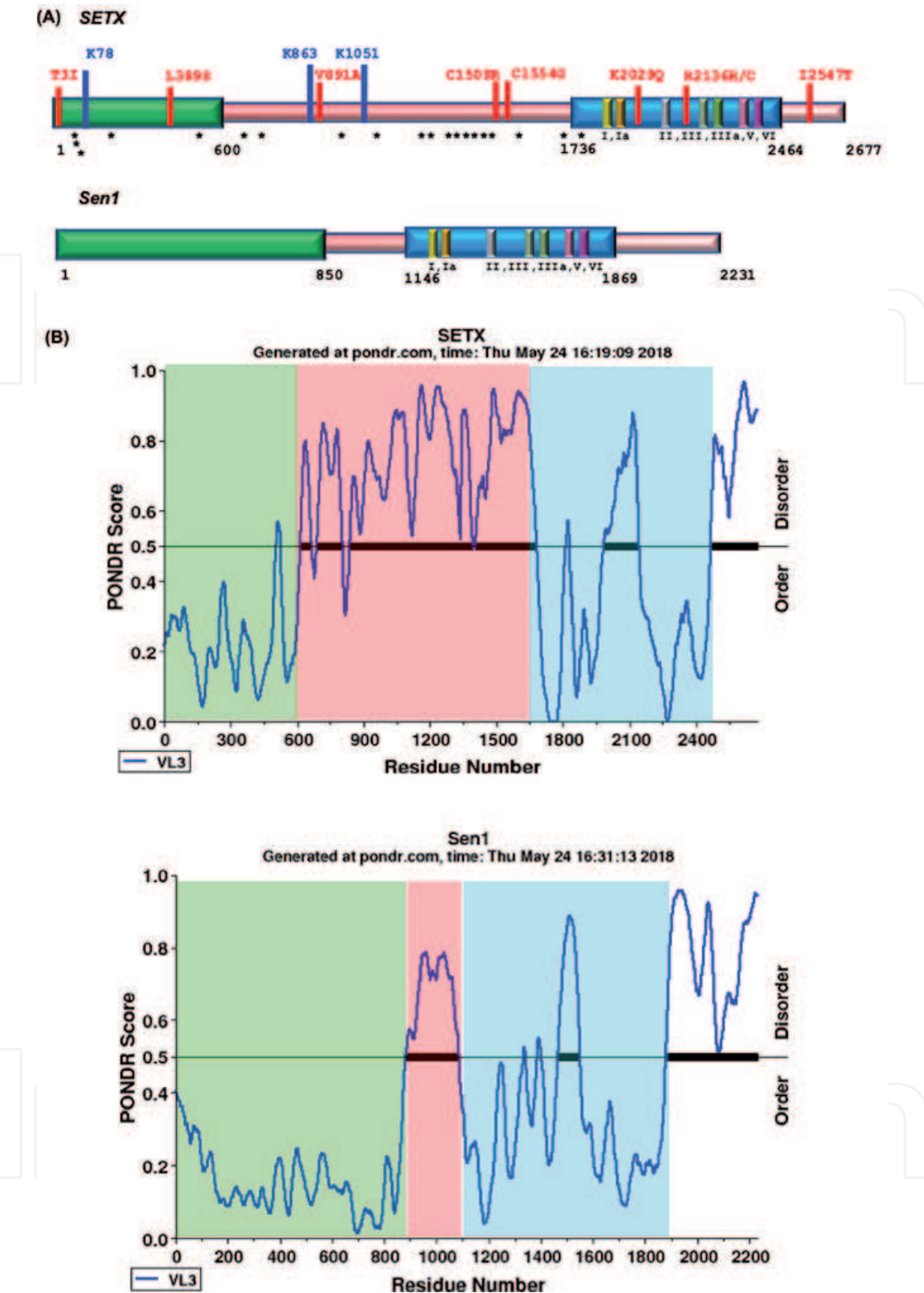
Figure 1.
*(A) Schematic diagram of SETX, indicating N-terminal domain (green), central domain (red), and C-terminal helicase domain (blue); conserved motifs are highlighted: Motif I interacts with Mg2+ and NTP, conserved G maintains a flexible loop, motif 1a binds with substrate nucleic acid and transduces energy from the ATP-binding site to the DNA-binding site, motif II binds and hydrolyses ATP, motif III couples ATP hydrolysis with helicase activity, motif V binds substrate nucleic acid, and motif VI couples ATP hydrolysis with helicase activity; ALS4 mutation residues (red) are T3I, L389S, V891A, C1554G, K2029Q, R1236H/C, and I2647T; predicted sumoylation residues (blue) are K78, K863, and K1051 [119]; and cysteine residues predicted by CYSPRED (reliability≥8) to form disulfide bonds (indicated by stars) are C4, C5, C7, C145, C555, C637, C688, C997, C1080, C1123C,1153, C1262, C1277, C1398, C1442, C1509, C1672, C1719, and C2622.
(B) Prediction of natural disordered region of SETX (upper panel), and Sen1 (lower panel), with the in silico metapredictor PONDR-VL3 [120]. N-terminal domain (green), central disordered region (red), C-terminal helicase domain (blue).*

ALS, which are known to form stress granules in diseased neurons. It could be that SETX, through a phase separation mechanism, forms macromolecular complexes with factors associated with transcription and DNA damage repair. Pathological mutations in SETX could then lead to protein aggregation and loss of protein function in ALS4. This premise awaits experimental testing.

2.1.2 SETX structure could be regulated via disulfide bonding

Multiple neurodegenerative diseases including ALS have been classified among protein misfolding disorders, with disruption of protein disulfide isomerases (PDIs) causing aggregation of superoxide dismutase (SOD1) and TDP-43 in ALS neurons [36]. PDIs are a family of proteins that catalyze formation of disulfide bonds and proper folding of proteins, particularly especially those that harbor an IDR [37]. SETX has 31 cysteine residues in its IDR, and in silico analysis of this region using two independent neural network based predictors, CYSPRED [38] and DIpro [39], revealed that at least 14 cysteine residues in the SETX IDR could engage in disulfide bonding (**Figure 1A**), which is expected to be catalyzed by a PDI. This notion is supported by a proteomic analysis where PDIA6 was detected as a component of the SETX-interactome (**Figure 2**), [40]. We also note that amino acid residue C1554, expected to engage in disulfide linkage with C1509 (**Figure 1A**), is mutated in a sporadic case of ALS4 [3]. Testing of SETX regulation via redox homeostasis [41, 42] merits the effort of ALS researchers.

2.2 Involvement of SETX in RNA metabolism

2.2.1 Role in transcription termination

The role of SETX in regulation of coding and noncoding transcripts is highly conserved. RNA-seq analysis showed that SETX mutations that cause either ALS4 or AOA2 induce unique changes in gene expression patterns [13]. Studies in yeast have shown that Sen1 interacts directly with RNA pol II and is an integral component of the transcription termination machinery consisting of two other
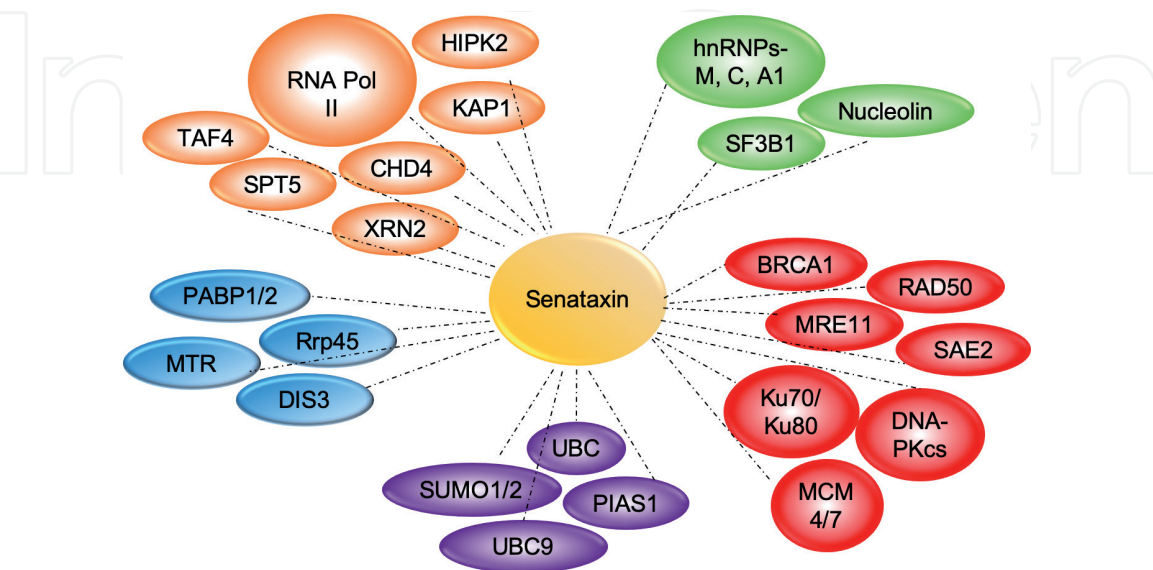

Figure 2.
SETX interactome: DNA repair factors (red), sumoylation and ubiquitination-associated factors (purple), RNA exosome factors (blue), RNAP II and transcription-associated factors (orange), splicing factor and RNA-binding proteins (green), adapted from [40].

factors (Nrd1 and Nab3) that regulate the generation of small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) [43–45]. During aberrant RNA pol II pausing, the Nrd1-Nab3-Sen1 (NNS) complex is recruited via direct interaction of Sen1 and Nrd1 with the C-terminal domain (CTD) of RNA pol II [46, 47]. Moreover, Pcf11, a component of the cleavage and polyadenylation complex (CPAC), facilitates RNA pol II CTD Ser2 phosphorylation and handoff of Sen1 from the NNS complex to RNA pol II [48]. NNS complex also captures polyadenylated RNAs and channels them to the RNA exosome complex for degradation, which we will discuss further in Section 2.2.2 [49]. Sen1 is also necessary for recruitment of Rat1/Xrn2, a 5′ → 3′ exoribonuclease at G-rich RNA pol II pause sites for degradation of the nascent transcripts and to prevent the accumulation of pathogenic R-loops [18, 50, 51]. Human lymphoblastoid and fibroblast cells with loss of both SETX or XRN2 result in increased R-loops and DNA double-strand breaks (DSBs) at transcriptional pause sites and hypersensitivity of cells to replications of stress and DNA damage induced by ionizing radiation, ultraviolet light, and oxidative stress [52, 53], which will be discussed further in Section 2.3.3. Thus, defects in pathways of RNA metabolism can lead to the induction of DNA damage.

2.2.2 Role in RNA surveillance machinery

SETX interacts with the RNA exosome, a highly conserved multiprotein ribonuclease complex that processes or degrades a diverse spectrum of RNAs in cells [54]. The exosome removes improperly processed coding and noncoding RNAs (ncRNAs) in the nucleus and regulates mRNA turnover in the cytoplasm. Other critical functions of the exosome include generation of mature ribosomal RNAs, processing of ncRNAs into snRNAs and snoRNAs, and turnover of tRNAs. The human RNA exosome is a ten-subunit complex with a central six-subunit core that constitutes a channel (EXOSC4–9), a three-subunit cap (EXOSC1–3) and a ribonuclease (EXOSC11) subunit located at the bottom of the channel. The nuclear form of the exosome also harbors a riboexonuclease subunit, EXOSC10 [54, 55]. The current model posits that a RNA strand enters the exosome through the cap and is threaded through the channel to be fed to the ribonuclease module for nucleolytic processing [55].

Importantly, SETX interacts with EXOSC9, and complex formation requires SUMOylation of the N-terminal domain of SETX [27]. It has been inferred that SETX-exosome interaction reflects a vital mechanistic axis for resolving co-transcriptional R-loops and preventing genomic instability at heavily transcribed regions in neurons. It might also be surmised that the RNA exosome is recruited via SETX at R-loops to help resolve these pathogenic structures via degradation of the RNA moiety.

Interestingly, the RNA exosome has also been linked to spinal SMA-type neuropathies. Familial missense mutations in EXOSC3 [56] and EXOSC8 [57] are linked to an infantile neuronal disorder, pontocerebellar hypoplasia type 1 (PCH1), that is marked by cerebellar atrophy and progressive microcephaly along with developmental defects and degeneration of spinal motor neurons. Hereditary mutations in EXOSC10 also cause similar neurological defects [58]. Taken together, the available evidence points to a critical role of the exosome in the avoidance of motor neuropathies. Given the interaction noted for SETX and exosome, it might be contemplated that an R-loop removal defect in spinal motor neuronal precursor and differentiated cells could represent the underlying basis for PCH1.

2.3 SETX: a guardian of genomic stability across highly transcribed genomic landscapes

2.3.1 Transcription-coupled (TC) repair

Nucleotide excision repair (NER) is a conserved DNA repair pathway that removes bulky DNA lesions such as those induced by ultraviolet light. When the RNA polymerase II ensemble is obstructed by such a bulky lesion, Cockayne syndrome B (CSB) protein, which interacts with RNA pol II, mediates the recruitment of NER factors such as the Cockayne syndrome A (CSA)-E3-ubiquitin ligase complex [59] and the endonucleases ERCC1-XPF and XPG to mediate the removal of the DNA lesion. In yeast cells, Sen1 has been shown to play a direct role in TC-NER via interaction with Rad2, the yeast XPG ortholog [47]. Whether SETX also functions in TC-NER in humans remains an open question. However, in the absence of SETX, the TC-NER endonucleases XPF and XPG generate DSBs at R-loops, leading to the activation of DNA damage response pathways and repair via HR or the alternate DSB repair pathway of nonhomologous DNA end joining (NHEJ) [60].

2.3.2 Resolution of R-loops

R-loops are RNA–DNA hybrid structures with a displaced single DNA strand and are generated upon reannealing of a nascent transcript with the sense strand [61]. R-loops are transiently formed in many regions of the genome, including those transcribed by RNA pol I, II, and III [62]. R-loops are abundant at promoters of RNA pol II-transcribed genes [63–65], at sequences that are prone to forming G-quadruplex or hairpin structures in the non-template DNA strand [66]. Perturbations of transcription-coupled processes, such as mRNA splicing, also result in R-loop formation [61, 67]. R-loops are detected in the genome via DNA–RNA immunoprecipitation (DRIP) [68] and immunofluorescence assays with the monoclonal antibody S9.6, which has high affinity for RNA–DNA hybrids [69]. Typically, to ensure that the signal detected is specific for RNA–DNA hybrids, one would include the expression of RNase H in cells (to digest the hybrids) or pretreat samples for sequencing with this enzyme.

Depending upon their location and size, R-loops could impart beneficial or harmful effects. R-loops could extend from a few hundred base pairs to kilo base pairs in size. In immunoglobulin (Ig) class switch regions, R-loops serve an important role in Ig class switch recombination by promoting the induction of DNA breaks via the action of activation-induced cytidine deaminase (AID) and base excision repair factors [70]. R-loops also prime DNA replication in the mitochondrial genome [71]. In human fibroblast cells, R-loops can influence the expression of over 1200 genes by facilitating transcription via suppression of DNA methylation [72] and recruitment or eviction of chromatin remodeling complexes [73]. On the contrary, R-loops could interfere with transcription at certain genomic loci like rDNA [62, 74]. The major threat from unscheduled R-loops is the generation of lethal DSBs because of head-on collisions with the DNA replication machinery [75, 76].

Because of the potential harm that R-loops could cause, their levels are tightly regulated via a variety of mechanisms. In this regard, RNAseH1/2 provides a major means for R-loop clearance via ribonucleolytic cleavage of RNA strand [77, 78]. While topoisomerase I prevents R-loop formation by reducing negative supercoiling behind the elongating RNA pol II, TRanscription EXport (TREX) complex factors (THOC1–7, UAP56) and serine–/arginine-rich splicing factor 1 (SRSF1) suppress R-loops by removing the nascent mRNA [79]. RNA biogenesis factors like Trf4/Air2/Mtr4p polyadenylation

(TRAMP) complex and, as discussed earlier, the RNA exosome complex also participate in the regulation of R-loop formation or removal [80]. Moreover, R-loops can be dissociated via the nucleic acid unwinding activity of Sen1/SETX [23, 50, 81] and other helicase proteins such as Pif1 [82], DEAH box protein 9 (DHX9) [83], and Fanconi Anemia Complementation factor M (FANCM) [84]. It seems reasonable to postulate that each of the above-named factors operates at specific genomic milieu.

Studies so forth have suggested that SETX is involved in resolving R-loops at paused transcription sites [50] via forming a physiological complex with the tumor suppressor protein BRCA1 to prevent R-loop-associated DNA damage [25]. This warrants further investigation on SETX-BRCA1 axis to reveal the molecular mechanisms of R-loop resolution.

2.3.3 DNA double-strand break repair and replication fork stability

Occurrence of DSBs and their repair in terminally differentiated neurons were reported in the early 1970s [85, 86]. Recent studies have provided evidence that ALS is associated with a defect in DSB repair [87–89]. DSBs are generated in neurons via endogenous oxidative stress [90, 91] or a topoisomerase IIβ-dependent mechanism that is essential for expression of early genes regulating vital neuronal functions [92]. A recent study showed that neuronal cells from SMA express only low levels of SETX and DNA-PKcs, a highly conserved NHEJ factor. As a result, SMA neurons display higher levels of R-loops that culminate DSB formation, and cellular toxicity [93]. Importantly, these phenotypic manifestations can be corrected by the overexpression of SETX. These observations aptly underscore the genome protective role of SETX in neurons.

Importantly, SETX colocalizes at DSBs with various factors that function in the DNA damage response and repair factors, including γH2AX, 53BP1, and BRCA1, and it forms a co-immunoprecipitable complex with DNA-PKcs, MRE11, RAD50 [24, 25, 53, 94]. AOA2-pateint derived lymphoblastoid cell lines lacking SETX are sensitive toward topoisomerase I inhibitor, camptothecin, DNA crosslinking agent mitomycin C and hydrogen peroxide [53], again indicative of a role of SETX in the DNA damage response. Moreover, *Setx* −/− mice displays a defect in germ cell maturation due to defective meiotic recombination with unrepaired DSBs [81]. Interestingly, recent findings revealed that nascent transcripts or small ncRNAs could accumulate at DSBs via diverse mechanisms, and affect DSB repair via distinct pathways of HR or NHEJ [95–103]. This was further evidenced by the studies demonstrating that both excess removal and impaired clearance of RNA–DNA hybrids result in defective DSB repair [100], suggesting the role of RNA in DSB repair via processes that are yet to be characterized. In this context, SETX has been implicated in enhancing HR-mediated DSB repair that is catalyzed by the recombinase RAD51, via resolving RNA–DNA hybrids at DSBs [26]. Further biochemical investigations are required to dissect the mechanistic underpinnings of this process.

It should be noted that cycling cells face an incessant threat of genomic instability via replication-transcription collisions, wherein the replication and transcription machineries could engage in head-on collisions [104]. This could directly lead to formation of DSBs [76]. Importantly, SETX associates with DNA replication forks and promotes their progression across RNA pol II transcribed regions, a function that appears to be independent of its transcription termination role [105].

2.3.4 Telomere maintenance

Telomeres, which comprise repetitive DNA sequences, cap the ends of each chromosome, and their attrition leads to cellular senescence. Telomerase reverse

transcriptase (TERT), the catalytic subunit of telomerase that maintains the normal length of telomeres, is present at a low level in most differentiated cells including neurons [106]. TERT levels appear to be significantly lower in the spinal cord tissues of ALS patients than healthy individuals [107]. Ex vivo studies have suggested that while telomere damage induces neuronal cell death [108], the activation of telomerase can enhance neuronal cell viability [109, 110]. Interestingly, a novel compound that enhances telomerase activity in neurons also appears to ameliorate the symptoms of ALS [109].

Importantly, SETX is present at telomeres, and AOA2 lymphocytes and lymphoblasts showed reduced telomere length along with higher sensitivity toward oxidative stress and DNA-damaging agents [111]. Another study has implicated SETX in the maintenance of telomeres in *Myotis* bats [112]. These observations should constitute the basis for investigating the mechanistic role of SETX in telomere maintenance in motor neurons and other cell types.

3. Conclusion

Defects in RNA metabolism factors have been associated with multiple motor neuron diseases including ALS and SMA [113, 114]. Despite having distinctive pathological manifestations and clinical onsets, such motor neuropathies could stem from related underlying mechanisms pertaining to RNA homeostasis. In this chapter, we reviewed how defective RNA metabolic pathways could ensue genomic instability, an emerging mechanism in neurodegenerative diseases. Co-transcriptional R-loops are crucial for regulating gene expression in both dividing and postmitotic neurons; however, when not timely resolved, it will lead to genomic instability via generation of DNA strand breaks. While replication-transcription conflicts are the major source of R-loop-induced DSBs in dividing cells that need repair via HR or NHEJ, how R-loops trigger DSBs in postmitotic neurons remains to be investigated. Moreover, small RNAs at DSBs could impede repair and must be cleared nucleolytically or via unwinding of RNA–DNA hybrids. Genetic and cell-based studies of human SETX, together with biochemical characterization of its yeast ortholog Sen1, have suggested that SETX protects genomic stability via resolution of R-loops, assisting replication fork progression across transcribing genomic regions and promoting HR at DSBs. In the light of recent findings on implication of genomic instability in neurodegenerative diseases, as reviewed in [115–118], in-depth studies are required to precisely delineate role of SETX in ALS4. Thus, it is apposite to test if ALS4 gain-of-function mutations affect SETX activities pertaining to DSB repair.

Treatment of ALS4 or other JALS is currently limited to physical and occupational therapies to promote mobility and independence. While an FDA-approved glutamate inhibitor drug, riluzole, that slows down symptoms and prolongs survival is used clinically to treat ALS, there are currently no specific treatment for juvenile ALS diseases. Further studies are obligatory to recognize SETX as a therapeutic target for treatment of ALS4.

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Conflict of interest

The authors declare no conflict of interest.

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