HHS Public Access

Author manuscript

Trends Genet. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Trends Genet. 2023 May ; 39(5): 381–400. doi:10.1016/j.tig.2023.02.008.

Repetitive elements in aging and neurodegeneration

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Abstract

Repetitive elements (REs) such as transposable elements (TEs) and satellites comprise much of the genome. Here, we review how TEs and (peri)centromeric satellite DNA may contribute to aging and neurodegenerative disorders including amyotrophic lateral sclerosis. Alterations in RE expression, retrotransposition, and chromatin microenvironment may shorten lifespan, elicit neurodegeneration, and impair memory and locomotion. REs may cause these phenotypes via DNA damage, protein sequestration, insertional mutagenesis, and inflammation. We discuss several TE families, including *gypsy*, HERV-K, and HERV-W, and how TEs interact with various factors including TDP-43 and the siRNA and piRNA systems. Studies of TEs in neurodegeneration have focused on *Drosophila*. Further examination in mammals is needed. We suggest that therapeutic silencing of REs could help to mitigate neurodegenerative disorders.

Keywords

transposable elements; satellites; aging; neurodegeneration

Repetitive elements in the human genome

Repetitive elements (REs) make up approximately half of the genome, with classes of REs including **transposable elements** (TEs, see Glossary), **satellite DNA**, rDNA, and segmental duplications [1]. Until recently, REs were mostly ignored due to: (1) their repetitive nature, which complicates sequencing, and (2) the widespread perception that REs were “junk” DNA [2]. Advances in sequencing technology and computational analysis of repetitive sequences have enabled investigation of REs and recognition of their biological importance.

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Declaration of interests

K.E.C. has nothing to declare. J.S. is a consultant for Dewpoint Therapeutics, ADRx, and Neumora. J.S. a shareholder and advisor at Confluence Therapeutics.

Here, we focus on the relevance of TEs and (peri)centromeric satellite DNA in aging and neurodegeneration.

TEs: mobile REs

TEs move and reinsert within the genome. They were first discovered by Barbara McClintock in maize as determinants of kernel coloration [3]. TEs constitute ~45% of the human genome [1]. Yet, the diverse roles of TEs are just beginning to be appreciated, including their importance in somatic mosaicism, genome innovation, and disease [4].

The two major classes of TEs differ in their **transposition** mechanisms and **activity**. Active TEs are TEs capable of moving within the genome. However, activity status does not determine whether a TE exerts meaningful biological effects. **DNA transposons** have been inactive in primates for ~37 million years, presumably due to the progressive build-up of inactive DNA transposons decreasing overall transposition efficiency [1,5]. The **retrotransposon** class includes two sub-types: **long terminal repeats** (LTRs) and **non-long terminal repeats** (non-LTRs). LTRs are thought to be inactive in humans, whereas some non-LTRs mobilize via target-primed reverse transcription. These active non-LTRs are transcribed into RNA, which is then reverse transcribed into cDNA that is inserted into the genome utilizing endonuclease activity [6].

Subclasses of non-LTRs include long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs). The LINE-1 (L1) family constitutes ~17% of the human genome [1]. The first open-reading frame (ORF1) of L1 codes for a RNA-binding protein, whereas ORF2 codes for a reverse transcriptase and endonuclease [7,8]. Of the estimated 80–100 active L1s in humans, a small subset are “hot L1s” accounting for most retrotransposition [9]. L1s are autonomous, as they encode the proteins necessary for their retrotransposition. Other non-LTRs are non-autonomous, relying on L1 proteins for reverse transcription and integration [10]. Most active retrotransposition occurs within the evolutionarily youngest subfamilies of non-LTRs, underscoring their susceptibility to inactivation by mutation [11,12]. Figure 1 compares the abundance and activity of TE subclasses and families between humans, mice, and *Drosophila*. The activity and impact of TEs also differ between tissue types (Box 1).

Mechanisms to repress TEs

Retrotransposition is repressed via multiple mechanisms, including DNA methylation, histone modifications, Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and N^6-methyladenosine (m6A) RNA methylation [13–35]. All of these repressive mechanisms are employed in mammals, although DNA methylation and histone modifications may be the predominant active regulators of TE expression in human somatic cells [18–32,32,36,37]. DNA methylation at CpG sites and histone modifications suppress both evolutionarily young and older TEs. Histone modifications may play a more important role in suppressing evolutionarily older TEs, whereas DNA methylation may play a more important role in suppressing evolutionarily young TEs [20,21,23,24,38]. TEs are highly polymorphic sequences. New genomic insertions of active TEs create young non-reference copies, which are not found in the standard representation of the

human genome. Young non-reference copies are less densely methylated than reference copies, rendering young non-reference copies prone to transcriptional upregulation [20,38–40]. Most retrotransposition occurs in young non-LTR families [11,12]. Thus, impaired methylation is likely to elicit transcriptional upregulation of retrotransposition-competent TEs.

Histone modifications suppress young and old TEs in humans, although their role is relatively more important for old TEs [19,20,22–24]. Krüppel-associated box (KRAB) domain-containing zinc-finger proteins (KZFPs) are transcription factors that repress TEs by mechanisms such as recruiting TRIM28 and other proteins for deposition of trimethylation at lysine 9 of Histone H3, a repressive heterochromatin-associated mark [19,20,23,24,31,36]. Older TEs generally maintain binding sites for KZFPs, whereas young TEs can lose some KZFP binding sites [23,24]. This finding may explain the more important regulatory role of DNA methylation for young TEs. The importance of TE regulation by histone modifications is reinforced by evidence that disturbing these modifications induces inflammation [31,36]. TRIM28 knockdown in human cells upregulates LTRs and activates an interferon response dependent on an intracellular RNA-sensing pathway [31]. *In vivo*, TRIM28 knockout in mouse neural progenitors similarly elicits LTR upregulation concurrent with local microglial inflammation in the adult mouse cortex [36]. However, this study did not identify an interferon response, emphasizing the need to further investigate the cellular pathways connecting TEs and inflammation [36].

In addition to DNA methylation and histone modifications, piRNAs and siRNAs also serve as repressive mechanisms utilized by various species. piRNAs and siRNAs are classes of small RNAs that silence expression at transcriptional and post-transcriptional levels. piRNAs are 26–30nt-long RNAs that interact with Piwi proteins. piRNAs originate from single-stranded RNA precursors in specific clusters of the genome. piRNAs enact post-transcriptional silencing via degradation of target RNAs, or transcriptional silencing of target RNAs via promoting repressive histone marks [15,16,25,30]. siRNAs are 21–23nt-long RNAs produced upon cleavage of longer double-stranded RNAs (dsRNAs) by Dicer. As part of the RNA-induced silencing complex, siRNAs direct cleavage of target RNAs [14,26–29]. siRNAs can be produced from exogenous dsRNA or endogenous dsRNA (endo-siRNA) [14,28,29]. In *Drosophila*, the main regulators of TE expression are histone modifications, piRNAs, and siRNAs. piRNAs and siRNAs have established roles in repression of TEs in the *Drosophila* germline [13–17].

The piRNA pathway also regulates TEs in the mammalian germline [25,30,37]. Whether piRNAs regulate TEs in the central nervous system (CNS) is controversial. Difficulty in establishing the existence and role of the piRNA pathway in the CNS may partially be due to detection issues stemming frow low expression of piwi proteins and piRNAs in the CNS. Manipulating Piwi in *Drosophila* neurons alters TE expression, supporting the hypothesis that in addition to histone modifications, the piRNA pathway regulates TEs in the *Drosophila* CNS [17]. Studies have identified piRNAs in the mouse and human brain, with one study demonstrating interaction between piRNAs and Piwi [37,41–43]. While this work suggests that piRNAs may be active and regulate TEs in the mammalian CNS, manipulating Piwi proteins to impact TE expression is challenging to interpret. Piwi overexpression in

a human cancer cell line is insufficient to obtain a functional piRNA pathway, as piRNA-silencing complexes are not necessarily formed [44]. Studies attempting to manipulate the piRNA pathway could overexpress both piRNA biogenesis and effector factors, and would benefit from verifying that piRNA-silencing complexes are formed [44]. Further studies are needed to establish the functionality of the piRNA pathway in the mammalian CNS. Assessing Piwi expression, Piwi-bound small RNAs, and TE levels in human neurons would be valuable.

There is some evidence suggesting that the endo-siRNA pathway is active and represses TEs in mouse oocytes and embryonic cells, and human Flp-In 293 cells [26–29,32]. More studies are needed to confirm these findings, as well as studies in human germ cells. A further step would include examination of siRNA pathway activity in *Drosophila* and mammalian neurons.

Clearly, there are important differences in TE regulation between the *Drosophila* germline, *Drosophila* somatic cells, the mammalian germline, and mammalian somatic cells. These distinctions should be carefully considered when drawing parallels between findings in *Drosophila* to human biology. Nevertheless, studies in *Drosophila* facilitate formulation of hypotheses to test in human models, ultimately advancing our understanding of human biology.

TEs in aging

Mechanisms to repress TEs decline with age, potentially contributing to common aging phenotypes (Figure 2A). Increased expression of TEs (broadly or of individual elements) at the RNA level, protein level, or both with age has been documented in *Drosophila* [45,46], rodents [47–49], and humans [50,51] (Figure 2B). TE expression is also increased in senescent human cells [52,53] and cells from patients with premature aging disorders, including Hutchinson-Gilford progeria syndrome (HGPS) and Werner syndrome [51,54,55]. Active retrotransposition is elevated with age in humans [56], mice [47], *Drosophila* [45,46,57], and human senescent cells [52] (Figure 2C).

TE transcripts, particularly LINEs and LTRs, are elevated during aging in the *Drosophila* brain [45,46]. The protein levels [45] and retrotransposition [45,46] of the *Drosophila* LTR ***gypsy*** increase with age (Figure 2B–C). However, mutant flies expressing higher levels of heterochromatin-promoting genes exhibit attenuated TE expression over their lifetime, indicating that repressive histone modifications suppress TEs in *Drosophila* [46] (Figure 2D). De-repression of heterochromatic elements is relevant to TEs in humans, as DNA methylation of TEs decreases with age [56,58,59] (Figure 2D).

Upregulation of TEs at the RNA and protein levels has been observed in mutant flies with an impaired siRNA system, supporting the hypothesis that the siRNA pathway represses TE expression in *Drosophila* [45] (Figure 2E). Wild-type flies only display long-term memory (LTM) deficits in old age, whereas flies with impaired siRNA systems and increased TE expression display deficient LTM early in life [45]. This finding suggests that heightened TE expression may impair LTM (Figure 2A). The lifespan of flies with an impaired siRNA system (and high TE levels) is lengthened by a reverse-transcriptase inhibitor (RTI), which

decreases retrotransposition [46] (Figure 2A). Moreover, flies undergoing dietary restriction (DR) have lifespan increases correlated with delays in TE activation [46]. Taken together, these studies indicate that in the *Drosophila* nervous system TE expression increases with age and may contribute to aging phenotypes. These findings, combined with initial evidence that the endo-siRNA pathway represses TEs in mouse oocytes, mouse embryonic cells, and human Flp-In 293 cells, support assessing siRNA activity in regulating TEs in the mammalian CNS [26–29,32].

Age-related increases in TE expression may also occur in mammals. L1 RNA is upregulated with age in the mouse brain [49]. Similar to flies undergoing DR, anti-aging interventions reduce expression of all major TE subclasses in mice [60]. L1 protein has been detected in the human brain in a potentially age-dependent manner [50]. Multiple classes and subclasses of TEs are upregulated with age in two RNA-seq datasets of human fibroblasts [51] (Figure 2B). A linear regression model that predicts age based on expression of TE transcripts outperformed a model based on coding and non-coding RNAs [51]. The accuracy of the TE-based model highlights the strength of the connection between TE expression and aging. The TE-based model predicts that fibroblasts of prematurely aged HGPS patients are older relative to age-matched controls. Thus, TE expression may be related to biological rather than chronological age [51].

Another study suggests that TEs may play a causal role in aging in mammals [55]. L1 RNA is upregulated in HGPS patient fibroblasts compared to controls, preceding heterochromatin impairment and senescence phenotypes that appear at later passages [55]. In both HGPS and Werner syndrome patient-derived human mesenchymal stem cells (hMSCs), an L1 antisense oligonucleotide (ASO) rescues heterochromatin and reduces senescence phenotypes [55]. L1 RNA may impair heterochromatin by inhibiting the activity of SUV39H1, which deposits a repressive histone modification. L1 inhibition of SUV39H1 is evidenced by *in vitro* methyltransferase assays and the inefficacy of an L1 ASO in HGPS and Werner syndrome hMSCs with SUV39H1 knockdown [55]. In wild-type mouse fibroblasts, L1 overexpression elicits heterochromatin impairment, senescence phenotypes, and DNA damage. In a mouse model of premature aging with a *Lmna* mutation, an L1 ASO rescues heterochromatin and increases lifespan [55]. This study provides evidence that L1 dysregulation may act upstream of aging phenotypes, and that targeting L1 may serve as a therapeutic approach. Further research is needed to characterize the expression and activity of TEs in postmitotic human neurons with age. Longitudinal studies investigating the progressive nature of increased TE expression promise insight into the underlying biology.

TEs in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)

Neurodegenerative diseases are characterized by progressive neuronal loss and usually present later in life, making age a main risk factor. For many neurodegenerative diseases the etiology and mechanism(s) of pathology are incompletely understood, and cures have not yet been discovered. It is crucial to develop our understanding of the changes that occur in the brain both before and after disease onset.

TEs are heavily implicated in the neurodegenerative diseases, ALS and FTD. ALS is a fatal disease characterized by motor neuron death in the brain and spinal cord, resulting

in progressive motor dysfunction and eventually death. Approximately 10% of cases are familial ALS (fALS), in which the disease is inherited, while the other ~90% are sporadic (sALS) [61]. FTD patients present with behavioral changes, language deficits, and atrophy of the frontal and temporal lobes [62]. ALS and FTD exist on a disease spectrum, with some patients presenting with symptoms of both disorders [63]. Several molecular features are shared between the diseases, including cytoplasmic aggregation and nuclear depletion of **TDP-43**, an RNA-binding protein with a prion-like domain, in degenerating neurons [64]. A hexanucleotide **repeat expansion** (GGGGCC, G4C2) in the first intron of the *C9ORF72* gene is the most common genetic cause of both diseases [65]. Increased expression of TEs has been observed in many ALS/FTD models, including in *Drosophila* [66–68], mice [69,70], rats [71], human cell lines [72–74], and patient cells and brain tissue [72–78] (Figure 2B).

Expressing null alleles of the *Drosophila* homolog of TDP-43, TBPH, or overexpressing human TDP-43 in glia or neurons of flies leads to disease phenotypes (including impaired locomotion and reduced lifespan) and elevated TE transcripts [66,68] (Figure 2B). In both models, *gypsy* expression was elevated and the siRNA system was impaired, suggesting that in *Drosophila* TDP-43 dysfunction may upregulate TEs by impairing the siRNA system [66,68]. Flies with glial TDP-43 overexpression exhibit decreased levels of siRNAs targeting the upregulated TEs, suggesting that TDP-43 impacts production or stability of TE-regulatory siRNAs in flies [66]. If *gypsy* levels are reduced by RTIs or siRNA against *gypsy*, locomotor impairments and shortened lifespans are mitigated in both TBPH-null and TDP-43 overexpression *Drosophila* models [66,68] (Figure 2A).

TBPH-null flies display reduced expression of Dicer-2, a protein important in siRNA processing, and knockdown of TDP-43 reduces Dicer expression in human neuroblastoma cells [68]. Furthermore, increasing Dicer-2 expression in the TBPH-null *Drosophila* mitigates *gypsy* upregulation and locomotive defects, indicating a vital role of siRNAs in regulating TE expression [68] (Figure 2E). In sum, the siRNA system is impaired in multiple TDP-43 disease models, and this impairment may be causally relevant to disease phenotypes. Utilizing human neuronal cells with TDP-43 knockdown or induced TDP-43 mislocalization and aggregation would enable assessment of loss- and gain-of-function effects of TDP-43 on the siRNA system in an ALS/FTD-relevant context.

How are TDP-43 and TE pathologies related? One answer may be found in work showing that TE expression leads to DNA damage in the form of double-strand breaks (DSBs) (Figure 2F). DSBs elicit programmed cell death via a pathway involving the protein Chk2 [79,80]. Disruption of the Chk2 pathway to circumvent the TE-induced DSB response rescues lifespan and neuronal viability in flies with glial or neuronal TDP-43 overexpression [66]. These studies suggest that TEs may cause disease phenotypes such as shortened lifespan and locomotion deficits via DNA damage-induced cell death. DNA damage is already of interest due to its connection to TDP-43 and *C9ORF72* ALS/FTD [81–84]. TDP-43 functions in the classical non-homologous end joining DNA repair pathway in numerous cell types, including human neural progenitors, human stem cell-derived motor neurons, and mouse primary neurons [81,83]. The role of TDP-43 in DNA repair appears disease-relevant, as sALS patient spinal cord samples exhibit increased DNA damage, and

two ALS-causing TDP-43 missense mutations possess reduced DNA-repair capacity in primary mouse neurons [81,83]. *C9ORF72* patient-derived motor neurons harbor elevated DNA damage stemming from activation of transcription factor p53 [84]. Reduction of p53 mitigates DNA damage and neuronal death [84]. *C9ORF72* patient-derived motor neurons also undergo apoptosis mediated by elevated levels of DNA damage response protein Ku80 [82]. Dissecting if and how these various pathways leading to DNA damage in ALS/FTD synergize will be highly valuable.

The innate immune system may also connect TDP-43 and TE-mediated pathology. TDP-43 knockdown in primary rat astrocytes elicits inflammation along with increased TE transcripts and dsRNA levels (including TE dsRNA) [71]. This inflammation induction is dependent on PKR, a component of the cellular dsRNA-sensing pathway [71]. Overexpression of L1 in HEK293T cells induces an interferon response dependent on proteins vital to this dsRNA-sensing pathway [85]. Thus, TDP-43 dysregulation increasing TE expression may evoke pathology by activating the innate immune system.

Multiple studies in mammalian cells suggest that TDP-43 silences TEs [69,72–74,86]. TDP-43 knockdown in mouse embryos elevates DNA levels of evolutionarily young L1 families, as well as putative *de novo* L1 insertions, indicating that TDP-43 protects against L1 retrotransposition during the chromatin opening occurring in embryogenesis [86]. Liu and colleagues stained for TDP-43 and a neuronal marker, then performed fluorescence-activated cell sorting on brain tissue from ALS/FTD patients to select neurons lacking nuclear TDP-43 [73]. This process selects for disease-relevant cells, as opposed to a surviving population resistant to or not yet affected by TDP-43 mislocalization. **Assay for Transposase-Accessible Chromatin (ATAC)-seq** indicates that the chromatin environment of LINEs is less accessible in neurons with nuclear TDP-43 than those without (Figure 2D) [73]. Another study also identified changes in the chromatin environment of L1s, finding reduced CpG methylation in ALS patient motor cortex [87]. Neurons lacking nuclear TDP-43 harbor increased L1 DNA content, potentially indicating increased L1 retrotransposition (Figure 2C) [73]. Knocking out TDP-43 in Henrietta Lacks' (HeLa) cells increases L1 retrotransposition, providing orthogonal evidence that TDP-43 loss-of-function increases retrotransposition [73]. Global upregulation of TE RNA is detected in peripheral blood of symptomatic *C9ORF72* ALS/FTD patients compared to controls, including both LTRs and L1 [78]. Intriguingly, levels of the *L1HS* subfamily are predictive of both a dementia assessment score and thalamic volume. In these same patients, numerous genes in the interferon response pathway are upregulated, further supporting a putative mechanism wherein TE elevation elicits innate immune system activation [78].

Another study found that deletion of the N- or C-terminal domains of TDP-43 impairs its capacity to repress retrotransposition in HEK293T cells [86]. Intriguingly, co-immunoprecipitation indicates that while deletion of the N-terminal domain decreases interaction with L1 ORF1p, C-terminal deletion does not impair interaction with L1 ORF1p [86]. Thus, binding to L1 ORF1p may be necessary but is not sufficient for repression of retrotransposition. A study that stratified sALS patients into three subgroups, based on transcriptomics, revealed that the group with the highest TE expression displays the strongest hallmarks of TDP-43 dysfunction [72]. Recent work has similarly identified

upregulation of TEs in subgroups of ALS patient cortical transcriptomes [88]. Strikingly, in human neuroblastoma cells, TEs constitute about one-third of the RNA-interaction partners of TDP-43, and TDP-43 overexpression upregulates **HERV-K** *env* transcripts [72,74]. HERV-K is an LTR heavily implicated in ALS (Box 2). TDP-43:TE RNA interactions are also decreased in FTD patients [69]. Overall, these studies suggest that TDP-43 normally interacts with and silences TEs, and that this function may be disrupted in ALS/FTD. Further exploration of the mechanism by which TDP-43 silences TEs is needed, with current findings suggesting multiple overlapping mechanisms, including promoting heterochromatin, contributing to the expression of siRNA biogenesis factors, binding to TE RNA, and binding to L1 ORF1p.

Some work has challenged whether TDP-43 serves as the major link between ALS/FTD and TEs. One group found that TE expression is selectively elevated in the frontal cortex of *C9ORF72* ALS/FTD patients, but not in that of sALS patients (who also exhibit TDP-43 pathology) [75]. TEs were also broadly upregulated in peripheral blood mononuclear cells of *C9ORF72* ALS patients compared to sALS patients [78]. Another group demonstrated TE upregulation in a *C9ORF72* ALS mouse model without TDP-43 pathology [70]. They postulated that the increase in TE expression is due to the proline-arginine (PR) dipeptide repeat product of the *C9ORF72* mutation disrupting heterochromatin [70]. This study highlights the importance of physiological phase separation to TE biology (Box 3) (Figure 2G). Clearly, there is a need to investigate the mechanism underlying TE alterations in ALS/FTD, particularly whether TDP-43 has a vital role.

TEs in AD/tauopathy

Alzheimer’s disease (AD) is the most common dementia, characterized by memory deficits, beta-amyloid plaques, and tau neurofibrillary tangles [89]. Certain TE transcripts are increased in AD patient brain tissue, with levels of several TEs correlating with tau pathology [17,90] (Figure 2B). LTRs (including HERV-K) exhibit elevated expression, whereas many other TEs display decreased expression [17]. *Drosophila* expressing human wild-type, R406W, or V337M tau serve as tauopathy models [17,90]. Both wild-type and R406W tau flies exhibit increased transcripts of particular TEs, and V337M tau flies display an increase in retrotransposition of *gypsy* [17,90] (Figure 2B–C).

Neuronal knockdown of Piwi exacerbates neuronal death and locomotion deficits of R406W tau flies, whereas Piwi overexpression reduces TE expression and neuronal death [17] (Figure 2E,H). Feeding R406W flies a RTI mitigated neuronal death and locomotion deficits, and the RTI treatment decreased retrotransposition in V337M flies [17] (Figure 2A). These findings suggest that the piRNA pathway may prevent increased TE expression in tau-expressing flies, mitigating disease phenotypes. Similar results have been found in a heterozygous *Bmi1*-deficient AD mouse model [91]. *Bmi1*-deficient mouse cortices harbor elevated TE expression and reduced repressive chromatin marks at TE loci [91] (Figure 2B,D). This work underscores the need for studies investigating the prevalence of these alterations in AD/tauopathy patients and their importance for disease progression. It will be compelling to explore whether upregulation of TEs in AD elicits a piRNA pathway response as a protective mechanism, and whether boosting this response is a therapeutic avenue.

TEs in Aicardi-Goutières syndrome (AGS)

AGS usually presents in early infancy, and symptoms include inflammation, interferon response, and encephalopathy [92–94]. Mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, and *MDA5* cause AGS [92,93,95,96]. Numerous studies implicate TEs in the inflammation and interferon response characteristic of AGS, and indicate that TEs trigger these via DNA- and RNA-sensing pathways [85,93–98]. Strikingly, TREX1, SAMHD1, and ADAR1 suppress L1 retrotransposition in human cell lines [99–102]. AGS mutations in *TREX1* and *SAMHD1* impair suppression of L1 retrotransposition, and AGS mutations in *ADAR1* are predicted to disrupt interactions with dsRNA [95,99,100]. In cultured TREX1-deficient human neurons, siRNA against L1 reduces L1 DNA levels and mitigates neurotoxicity [94]. Initial mechanistic studies suggest that TREX1 degrades the L1 cytosolic DNA produced by reverse transcription and promotes degradation of ORF1 protein, whereas SAMHD1 reduces L1 ORF2 protein levels and ADAR1 interacts with L1 RNA and ORF1 protein [94,99,100,102]. The efficacy of RTIs as AGS treatments is unclear, as two studies employing RTIs to treat TREX1-deficient mice yielded conflicting findings [103,104]. In human AGS patients, RTIs reduced the interferon response, supporting further exploration of this treatment approach [97].

In sharp contrast to other AGS-relevant proteins, RNaseH2A promotes L1 retrotransposition in human cell lines, perhaps by facilitating a step in target-primed reverse transcription [105]. AGS-linked mutations in *RNASEH2A* yield proteins less effective at promoting L1 retrotransposition, suggesting that patients with these mutations possess less L1 activity [105]. Notably, patients with mutations in *RNASEH2B* are the patient subset most commonly lacking a heightened interferon response [93]. Investigation into the connection between RNaseH2 AGS mutations, TE activity, and the interferon response is needed. Initial studies suggest that TE-targeting treatments may only be appropriate for a subset of AGS patients, rather than universally applicable.

TEs in multiple sclerosis (MS)

MS is an autoimmune disease characterized by neuroinflammation, interferon response, and demyelination of CNS axons, leading to motor and cognitive impairments [106–109]. Initial studies detected viral particles in MS cell cultures, which were identified as belonging to the HERV-W family of LTRs [110,111]. MS patient brain tissue exhibits upregulated expression of certain HERV-W transcripts and proteins compared to control brain tissue, with many studies observing upregulation in lesions compared to unaffected MS brain regions [106,107,112–116]. While these numerous studies suggest that HERV-W is upregulated in MS patients, some studies report finding no differences in HERV-W transcripts between MS and control brain tissue, highlighting the needed for further studies with larger sample sizes [117,118]. Indeed, a recent longitudinal study with a large sample size connected Epstein-Barr virus (EBV) to MS [119]. Longitudinal investigation of HERV-W expression and MS incidence may reveal if HERV-W plays a causal role in MS. Studies of TE levels, particularly HERV-W, after EBV infection will also be of interest.

Numerous studies support that HERV-W elicits inflammation in MS cellular and animal models [107,109,115,116,120]. HERV-W env protein elicits inflammation in cultures of

human astrocytes, human microglia, rat microglia, or rat oligodendroglial precursor cells (OPCs) [107,115,116]. TEs may elicit inflammation in MS via RNA-sensing pathways [109,120]. Alu elements, a family in the SINE subclass, are a major component of dsRNA in MS patient leukocytes, and injecting certain identified Alu RNAs into human cell lines elicits an interferon response [109]. Additionally, there are deficits in ADAR1 adenosine-to-inosine dsRNA editing in MS leukocytes [120]. Most ADAR1 editing occurs in Alu elements, and application of unedited Alu or LINE RNAs that exhibit less editing in MS compared to control leukocytes elicits an interferon response in human cell lines via a RNA-sensing pathway [98,120]. Whether inflammation in MS is due to deficient ADAR1 editing, which usually masks TEs from innate immune system detection, warrants further investigation.

HERV-W env protein also leads to other MS-related phenotypes in murine models [107,115,116]. HERV-W env protein impairs rat microglia myelin uptake and OPC differentiation [115,116]. Treatment with a HERV-W virus reduces oligodendrocytes, and impairs myelination and locomotion in mice [107]. Altogether, these studies suggest that TEs may contribute to MS phenotypes in cellular and animal models. The connection between TEs and MS in humans is supported by findings that single nucleotide polymorphisms in HERV-Fc1, an element of the HERV-H/F family, are associated with MS risk [121,122].

TEs in other neurodegenerative disorders

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disease usually presenting with tremors, which is caused by a CGG-repeat expansion (55–200 repeats) in the *FMR1* gene [123]. In a *Drosophila* FXTAS model, some TE transcripts were elevated, and impairing the piRNA system exacerbated disease pathology [124] (Figure 2B,E,H).

Parkinson’s disease (PD) is also characterized by tremors, and dopaminergic neurons in the substantia nigra are particularly susceptible to degeneration [125]. Multiple PD models exhibit increased L1 expression [126,127] (Figure 2B). In a human neuronal-like cellular model, the elevated levels of reactive oxygen species (ROS) seen in PD induce DNA demethylation, which is important for increased L1 expression [126] (Figure 2D,I). In the heterozygous *Engrailed-1*-deficient PD mouse model, overexpression of a Piwi protein reduces L1 expression and neuronal death, further supporting the putative relationship between piRNAs and TE-associated pathology, and also the activity of the mammalian piRNA pathway [127] (Figure 2E,H).

Huntington disease (HD) is caused by a CAG repeat expansion in the *HTT* gene, and characterized by motor and cognitive deficits and neuronal death (especially of striatal medium spiny neurons) [128]. R6/2 mice are an HD model with transgenic expression of a fragment of human *HTT* containing 150 CAG repeats [129]. In R6/2 mice, L1 DNA exhibits decreased methylation, increased expression, and increased copy number in caudate tissue, a brain region affected in HD [129] (Figure 2B–D). These changes to L1 were associated with cell death in R6/2 mice, and expression of L1 protein impaired cell survival signaling in HEK293T cells, indicating that L1 expression may be toxic [129] (Figure 2A).

Ataxia telangiectasia (AT) is caused by mutations in *ATM* and characterized by cerebellar loss and impairments in coordination, speech, and the immune system [130]. In an AT mouse model, L1 retrotransposition is selectively increased in the brain [131] (Figure 2C). Decreasing ATM levels in human neuronal precursor cells increased L1 retrotransposition, indicating that ATM may regulate retrotransposition [131]. Moreover, increased L1 copy number in hippocampal neurons of AT patients indicates that L1 retrotransposition might be increased in AT patients [131]. AT patient cerebellar tissue exhibits upregulation of L1 RNA and transcripts of multiple interferon-stimulated genes, further supporting the interconnection between neurodegeneration, TEs, and the interferon response [132]. A transgenic mouse model with increased L1 expression displays progressive ataxia, with phenotypes including hindlimb clasping and impaired rotarod performance [132]. RTI treatment mitigates the upregulation of DNA damage and interferon-stimulated gene transcripts in the transgenic L1 mice [132]. These findings support the hypothesis that L1 expression may causally contribute to the etiology of AT and serve as a therapeutic target.

It is striking that changes in TEs appear to be common across the broad spectrum of neurodegenerative diseases, highlighting the need for examination of TEs in yet unexplored diseases. Phenomena precipitating TE upregulation appear to differ between diseases. For example, tau protein and dipeptide repeats stemming from the *C9ORF72* mutation in ALS/FTD both induce heterochromatin relaxation, potentially explaining the increased expression of TEs located in normally repressed genomic regions [70,90,133]. TDP-43 loss-of-function may also elicit heterochromatin relaxation [73,87]. However, TDP-43 loss-of-function may also upregulate TEs by reducing direct interactions between TDP-43 and TE RNA, eliciting global upregulation of TEs [69,72]. We suggest that therapeutic strategies that restore TDP-43 functionality may be particularly effective [134,135]. TREX1 degrades cytosolic DNA, suggesting that AGS-linked mutations in TREX1 upregulate TEs by reducing TE DNA degradation [94]. Further investigation might reveal a shared mechanism by which TEs contribute to neuronal death across diseases. Analysis of TE expression in larger patient cohorts will facilitate determination of whether there are reliable changes in TE expression that could be utilized as biomarkers, with initial studies in peripheral blood supporting this possibility [78]. Increased exercise and exposure to ultraviolet rays correspond to lower and higher levels of TE transcripts in humans, respectively [51,56]. It is intriguing to consider if the mechanism underlying environmental risk factors for neurodegeneration involves TEs. Studies directly manipulating TEs in models of neurodegenerative disease, such as increasing TE expression in young animals or lowering expression in old animals, could address whether TEs underlie age-dependent neurodegeneration.

Satellite DNA: immobile REs

Satellite DNA contains highly repetitive sequences that recur many times, forming large arrays with monomers organized in a head-to-tail fashion (tandem repeats) [136]. Satellites exist in most species, but their sequences vary significantly, even between evolutionarily close species [137,138]. Alpha satellite DNA constitutes over half of satellite DNA in humans [1]. Alpha satellite DNA consists of 171 bp repeats organized into higher order repeat units at the centromere [139,140]. Alpha satellite sequences differ between

chromosomes, even within the same individual [139,140]. Within each human chromosome (possibly excluding the Y chromosome), a subset of alpha satellite sequences include a CENP-B box, a 17-bp motif important for centromere formation [141]. While originally assumed to be transcriptionally silent due to its centromeric location, alpha satellite DNA is transcribed by RNA polymerase II [142]. TEs can reside between alpha satellite monomers in the intervening sections of the genome [143].

Satellite II (SATII) and satellite III (SATIII) are other human satellites. SATII and SATIII sequences reside in the pericentromere and are mostly transcriptionally silent, although these along with alpha satellite DNA have elevated transcription in several cancers [144–146]. Transcription of these pericentromeric sequences may enable heterochromatin formation at the pericentromere [28,147]. As with TEs, satellite transcripts are regulated by the siRNA pathway in mouse embryonic stem cells [28]. Heat shock induces SATIII transcription, with transcripts remaining at the transcriptional locus and coinciding with **nuclear stress body** (nSB) formation [148–150]. Increased SATIII transcription is elicited by other stressors [150] and nucleates nSBs [151]. DNA damage induces SATII transcription [152].

Satellite DNA in aging

Investigation of satellites in aging has been conducted in human fibroblasts and mouse tissues [47,51,153]. Increased RNA levels of satellites were found in aged human fibroblasts and mouse liver and muscle [47,51] (Figure 2B). Loss of epigenetic silencing may cause elevated expression, as methylation of satellites is reduced in aged mouse liver [153] (Figure 2D). Calorie restriction extends mouse lifespan and reduces satellite RNAs [47] (Figure 2A). Utilizing animal models to manipulate expression of satellites will help determine if expression changes are necessary and sufficient for certain aspects of aging and lifespan determination.

Satellite DNA has been investigated in cellular senescence and HGPS models. Senescent human fibroblasts exhibit distended satellite DNA sequences, i.e. decondensed DNA without the physical compaction normally associated with heterochromatin [52,154–157] (Figure 2D). They also exhibit elevated alpha satellite, SATII, and SATIII transcripts, although which of these satellites are changed is debated across studies [52,154–157] (Figure 2B). The increased expression could be via loss of surrounding repressive chromatin [52,154,156] (Figure 2D). SIRT6 depletion promotes cellular senescence, providing a simple senescence model [158]. SIRT6-depleted U2OS cells displayed increased active chromatin marks on satellites and corresponding increased satellite expression [158] (Figure 2B,D). These cells presented with mitotic defects and increased senescence (Figure 2A,J). Strikingly, SATIII knockdown rescued these phenotypes. In wild-type U2OS cells, SATIII overexpression increased senescence [158] (Figure 2A). DNA distension, loss of repressive chromatin modifications, and increased expression of satellites also occur in HGPS patient fibroblasts [55,155,159] (Figure 2B,D). Analyses of satellites in human tissue are needed to establish if expression increases with age in humans and to gain insight into their role in aging.

Satellite DNA in neurodegeneration

As with TEs, satellite DNA is implicated in neurodegeneration. Hajjar and colleagues examined cortical tissue of heterozygous *Bmi1*-deficient AD mice and found increased transcripts of centromeric minor satellites [91] (Figure 2B). They also observed reduced repressive marks and increased DNA damage marks at satellites (Figure 2D, F). Similarly, satellites display reduced repressive marks and increased DNA damage marks in AD patient versus control frontal cortex [91] (Figure 2D, F). These findings support assessing expression of satellites in AD patient brain tissue, which could provide vital information regarding whether satellite expression patterns vary with disease progression.

Elevated satellite transcripts, including alpha satellite, SATII, and SATIII, have been reported in PD patient blood [160] (Figure 2B). This elevation was not observed in skin tissue of these same patients, pointing to a tissue-specific expression pattern [160]. These data highlight the need for analyses of satellites in pathologically afflicted PD brain tissue.

Chung and colleagues investigated SATIII in a *Drosophila* model of ALS/FTD [161]. *Drosophila* expressing human TDP-43 have increased transcripts of the fly ortholog of SATIII, hsrω, in head tissue (Figure 2B). Strikingly, reducing hsrω expression rescued eye degeneration in the TDP-43 flies (Figure 2A). Elevated SATIII transcripts were also found in FTD cortical tissue and a human cell line with TDP-43 overexpression (Figure 2B). ChIP-seq data indicated that TDP-43 binds to the hsrω locus in *Drosophila*, suggesting that increased SATIII expression upon TDP-43 dysfunction might stem from a loss of TDP-43 binding to the SATIII locus [161]. Alternatively, increased levels of SATIII RNA may sequester TDP-43, inducing TDP-43 loss-of-function. For ALS/FTD models, further investigation should include examination of other satellites and exploration of the interactions between RNA-binding proteins (e.g. TDP-43) and these sequences.

Some evidence supports the disease relevance of changes in satellites in AD, PD, and ALS/FTD, but it will be important to conduct detailed investigations of the underlying mechanisms. Manipulating the levels of satellites in disease models, preferably in disease-relevant cell types, will help establish the causal relevance of these changes to disease. Experiments exploring effects of alterations in satellites and TEs in disease should be designed keeping their known biological impacts in mind (e.g. inflammation, loss of heterochromatin, and aberrant stress response) (Box 4) (Figure 2K–M).

Concluding Remarks

The importance of REs in aging and neurodegeneration is supported by a broad spectrum of studies focusing on numerous types of REs, aspects of aging, and forms of neurodegeneration [45,47,51,66,90,161]. A critical need is investigation of these sequences in human brain tissue, preferably in disease-relevant brain regions (see Outstanding questions). Some studies in this area have been conducted, but have been limited by small sample sizes [17,50,69,72,73,75,87,90,91,161,162]. Alterations in REs with age underscore the importance of age-matched controls when examining REs in neurodegeneration. Utilizing model systems to investigate REs is an attractive prospect [163]. Manipulation of animal and cellular models could enable sophisticated examination of the mechanisms

underlying alterations in REs, and their functional consequences. Deeper insight into the normal function of REs is necessary for understanding their importance in aging and disease. As the roles of REs become more evident, the potential for targeting these sequences with therapeutics may emerge as a novel approach to tackling fatal diseases. Future work on REs holds promise for enhancing our understanding of neurodegenerative disease etiology and revealing new therapeutic strategies.

Acknowledgements

We thank Andrew Modzelewski, Zissimos Mourelatos, Charlotte Fare, Jack Rubien, Hana Odeh, Erica Gorenberg, Bede Portz, and Linamarie Miller for feedback. K.E.C. is supported by National Institutes of Health (NIH) grants T32GM132039 and F31NS129101. J.S. is supported by grants from The Packard Center for ALS Research at Johns Hopkins, Target ALS, The Association for Frontotemporal Degeneration, the Amyotrophic Lateral Sclerosis Association, the Office of the Assistant Secretary of Defense for Health Affairs through the Amyotrophic Lateral Sclerosis Research Program (W81XWH-20-1-0242 and W81XWH-17-1-0237), the G. Harold and Leila Y. Mathers Foundation, Sanofi, and NIH grants R01GM099836, R21AG061784, R21AG065854, and R21NS090205.

Glossary

Transposable elements (TEs)
Mobile repetitive elements that move within the genome, although inactive copies are no longer capable of movement. TEs are subdivided into two major classes: DNA transposons and retrotransposons.

Satellite DNA
Immobile repetitive elements present in the centromeric or pericentromeric regions of chromosomes. Satellite DNA is organized as tandem repeats.

Transposition
The movement of a TE within the genome, consisting of either direct movement of the TE or movement of a copy of the TE (retrotransposition, which is based on a reverse transcription mechanism).

TE Activity
The ability of a TE to move within the genome. Active TEs can successfully (retro)transpose, whereas inactive TEs are incapable of (retro)transposition. Inactive TEs can still be transcriptionally expressed and significantly impact biology.

DNA transposon
The class of TEs utilizing direct transposition of the sequence from one location in the genome to another (cut-and-paste). DNA transposons are inactive in humans.

Retrotransposon
The class of TEs utilizing retrotransposition, which involves a copy-pasting mechanism to move the sequence via a RNA intermediate, with the template remaining in its initial locus. Retrotransposons are further subdivided into long terminal repeats and non-long terminal repeats.

Long terminal repeat (LTR)

Retrotransposons that contain long terminal repeats on either end of the TE sequence. LTRs are believed to be inactive in humans.

Non-long terminal repeat (non-LTR)
Retrotransposons that lack long terminal repeats on the ends of the TE sequence and are active in humans.

Gypsy
An endogenous retrovirus LTR family in *Drosophila* that has been implicated in *Drosophila* models of aging, ALS, and tauopathy.

TDP-43
transactive response (TAR) DNA-binding protein 43 kDa, an essential RNA-binding protein which undergoes nuclear depletion and cytoplasmic aggregation in almost all ALS cases as well as approximately half of FTD cases.

Repeat expansion
A sub-type of repetitive element in which a repeat that normally consists of few repeat units expands to contain more repeat units, sometimes in a disease context. Repeat expansions are unstable and can expand in repeat number, but are immobile within the genome.

Assay for Transposase-Accessible Chromatin (ATAC)-seq
A sequencing methodology that reveals the accessibility of chromatin throughout the genome. It relies upon the greater ability of the Tn5 transposase to add sequencing primers in regions of the genome that are more accessible.

HERV-K
A human endogenous retrovirus LTR which has been implicated in ALS, FTD, and Alzheimer's disease. There is evidence to suggest that HERV-K is active or can become active in humans.

Nuclear stress body (nSB)
A membraneless phase-separated organelle induced upon stress (e.g. heat shock). nSBs form at SATIII loci and contain SATIII RNA, HSF1, and various RNA-binding proteins. nSBs are involved in transcriptional silencing induced by stress.

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Box 1:

Tissue-specific expression of TEs

The first demonstration of active retrotransposition in the mammalian brain was in 2005, with L1 retrotransposition observed in rat neuronal precursor cells and mouse brains *in vivo* [168]. Since then, retrotransposition events have been documented with L1 as well as other non-LTRs in human cells *in vitro* and in human brain tissue [11,169–171]. These events occur in both mature neuronal cells and neuronal precursor cells [169]. Furthermore, retrotransposition events, TE transcripts, and TE-encoded proteins are more prevalent in brain cells relative to other somatic cell types in humans [50,170,172,173]. This differential expression is not solely due to the locus of the TE, as expression of L1 even at the same locus can vary depending on the cell type or cell line [174]. These findings support the existence of tissue-specific expression and activity patterns for TEs in humans, including heightened levels in brain tissue. Mice exhibit striking tissue- and sex-dependent differences in L1 RNA expression broadly, as well as in which L1 loci are expressed [49]. This finding emphasizes the importance of rationally selecting which tissue to examine and including both sexes in mouse studies of TEs. On top of tissue-specific analysis, it is best to conduct locus-specific analysis when possible, as meaningful changes in expression of unique TE loci presumably occur regardless of whether overall expression of that TE family is altered [49].

Long intergenic noncoding RNAs (lincRNAs) represent a potential mechanism by which tissue-specific expression and impact of TEs is conferred. lincRNAs are much more likely to contain TEs versus protein-coding genes [175]. lincRNAs also have a higher average TE composition [175]. TEs can act as alternative promoters and affect general expression of lincRNAs, and even directly lead to the appearance of new lincRNAs in the genome [175–177]. In some cases, the action of TEs as alternative promoters can alter the tissue-specific expression pattern of lincRNAs [175]. The ability of TEs to alter tissue-specific expression has implications for the concept of selective vulnerability, which refers to the degeneration of specific types of neurons that occurs in various forms of neurodegeneration [178]. Investigating whether alterations of TEs lead to changes specifically in neuronal subtypes that are vulnerable in each disease could shed light on this poorly understood feature of neurodegeneration.

Box 2:

HERV-K in ALS/FTD

Human endogenous retroviruses are a subset of LTRs, a subclass that is thought to be inactive in humans [1]. Several studies indicate that this notion requires reconsideration for human endogenous retrovirus K (HERV-K) in ALS. Early work demonstrated that ALS patients exhibit a heightened immune response to a protein encoded by HERV-K [179]. There is now evidence showing increased expression of a HERV-K transcript, HERV-K *pol*, in ALS patient brain tissue, with levels of intact transcript highest in motor cortex (Figure 2B). This study detected HERV-K protein in ALS patient neurons, and noted a correlation between the levels of HERV-K and TDP-43 transcripts, as well as colocalization of these proteins, in ALS patient brain tissue [162]. Li and colleagues replicated these findings, observing increased expression of HERV-K RNA and protein in ALS patients (Figure 2B). Li et al. demonstrated that HERV-K expression in human neurons elicits death and neurite retraction (Figure 2A). Furthermore, they found that HERV-K expression in mice results in motor cortex atrophy, increased DNA damage, impaired locomotion, and shortened lifespan [180] (Figure 2A,F). In line with other work connecting TEs and inflammation, ALS patient motor cortex exhibits increased HERV-K protein and interferon pathway activation [181]. In human cell lines HERV-K *pol* expression is increased by IRF1, an interferon-stimulated transcription factor, presumably via IRF1 binding sites in its 5’ LTR [181]. It would be valuable to investigate a possible positive feedback loop between HERV-K levels and innate immune system activation in ALS.

Some HIV patients exhibit symptoms of motor neuron disease and increased HERV-K levels [182]. Antiretroviral therapy rescues motor symptoms, consistent with a role for HERV-K in eliciting motor dysfunction [182]. Antiretroviral therapy decreases serum levels of HML-2, a HERV-K subtype, in most treated ALS patients. Strikingly, patients with decreased HML-2 levels exhibited slowed disease progression [183]. Additional work is needed to establish if HERV-K retrotransposition occurs in ALS patients, or whether increased expression occurs from static HERV-K copies. HERV-K could become mobile in humans with a single recombination event between two copies [184]. One study identified a potentially active HERV-K element in humans [185]. However, two studies did not find increases in HERV-K transcripts or proteins in ALS patients [186,187]. Further work is needed to assess how prevalent HERV-K changes are in patients. As *gypsy*, of interest in *Drosophila* ALS/FTD models, is also an endogenous retrovirus, experiments comparing the effects of HERV-K and *gypsy*, and whether they act via similar mechanisms, would be valuable. HERV-K has received more attention in ALS compared to FTD. Recent work demonstrates elevated HERV-K *env* transcripts in FTD versus control patient cortex, and detects HERV-K protein in FTD cortical neurons [74]. This finding supports further study of HERV-K in FTD.

Box 3:

Phase separation of REs

Phase separation is a process by which molecules can self-associate to create two compositionally distinct phases from a homogenous solution: (1) a dense phase containing a high concentration of the molecule(s), and (2) a light phase relatively depleted of the molecule(s). Highly repetitive RNAs can phase separate [188]. Due to the repetitive nature of TEs and satellites, it is worth investigating the propensity of these sequences themselves, and the proteins they encode, to undergo phase transitions (Figure 2G). Indeed, a recent paper shows that L1 ORF1 protein undergoes phase separation *in vitro* [189]. L1 ORF1 mutant constructs that undergo phase separation to a diminished extent *in vitro* display reduced retrotransposition in cells, supporting the functional importance of phase separation for L1 elements [189]. Other work has shown that various types of RNA transcripts, including SATIII transcripts, are capable of nucleating condensates in cells [151]. The phase behavior of these transcripts could be tightly regulated by cellular conditions to determine whether they perform certain functions. The formation of condensates containing these transcripts could sequester other biomolecules. This sequestration could either enable functional processes in cells or disrupt cellular function, depending on the specific biomolecules involved.

What role might phase separation play in the impact of REs on human health? One hypothesis is that in aging and neurodegenerative disease, proteins and these repetitive RNAs display aberrant phase behavior. Aberrant phase behavior of regulators of REs may also occur. For instance, PR dipeptide repeats from the ALS/FTD-related *C9ORF72* mutation can disrupt phase separation of a vital protein component of heterochromatin, HP1α [70]. This disruption of heterochromatin is postulated to be responsible for increased RE expression in mice with poly-PR dipeptide repeat expression [70]. Altered RE expression could alter any condensates composed of RE RNA. Another potential connection between phase separation and REs is suggested by recent work finding that the C-terminal prion-like domain of TDP-43 is necessary for its repression of L1 retrotransposition in HEK293T [86]. The C-terminal domain is critical for TDP-43 phase separation [190], indicating the need to investigate the importance of TDP-43 phase separation for repression of L1 retrotransposition. Further work is needed to characterize the ability of TE and satellite RNA to undergo phase separation *in vitro* and in cells. Future work exploring the phase separation of these transcripts in disease contexts will be highly interesting.

Box 4:

Biological impacts of REs

Numerous mechanisms exist by which TE insertion changes the sequence and transcription of its destination locus (Figure 2C). For example, L1 insertion into the neuronal gene *Psd-93* in mammalian neural progenitor cells elevates Psd-93 expression and the propensity for neuronal differentiation [168]. L1 insertion into the *F8* gene causes hemophilia A via duplicating part of the *F8* sequence [191]. TE insertion can also delete portions of the gene [192,193]. Insertion can truncate transcripts by introducing premature polyA signals or promoting dissociation of RNA polymerase during transcriptional elongation [194]. 5' and 3' transduction events occur when the sequence before or after, respectively, the TE in the original location is also inserted [193,195,196]. 5' transductions can introduce new transcription start sites or alternative promoters [193,196]. Insertions can invert portions of the sequence [193]. If the TE inserts into the 3'UTR of its target or causes epigenetic repression of the adjacent sequence, this can reduce gene expression [196,197].

Another biological impact of TE insertion is DNA damage. L1 retrotransposition results in DSBs [198,199] (Figure 2F). L1 can elicit DSBs even with defective reverse transcriptase or endonuclease activity, indicating that successful retrotransposition is not required to generate DNA damage [198,199]. Excess TEs may activate inflammation pathways via increased cytosolic DNA or dsRNA eliciting an interferon response [31,71,85,93–97,107,109,115,116,120,161,200–203] (Figure 2K). L1 expression can increase apoptosis [204]. Alu insertion variants are enriched at disease-risk loci, suggesting that TE insertion negatively affects these genes. Indeed, the presence or absence of an Alu insertion can predict if a trait-associated single nucleotide polymorphism is present [205] (Figure 2A).

Satellite DNA alterations also have far-reaching cellular consequences. Transcription of alpha satellite DNA is vital for mitosis [142]. Reducing or increasing alpha satellite DNA transcripts impairs centromeres, disrupts mitosis, and generates DNA damage [206,207] (Figure 2F,J). The appropriate expression of pericentromeric satellites SATII and SATIII is important for heterochromatin formation at the pericentromere [28,147] (Figure 2L). Aberrant heterochromatic marks on pericentromeric satellites will likely elicit expression changes of other pericentromeric sequences, perhaps even of TEs.

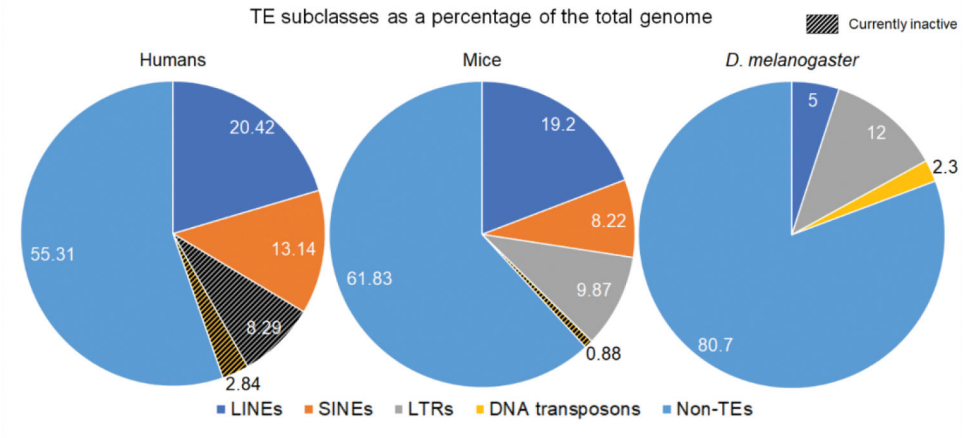
SATIII expression plays a vital role in the stress response [148–150]. Depletion of SATIII transcripts decreases survival of stressed cells [208] (Figure 2M). This decreased survival is presumably due to the role of SATIII transcripts in recruiting transcription factors and enabling global transcriptional repression [208]. Aberrant increases in SATIII transcripts under normal conditions can also be detrimental. SATIII overexpression in unstressed cells elicited formation of nuclear stress bodies, transcriptional repression, and decreased survival [208].

Highlights

- Increased expression of TEs and satellites is commonly observed in models of aging and neurodegenerative disease
- Disruption of heterochromatin, the siRNA system, or the piRNA system may lead to increased expression of TEs and satellites
- Upregulation of TEs is implicated in impairing long-term memory, lifespan, locomotion, and neuronal survival
- Increased expression of LTR elements of the *gypsy* family occurs in *Drosophila* models of aging, ALS/FTD, and tauopathy
- TDP-43 dysfunction leads to upregulation of TEs, potentially via impairing the siRNA system

Outstanding Questions

- Are alterations in REs more pronounced in the disease-relevant tissue type? Does tissue-specific expression of REs contribute to the poorly understood phenomenon of selective vulnerability in neurodegeneration?
- What are the functional roles of specific REs in human cells? What are the biomolecular interaction partners (e.g. proteins and RNAs) of these REs?
- Are the impacts of REs in aging and neurodegeneration mediated by loss-of-function or gain-of-function mechanisms, or both? What are the effects in animal and cellular models when these sequences are targeted?
- Can neurodegeneration be rescued by targeting REs? What are the effects of targeting specific REs with ASOs or gene therapy approaches? What are the effects of broadly targeting REs with antiretroviral drugs or drugs boosting the siRNA system?
- Does active retrotransposition underlie expression changes of TEs in aging and neurodegeneration?
- What is the relationship between alterations in REs and environmental risk factors in neurodegeneration?
- What are the biological interconnections between TDP-43, the siRNA system, and alterations in TEs? Are the effects of TDP-43 on the siRNA system predominantly mediated by impairing the expression or function of proteins vital for siRNA processing, or by reducing production or stability of antisense siRNAs?
- Do piRNA and siRNA pathways regulate TEs in the human CNS?



TE families in humans

LINE families	Percent of the human genome (%)
LINE1	16.89
LINE2	3.22
LINE3	0.31

SINE families	Percent of the human genome (%)
Alu	10.60
MIR	2.20
MIR3	0.34

LTR families	Percent of the human genome (%)
ERV-class I	2.89
ERV(K)-class II	0.31
ERV(L)-class III	1.44
MaLR	3.65

DNA transposon families	Percent of the human genome (%)
hAT	1.55
Tc-1/mariner	1.15

TE families in mice

LINE families	Percent of the mouse genome (%)
LINE1	18.78
LINE2	0.38
LINE3	0.05

SINE families	Percent of the mouse genome (%)
B1*	2.66
B2	2.39
B4/RSINE	2.36
ID	0.25
MIR/MIR3	0.57

LTR families	Percent of the mouse genome (%)
ERV-class I	0.68
ERV(K)-class II	3.14
ERV(L)-class III	0.58
MaLR	4.82

DNA transposon families	Percent of the mouse genome (%)
hAT	0.68
Tc-1/mariner	0.18

Figure 1. Abundance of TE subclasses and families across species.

Pie charts display the percentage of the respective genome (human, mouse, or *Drosophila melanogaster*) constituted by the various subclasses of TEs [1,164,165]. Subclasses that are thought to be inactive in the respective genome are indicated by striped patterns [1,164–166]. Tables display the percentage of the respective genome (human or mouse) that the various families of TEs constitute [1,164]. These percentages vary between studies, likely due to differences in sequencing methodology and the percentage of heterochromatic sequence analyzed. The data reported here comes from the referenced studies. *The B1 SINEs found in mice and Alu SINEs found in humans are thought to share a common origin, from which they then evolved distinctly in each species [164,167]. Created with BioRender.com.

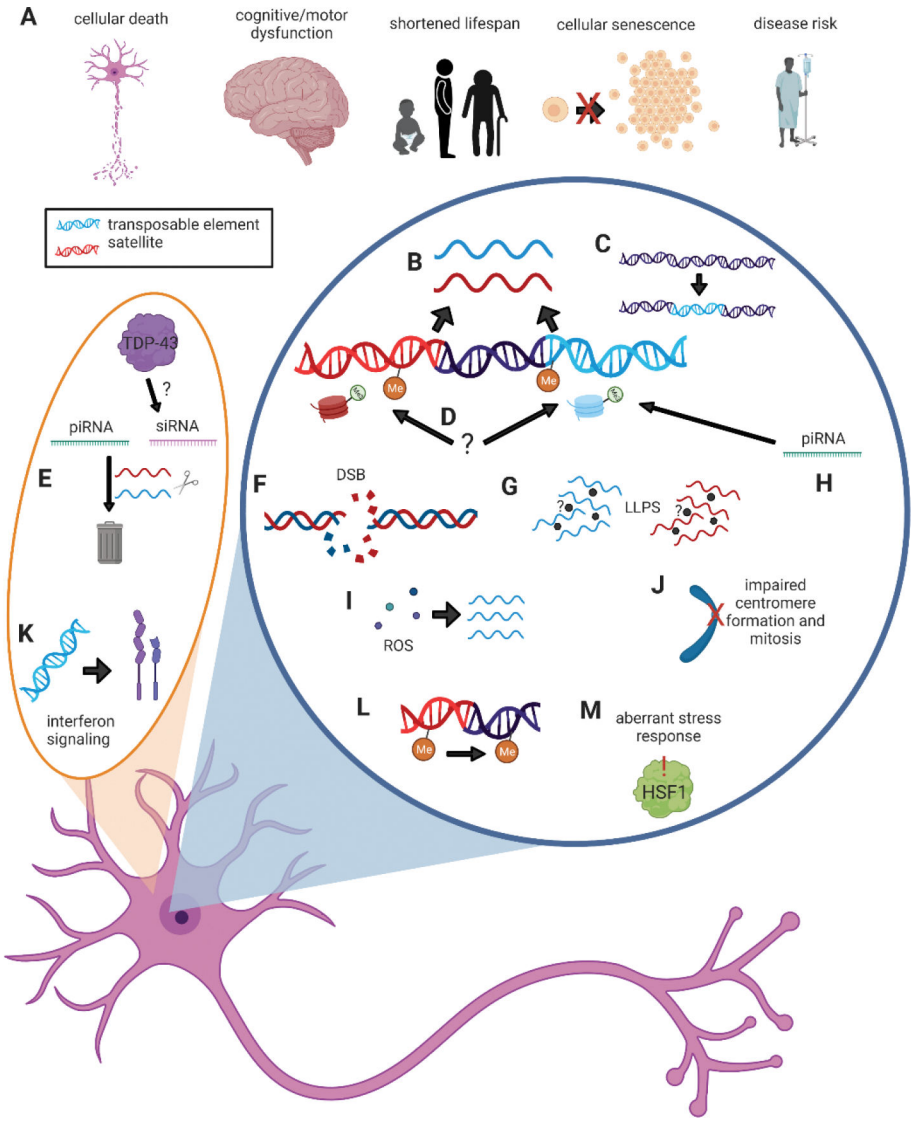


Figure 2 Key Figure. Alterations in REs with age and neurodegeneration and their potential causes and effects.

Long-term implications of changes in REs with age and neurodegeneration include neuronal cell death, cognitive and motor dysfunction, shortened lifespan, and disease risk **(A)**. Observed changes in TEs with age and neurodegeneration include increased transcript levels **(B)**, increased successful retrotransposition **(C)**, and decreased repressive marks **(D)**. Possible upstream causes for the increase in transcript levels include a loss of heterochromatin **(D)** and impairments in post-transcriptional silencing via the siRNA system, piRNA system, or both **(E)**. Increased TE expression correlates with increased levels of DSBs **(F)**. TEs may also exert effects via phase separation **(G)**. Dysfunction of the piRNA system may impair TE silencing at the transcriptional level **(H)**. Reactive oxygen species (ROS) may increase TE expression **(I)**. Observed changes in satellites with age and neurodegeneration so far also include increased transcript levels **(B)** and decreased repressive marks **(D)**. Like TEs, possible causes for changes in satellite DNA expression involve impairments in heterochromatin **(D)** and the siRNA system **(E)**. Potential effects of

the alterations in TEs and satellites include alterations in the sequence or transcription of the recipient gene **(C)**, increased DSBs **(F)**, phase separation of transcripts **(G)**, impaired mitosis and centromere formation **(J)**, inflammation triggered by cytosolic DNA **(K)**, a loss of heterochromatin from adjacent sequences **(L)**, and an aberrant stress response **(M).** Consequences of satellite DNA alterations may include shortened lifespan, increased senescence, and cellular death **(A)**. The direct causes of changes to both TE and satellite DNA expression, as well as the mechanisms of their detrimental effects, warrant further examination. Created with BioRender.com.