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Transposable elements as new players in neurodegenerative diseases

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Neurodegenerative diseases (NDs), including the most prevalent Alzheimer's disease and Parkinson disease, share common pathological features. Despite decades of gene-centric approaches, the molecular mechanisms underlying these diseases remain widely elusive. In recent years, transposable elements (TEs), long considered 'junk' DNA, have gained growing interest as pathogenic players in NDs. Age is the major risk factor for most NDs, and several repressive mechanisms of TEs, such as heterochromatinization, fail with age. Indeed, heterochromatin relaxation leading to TE derepression has been reported in various models of neurodegeneration and NDs. There is also evidence that certain pathogenic proteins involved in NDs (*e.g.*, tau, TDP-43) may control the expression of TEs. The deleterious consequences of TE activation are not well known but they could include DNA damage and genomic instability, altered host gene expression, and/or neuroinflammation, which are common hallmarks of neurodegeneration and aging. TEs might thus represent an overlooked pathogenic culprit for both brain aging and neurodegeneration. Certain pathological effects of TEs might be prevented by inhibiting their activity, pointing to TEs as novel targets for neuroprotection.

Keywords: aging; Alzheimer's disease; gene dysregulation; genomic instability; heterochromatin destructureation; neurodegenerative diseases; neuroinflammation; oxidative stress; Parkinson disease; retrotransposons

Neurodegenerative diseases (NDs) affect several million people worldwide and have become a major hurdle in societies with aging populations. They result from the progressive loss of brain functions, which inexorably leads to severe disability and death [1]. The elucidation of the molecular mechanisms underlying these diseases and the development of effective therapies that either slow down or reverse the neurodegenerative process are urgently needed. Unfortunately, despite extensive gene-centric research carried out during the past several decades, our

knowledge of the etiology of NDs remains rudimentary [2,3].

Since protein-coding DNA represents only about 2–3% of the human genome, the focus has shifted in recent years to exploring the noncoding portion of human DNA with the hope that this endeavor may provide novel clues for a better understanding of the molecular basis of NDs and human diseases, in general. A large proportion of the human genome is composed of repetitive DNA sequences [4], which were considered junk DNA for decades. The initial

Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DNMT, DNA methyltransferase; ERV, endogenous retrovirus; FTD, frontotemporal dementia; HDAC, histone deacetylase; HERV, human ERV; LINE-1, long interspersed repeat-1; LTR, long terminal repeat; NDs, neurodegenerative diseases; PD, Parkinson disease; RTE, retrotransposon; SINEs, short interspersed elements; TDP-43, TAR DNA-binding protein 43; TEs, transposable elements.

sequencing of the human genome revealed that about 45% of the human DNA is derived from transposable elements (TEs) [5]. First discovered in maize by Barbara McClintock more than 70 years ago as ‘controlling elements’ implicated in the regulation of genes [6], TEs have long been considered selfish genetic elements that jump from one genomic location to another. It has become evident from the research performed during the past decades that TEs have played an important role in shaping mammalian genomes during evolution and TE-derived sequences have been co-opted for many gene regulatory functions in different organisms [7,8]. Noteworthy, certain TEs are still capable of mobilization in mammalian genomes, but they normally remain ‘dormant’ in somatic tissues. However, a partial reawakening of TEs in somatic tissues has been observed in many human diseases [9,10] and is well documented in cancer [11]. In recent years, several studies have provided evidence that TE activity is associated with neurodegeneration [12,13].

This review elaborates on the emerging concept that TEs might be unsuspected pathogenic drivers of neurodegeneration through diverse mechanisms. We will discuss how the activity of TEs, certain pathological hallmarks of aging and NDs, could be interconnected and why TEs may provide novel druggable therapeutic targets in NDs.

Hallmarks of NDs

Striking characteristics and shared pathological features

The clinical manifestations of NDs, among which Alzheimer’s disease (AD) and Parkinson disease (PD) are the most common, depend upon the neuronal populations affected in selected regions of the brain. For instance, degeneration of hippocampal and cortical neurons is associated with memory loss, cognitive impairment, and dementia in AD, whereas a progressive loss of dopaminergic neurons in the *substantia nigra par compacta* (SNpc) in the midbrain leads to the cardinal motor symptoms (resting tremor, bradykinesia, and rigidity) in PD. Dopaminergic neurons of the SNpc send long projections to innervate the dorsal striatum, forming the nigrostriatal pathway, and progressively degenerate in PD in a retrograde manner [14,15]. Among other devastating adult-onset NDs, amyotrophic lateral sclerosis (ALS) results from degeneration of upper and lower motor neurons (causing fatal paralysis with respiratory failure), while frontotemporal dementia (FTD) arises from progressive degeneration of frontal and temporal lobes. The

mechanisms underlying the selective vulnerability of specific neuronal populations affected in different NDs remain unknown [16].

One of the major hallmarks shared by several NDs is protein aggregation [17]. Senile plaques, specific to AD, are formed by insoluble fibrillar aggregates of amyloid- β (A β). Neurofibrillary tangles found in many neurodegenerative conditions, including AD and FTD, contain the hyperphosphorylated fibrillar forms of microtubule-associated protein tau and are hence referred to as tauopathies. Similarly, PD is characterized by the widespread presence of α -synuclein aggregates in Lewy bodies and neurites in the nervous system [18]. ALS is known to have inclusions of TDP-43 (TAR DNA-binding protein 43), a protein involved in RNA metabolism. FTD can be driven by tauopathy or TDP-43 pathology. A subset of FTD patients with TDP-43 pathology is thought to have an FTD-ALS spectrum disorder considering the closely related pathologies of these two diseases [19]. TDP-43 aggregation can also be found in 37% of AD patients [20], illustrating that these different protein aggregations overlap among these NDs. A striking feature of aberrantly folded and aggregating proteins (*i.e.*, A β and α -synuclein) is their ability to spread in the nervous system in a prion-like manner [21,22]. Where the formation of these aggregates begins remains unclear. The Braak hypothesis stipulates that protein aggregation in AD and PD may initiate in the gut or the olfactory bulb and then progressively ascend to different brain regions [23].

Genetic studies of familial forms of NDs have identified mutations in several genes. These include the following: SNCA (α -synuclein), LRRK2 (leucine-rich repeat kinase 2), PRKN (or Parkin; parkin RBR E3 ubiquitin protein ligase), Pink1 (PTEN-induced kinase 1), and PARK7 (or DJ-1; parkinsonism-associated deglycase) in PD [24]; APP (amyloid beta precursor protein), PSEN1 (presenilin 1), PSEN2 (presenilin 2), and MAPT (microtubule-associated protein tau) in AD/tauopathies [25]. Although TDP-43 pathology is observed in about 95% of ALS patients and all FTD-TDP patients, TDP-43 mutations are not common drivers of these pathologies. Among many mutations with large effects found in ALS, the most common are repeat expansions in C9orf72 (C9orf72-SMCR8 complex subunit). For familial forms of ALS, the overlap with FTD drivers is very high, but this represents only 10% of all ALS patients [19]. Studies involving genome-wide associations have also revealed many disease risk loci that are associated with NDs. The genetic basis of the common idiopathic or sporadic forms of NDs remains largely unknown. Functional

studies of genes mutated in the familial forms of NDs have been instrumental in shedding some light on the mechanisms that may contribute to neurodegeneration.

Besides protein aggregation, the pathological features shared by NDs include mitochondrial dysfunction, oxidative stress, impaired ubiquitin-proteasomal pathway, altered autophagy, and neuroinflammation [17]. Mitochondrial dysfunction has received particular attention in PD ever since the discovery that inhibition of mitochondrial complex I activity by certain neurotoxins (*e.g.*, 1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine, MPTP) or pesticides (*e.g.*, rotenone) can lead to parkinsonism in humans [26,27]. It was shown that genes mutated in PD (*i.e.*, Pink1, Parkin) directly or indirectly affect mitochondrial activity [28]. Many other disease-related proteins (*i.e.*, A β or phosphorylated tau in AD) have been reported to interact with mitochondria and alter mitochondrial processes, such as mitophagy [29,30]. Mitochondrial function/dysfunction and different energy requirements of the diverse neuronal populations in various brain regions could partly explain selective neuronal vulnerability in different NDs [31]. In addition to producing ATP, mitochondria also play an important role in the quality control of proteins produced and the disposal of protein aggregates [32]. Unfortunately, most efforts to develop animal models of NDs were unsuccessful as many of the mutations linked to these diseases did not fully recapitulate the disease symptoms [33]. In the context of PD, it is noteworthy that certain transcription factors (*i.e.*, Engrailed), required for the development of dopaminergic neurons, continue to be expressed in adulthood and play a critical role for the lifelong survival of these neurons [34]. Interestingly, targeted disruption of one *Engrailed-1* (*En1*) allele in mice provides a valuable PD model with progressive loss of dopaminergic neurons in the SNpc [35]. These *En1*^{+/-} mice recapitulate several pathological features of PD, including altered mitochondria, impaired autophagy, retrograde degeneration, and inflammation [36,37]. Other studies lend support to the idea that genes involved in the development of dopaminergic neurons could also be involved in the development of PD [38].

Aging and neurodegeneration: Is a key player missing?

Although genetic and environmental factors are certainly at play, age remains the major risk factor for NDs [39,40]. In PD, for instance, the appearance of the first classical motor symptoms is preceded by a prodromal (nonsymptomatic) pre-ND phase typically

presenting nonmotor symptoms (*i.e.*, olfaction loss, constipation, sleep disorders) that can last up to 20 years [41]. How the aging process contributes to neurodegeneration remains unknown. It is noteworthy that many pathological features of NDs are aggravated hallmarks of brain aging [42]. Neurodegeneration might thus be seen as a continuity of aging and the manifestation of NDs as accelerated aging (Fig. 1). To date, nine established hallmarks of aging have been defined: mitochondrial dysfunction, loss of proteostasis, DNA damage and genomic instability, epigenetic alterations, dysregulated nutrient sensing, cellular senescence, telomere attrition, stem cell exhaustion, and altered intercellular communication [43] of which genomic instability and epigenetic alterations are considered to be the primary hallmarks. The brain shows aging hallmarks very similar to those of other tissues, and many processes altered during aging have also been implicated in different neurodegenerative contexts [40,42]. As mentioned above, mitochondrial dysfunction is an established hallmark of aging and plays an important role in age-related NDs. Mitochondria are critical regulators of cell death, which is a common feature of NDs. Mitochondrial insults can lead to increased reactive oxygen species (ROS) production, and mutations in mitochondrial DNA (mtDNA) and oxidative stress can both contribute to the aging and development of NDs [29]. Several DNA repair pathways keep mtDNA intact to minimize these alterations [44]. Strategies that target mitochondrial processes such as energy metabolism, ROS production, or the interaction of disease-related proteins with mitochondria may have therapeutic potential. We will mainly focus here on the two primary hallmarks of brain aging, namely genomic instability and epigenetic alterations, which have so far remained widely unrecognized as potential pathogenic drivers of neurodegeneration.

A feature unequivocally linked to brain aging is the accumulation of unrepaired DNA that can jeopardize genome integrity [45]. High energy consumption, especially by neuronal cells, must impose a significant oxidative burden (*i.e.*, ROS production), which is considered a major source of DNA damage in the brain [46]. It is noteworthy that sheer physiological neuronal activity causes DNA strand breaks, which are rapidly repaired [47]. Postmitotic neurons mainly rely on non-homologous end-joining for DNA repair, which is error-prone. This leads to the accumulation of small deletions in the genome, compromising genome integrity over time [48,49]. Acceleration of this process by genetic or environmental factors could deteriorate genome integrity to a point where normal cellular functions can no longer be sustained. A progressive decline

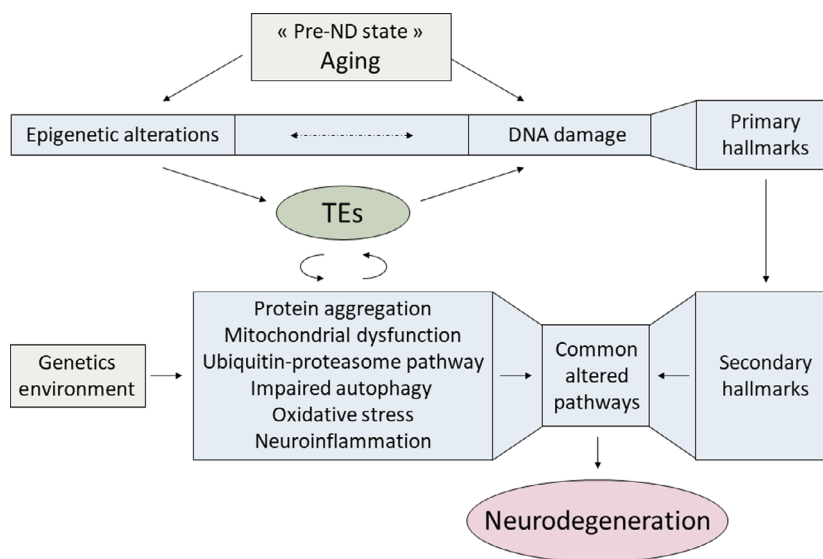


Fig. 1. Aging hallmarks and neurodegeneration—TEs as a missing link. Age is a major risk factor for NDs like AD and PD, and aging is considered an accelerating factor for the development of NDs, inducing a ‘pre-ND’ state. Primary hallmarks of aging are DNA damage and epigenetic alterations, which are both related to TE activity. Epigenetic alterations derepress TEs, some of which are themselves a source of DNA damage (and epigenetic alterations). Secondary hallmarks of aging show a significant overlap with known altered pathways of neurodegeneration, which are thought to result from a combination of genetic and environmental factors. TE activation might be amplified by several deregulated pathways like mitochondrial dysfunction, oxidative stress, impaired autophagy or neuroinflammation, and TEs might maintain or amplify this dysregulation (*i.e.*, neuroinflammation). Subsequently, these deregulated pathways could progressively lead to neurodegeneration.

in DNA repair mechanisms during brain aging might lead to the accumulation of unrepaired DNA strand breaks. The presence of unrepaired DNA lesions initiates altered cellular processes, including senescence and apoptosis [50], which altogether could be sufficient to initiate a neurodegenerative process [51]. A potential link between DNA damage/repair and neurodegeneration is further emphasized by the fact that mutations in several genes encoding DNA repair enzymes such as ataxia telangiectasia mutated (ATM) are associated with NDs [48]. Furthermore, accumulation of DNA strand breaks has been reported in the brains of AD, PD, and ALS patients [52–54], and a number of proteins (*e.g.*, tau, α -synuclein, TDP-43) involved in these diseases also participate in DNA repair [55–57]. Malfunctioning of the DNA repair machinery leads to the degeneration of the nigrostriatal pathway in different mouse models [58]. Inefficient DNA repair has also been suggested to be an aging-related disease modifier in a mouse model of PD [53]. Indeed, mice lacking the DNA excision repair protein ERCC-1 (excision repair cross-complementation group 1) in dopaminergic neurons become more vulnerable to MPTP. The DNA repair system is also impaired in AD [59,60]. In addition, A β aggregates have been shown to exacerbate the levels of DNA strand breaks in models of tauopathy [47]. It is noteworthy that

DNA repair involves transient and local chromatin relaxation [61]. However, excessive chromatin disorganization could be deleterious and contribute to neurodegeneration.

DNA is structured and compacted into chromatin, which can be further organized in euchromatin (transcriptionally active) or heterochromatin (denser, transcriptionally inactive). Constitutive heterochromatin is enriched in repetitive sequences and has structural functions [62]. In contrast, facultative heterochromatin contains coding sequences and is essential during development and in determining cell-type specificity [62]. Chromatin in these domains is more versatile and can revert to euchromatin under certain conditions [63]. It is now well established that epigenetic modifications, namely DNA methylation and post-translational modifications (*i.e.*, methylation or acetylation) of various histones, play crucial roles in the structuration of DNA into euchromatin or heterochromatin domains [64]. There is mounting evidence that epigenetic changes are implicated in normal brain aging and NDs [65–68]. Such modifications could alter gene expression and regulation. In accordance, many enhancers associated with genes involved in the early cell cycle, inflammation, and amyloid neuropathies have recently been shown to be differentially methylated in AD [69]. Dysregulation of histone acetylation has been reported

near genes involved in aging and AD or tauopathy [70,71]. Widespread alterations in histone acetylation have also been documented in the brains of PD patients [72]. Genome-wide epigenetic changes could disorganize the entire chromatin landscape, resulting in altered gene expression and regulation during aging and neurodegeneration. Similar to the heterochromatin loss model of aging [73], this suggests that normally repressed genes contained in heterochromatin domains may become accessible and re-expressed during aging. Global heterochromatin loss in the brain during aging could indeed be a key feature of NDs. Widespread destructure of heterochromatin resulting in aberrant gene expression has been reported in drosophila and mouse models of tauopathies and in AD patients [74]. Furthermore, the distribution of histone H3 lysine 9 trimethylation (H3K9me3) and heterochromatin binding protein 1 α (HP1 α) was altered in neurons from tau-deficient mice [75]. Interestingly, gene expression profiles obtained by analyzing transcriptomes from AD brains were similar to those of a fetal brain [74], suggesting that heterochromatin structure in postmitotic neurons might be reverted to a de-differentiated state. Heterochromatin decondensation (indicated by the loss of repressive histone marks) was also reported in the *En1*^{+/-} mouse model of PD and in cellular models of oxidative stress [31].

Importantly, epigenetic alterations and heterochromatin loss could cause the activation of dormant TEs. TEs, in turn, might become an additional source of DNA damage and genome instability and possibly contribute to several other pathological features of aging. We discuss below the emerging concept that TEs may represent new pathogenic players in NDs and a missing link between aging and neurodegeneration (Fig. 1).

TEs as sleeping culprits within the genome

Overview of TEs

As mentioned above, a large portion of the human DNA is composed of repetitive sequences derived from TEs (also known as ‘jumping’ genes or mobile elements), which have self-amplified in the mammalian genomes during evolution (Fig. 2A) [76]. TEs comprise DNA transposons and retrotransposons (RTEs). DNA transposons, the TE class discovered by Barbara McClintock, mobilize using a ‘cut-and-paste’ mechanism. They have been very active during primate evolution but are now inactive in humans [77]. RTEs use a ‘copy-and-paste’ mechanism to self-amplify *via* an

RNA intermediate (retrotransposition). Depending upon the presence or absence of long terminal repeats (LTRs), they are divided into LTR RTEs (*i.e.*, endogenous retroviruses, ERVs or human ERVs, HERVs; Ty1-copia, Ty3-gypsy; terminal-repeat retrotransposon in miniature, TRIM) and non-LTR RTEs (*i.e.*, Long Interspersed Repeat-1, LINE-1; Short Interspersed Elements, SINEs; SINE-VNTR-Alu, SVA). SVA elements are evolutionarily derived from SINEs. While the LTR RTEs seem to have lost the ability to mobilize, and most of them have recombined to generate solo LTRs, the non-LTR RTEs are still mobile in humans [78]. LINE-1 elements are autonomous RTEs, whereas SINEs, comprised of human Alu sequences, and SVAs are nonautonomous RTEs that hijack the LINE-1 machinery for self-amplification (Fig. 2A) [79,80]. LINEs are the most widespread TEs, representing about 21% of the human genome. There are roughly 500 000 LINE-1 copies in the human genome, but most of them are fossilized (either mutated or truncated) and unable to move. Yet, more than 100 full-length LINE-1 (human-specific LINE-1 L1HS and older L1PA2 LINE-1) have retained their coding capacity and can potentially retrotranspose. However, only a limited number of these LINE-1 loci seem to account for the bulk of retrotransposition in the human population [81–83]. The number of potentially active, full-length LINE-1 elements in the mouse (L1Md-Tf, -A, and -Gf families) is much higher (around 3000) [84]. Full-length LINE-1 is composed of a 5′ untranslated region (UTR) containing two promoters on the sense and antisense DNA strands followed by two open reading frames (ORFs) and a 3′UTR, which contains a polyadenylation signal.

ORF1 codes for an RNA binding protein (ORF1p) whereas ORF2 codes for ORF2p that encompasses endonuclease and reverse transcriptase activities (Fig. 2A). The antisense transcript codes for ORF0 and could possibly yield fusion proteins and contribute to retrotransposon-mediated diversity at the level of gene expression [85]. LINE-1 retrotransposition involves several steps. Following transcription, LINE-1 mRNA is translocated to the cytoplasm for translation. The resulting proteins, ORF1p and ORF2p, bind to the LINE-1 mRNA forming ribonucleoprotein particles (RNPs), which translocate to the nucleus. The endonuclease activity of ORF2p generates a nick in the genomic DNA at a consensus site (5′TTTT/AA3′). The reverse transcriptase activity of ORF2p makes use of the exposed poly-T stretch as a primer to generate LINE-1 cDNA (target-primed reverse transcription, TPRT), which results in LINE-1 insertion within the genome [86–88]. Most insertions result in truncated

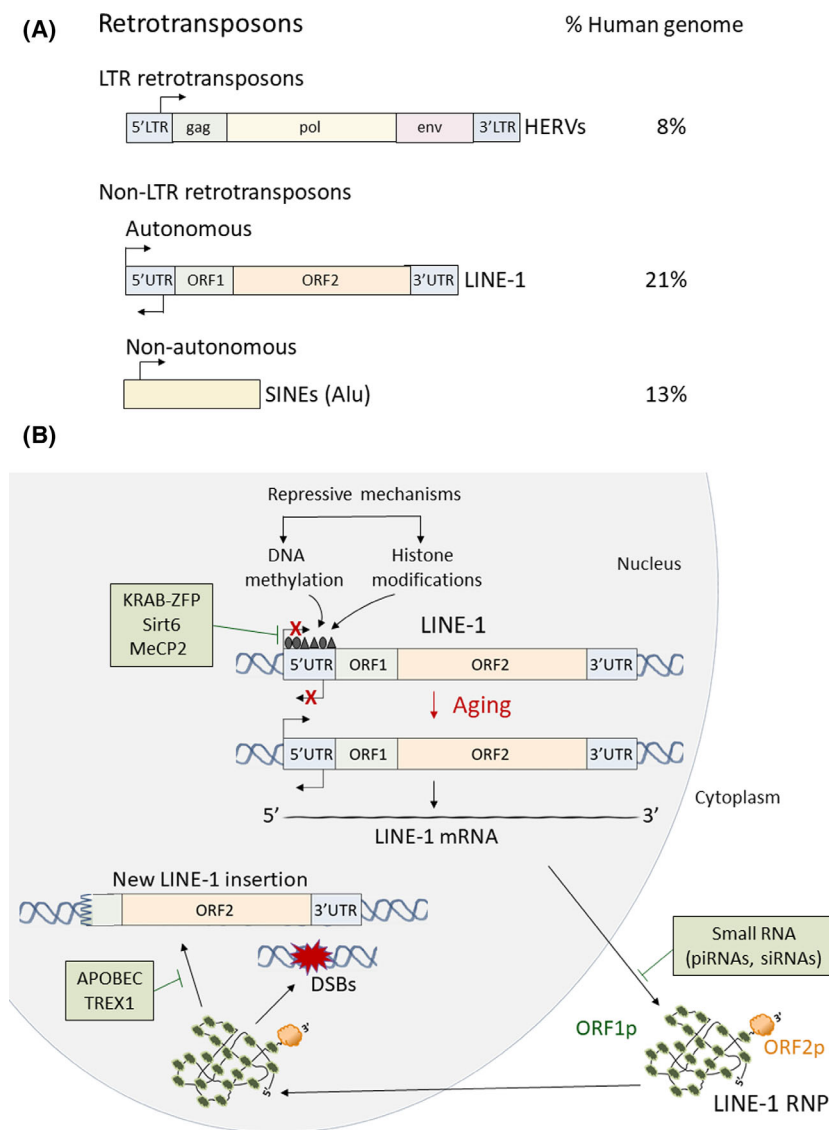


Fig. 2. RTE structure and their potential involvement in DNA strand breaks and genome instability. (A) Structure of LTR and non-LTR RTEs that have self-amplified in the human genome by a 'copy and paste' mechanism during evolution. The percent human genome represented by these RTEs is indicated on the right. (B) Failure of epigenetic repressive mechanisms with aging and LINE-1 activation could lead to DNA strand breaks and genomic instability. See text for details.

LINE-1 copies, as DNA repair pathways disrupt retrotransposition (Fig. 2B) [89,90]. It was recently shown that LINE-1 ORF2p binding in *cis* to the 3' poly(A) tail of LINE-1 RNA is required for LINE-1 retrotransposition, and binding in *trans* to the 3' poly(A) tract of cellular or other RNAs is required for their mobilization [91]. The 3' poly(A) tails of Alu RNAs efficiently compete with LINE-1 3' poly(A) tracts for the binding of LINE-1 ORF2p. Although TEs have played an important role in generating diversity and shaping the human genome throughout evolution, TEs can be an important source of mutation and genomic instability at the level of an individual. Indeed, LINE-1 insertions, depending upon the location, can lead to deleterious mutations, and ORF2p endonuclease activity, required for retrotransposition, can generate numerous

additional DNA strand breaks, compromising genome integrity (Fig. 2B). To date, over a hundred human diseases have been linked to retrotransposition events [9]. Several means to restrict LINE-1 activity exist at a cellular level, but as discussed in the following section, these repressive mechanisms start to fail with age.

Failure of mechanisms repressing TEs with aging

The activity of TEs is kept in check by several epigenetic modifications (DNA methylation and/or histone methylation) favoring heterochromatin formation (Fig. 2B) [92,93]. TEs silencing pathways work the same way for most transposons [94,95]. We illustrate here some of the mechanisms used for LINE-1 repression in particular. The CpG islands within the 5'UTR

of LINE-1 become methylated during early development. These repressive marks are maintained by DNA methyltransferases (*i.e.*, DNA methyltransferase 1, DNMT1) and allow negative regulation (suppression of LINE-1 expression) by the methyl-CpG-binding protein 2 (MeCP2) [95–97]. LINE-1 repression also involves histone modifications. For instance, nucleosomal and remodeling deacetylase (NuRD) multiprotein complexes form on LINE-1 promoters [98,99], which also possess binding sites for repressive transcription factors like Rb (retinoblastoma) or E2F that can recruit histone deacetylases (HDAC1, HDAC2). Kruppel-associated box (KRAB)-associated protein 1 (KAP1), a scaffolding protein, plays a central role in silencing LINE-1 elements [100]. KAP1 is recruited by KRAB-containing zinc finger proteins, a large family of transcription factors, upon binding to LINE-1 promoters. KAP1 then recruits SET domain bifurcated histone lysine methyltransferase 1 (SETDB1), a histone methyltransferase (HMT) that deposits H3K9me3 marks, as well as HDACs, NuRD complex proteins, and DNA methyltransferases (DNMTs). Similarly, the human silencing hub (HUSH) complex deposits H3K9me3 marks to repress young retrotransposons, including LINE-1 [101]. In addition, the sirtuin 6 (SIRT6) also participates in LINE-1 repression by ribosylating KAP1 [102]. This modification facilitates the interaction of KAP1 with its partners, particularly HP1 α (heterochromatin binding protein 1 α) that contributes to transcriptional repression through heterochromatinization of LINE-1 promoters. H3K9me3 is an important repressive chromatin mark, which contributes to LINE-1 silencing. H1 linker histones also silence repetitive elements by promoting both histone H3K9 methylation and chromatin compaction [103]. Polycomb repressive complex 2 (PRC2) also participates in repressing young LINE-1 elements and other TEs through deposition of histone H3 lysine 27 trimethylation (H3K27me3) marks [94,104–106]. In addition, DNMT1 has been recently shown to recognize histone H4 lysine 20 trimethylation (H4K20me3) marks in heterochromatin to reinforce LINE-1 methylation [107]. Human TRIM5 α (tripartite motif-containing protein 5 α) also senses and restricts LINE-1 elements [108]. In the germline, the small RNA-based P-Element induced wimpy testis (PIWI)-PIWI interacting RNA (piRNA) system silences TEs at the transcriptional level by promoting the recruitment of DNMTs and HMTs to TEs promoters, as well as at the post-transcriptional level [109]. Small interfering RNAs (siRNAs) resulting from bidirectional transcription of LINE-1 5'UTR [110] and microRNAs are involved in the degradation of LINE-1 mRNA in somatic cells; for

example, the microRNA mir-128 was shown to bind to LINE-1 mRNA and promote its degradation [111]. LINE-1 activity is also restricted at the post-transcriptional level by proteins such as APOBEC (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like) cytidine deaminases or TREX1 (the three prime repair exonuclease 1) [112,113]. Several host factors binding to the ORF1p protein were recently identified, which control LINE-1 retrotransposition at the post-transcriptional level [114–116]. Despite these multiple layers of repressive mechanisms, LINE-1 repression seems to decline with age (Fig. 2B). Expression of TEs, generally low in somatic tissues, increases with age in several tissues, including the brain [117–119]. The derepression of LINE-1 could thus contribute to the loss of genome integrity that characterizes aging [120].

In this context, it is interesting to recall the ‘transposon theory of aging’, which hypothesizes that epigenetically silenced TEs become reactivated as cellular defense and surveillance mechanisms break down with age [121,122]. It was indeed reported in drosophila that loss of heterochromatin with aging leads to unsilencing of heterochromatin repressed genes, including TEs [121]. Overexpression of proteins involved in heterochromatin maintenance was shown to stabilize chromatin, mitigate the age-related derepression of TEs, and increase healthy lifespan. Healthy aging was also promoted by degrading TE mRNAs or by blocking the reverse transcriptase activity of TEs. In contrast, inhibition of TE mRNA degradation following argonaute RISC (RNA-induced silencing complex) catalytic component 2 (Ago2) mutation led to a shortened lifespan [121]. Another striking example of the failure of TE repressive mechanisms with aging is provided with SIRT6 (sirtuin 6). As mentioned above, SIRT6 is an important LINE-1 repressor, but it also promotes longevity through different pathways, that is, promoting DNA repair, suppressing inflammation, and tumorigenesis. As DNA damage increases with age, SIRT6 accumulates at DNA strand breaks to coordinate DNA repair. This leads to a depletion of SIRT6 from LINE1 promoters, which results in their derepression [102]. Altogether, these results suggest that unsilencing of TEs resulting from heterochromatin loss could be an important contributor to aging.

The fact that activation of TEs during normal brain aging can be linked to functional neuronal decline was first shown in drosophila [117]. Bearing in mind that aging is the major risk factor for NDs, several groups have started to explore the role of TEs in the pathogenesis of NDs. Although previously seen as sleeping dogs in the genome, the reawakening of TEs is now

beginning to be documented in the context of NDs and provides a previously unrecognized link between aging, TEs, and neurodegeneration.

Reawakening of TEs in neurodegeneration

Heterochromatin decondensation and TE derepression have now been documented in many models of NDs. Mutant tau (R406W) was shown to induce heterochromatin loss and neurodegeneration in a drosophila model of tauopathy [74]. Recently, an increase in TE transcripts has also been observed in these flies [123,124]. Pathogenic tau seems to accelerate the age-associated activation of TEs in the mouse central nervous system [125]. Dysregulated expression of TEs was also reported in the post-mortem brain tissues of patients with AD and progressive supranuclear palsy (another tauopathy) [126]. Hence, this pathologic characteristic might be conserved in human tauopathies. The fact that heterochromatin loss and derepression of TEs could be linked to neurodegeneration is further supported by the AD-like phenotype of mice lacking *Bmi1* (*BMI1* Proto-Oncogene, Polycomb Ring Finger), a protein involved in chromatin compaction. Indeed, in addition to the heterochromatin loss induced by *Bmi1* haplo-deficiency, these mice develop cognitive deficits with age and present neurodegenerative features similar to AD in addition to a derepression of repetitive elements [127]. Interestingly, *Bmi1* levels were also decreased in the brain of AD patients [128].

In the context of PD, epigenetic alterations reflecting heterochromatin loss and increased LINE-1 expression were also observed in dopaminergic neurons subjected to oxidative stress and in the *En1*^{+/-} mouse model of PD [129]. Furthermore, global disruption of the DNA methylation landscape, induced by overexpression of *Gadd45b* (growth arrest and DNA damage-inducible beta, a protein involved in the brain in active DNA demethylation in the brain), was sufficient to induce chromatin disorganization, altered expression of key genes, and loss of dopaminergic neurons of the SNpc [130]. These alterations were accompanied by enhanced sensitivity to oxidative stress, extensive DNA damage, and increased LINE-1 transcripts and Orf1p protein levels, all preceding neurodegeneration. Derepression of LINE-1 and other TEs remains to be examined in PD patients.

The reawakening of TEs has also been reported in ALS and FTD [131]. These neurodegenerative diseases are characterized by cytoplasmic aggregates, which result in a loss of nuclear TDP-43 [132]. The nuclear RNA- and DNA-binding protein TDP-43 has been

shown to bind to LINE-1 DNA and TE transcripts [131,133,134]. Indeed, TDP-43 directly binds to TE mRNAs, and loss of TDP-43 results in overexpression of those particular LINE-1 targets and other TEs [134]. A good correspondence was found between the genomic TDP-43 targets and the specific mRNAs that are upregulated in ALS patients with TDP-43 pathology. These observations suggest that this protein either silences or regulates TE expression in the nucleus. A recent study further showed that neuronal nuclei lacking TDP-43, isolated from ALS patients, display increased chromatin accessibility around LINE-1 elements, indicating that TDP-43 is implicated in the silencing of TEs [133]. LINE-1 DNA copy numbers were also increased in TDP-43 negative nuclei [133], consistent with previous reports of increased reverse transcriptase activity in ALS [135,136]. This suggests that LINE-1 retrotransposition events might take place in ALS, but this still needs to be established [137]; this aspect is further discussed below. However, quantitative PCR (qPCR) measures of LINE-1 DNA must be taken with caution since they may also reflect aberrant or abortive reverse transcription events rather than retrotransposition [138–140]. Fly models of human TDP-43 also display impaired siRNA-mediated silencing and derepression of TEs, including LINE-1 and ERVs [141]. Derepression of HERV-K, a human ERV encoding the gag, pol, and env proteins, has also been documented in ALS, and derepression of the highly active mouse ERV IAP (intracisternal A-type particles) and production of IAP-encoded gag protein were reported in AD mouse models [125,142]. The role of ERVs in neurological disorders has been discussed in more depth in a recent review [143].

Altogether these studies support a pathogenic mechanism common to several NDs where epigenetic alteration and chromatin destructure could lead to the derepression of normally silenced TEs. However, other TE repressive cellular functions, such as impaired autophagy or mitochondrial dysfunction, are impaired in NDs and might contribute to TE activation. Autophagy has been shown to support genomic stability by degrading RTE RNA [144]. Impaired autophagy might thus lead to the accumulation of LINE-1 transcripts and eventually proteins. Mitochondrial dysfunction, a prominent feature of several NDs, might also trigger TE activity. A recent study using a reporter system revealed that mitochondrial stress increases LINE-1 retrotransposition in cultured cells [145]. In addition, ORF1p binds to several mitochondrial genome-encoded RNAs, and these RNAs are presumably released from dysfunctional mitochondria [146].

Through various downstream events following TE derepression that are not dependent on retrotransposition *per se*, the activation of TEs could contribute to, maintain, amplify, or even initiate neurodegeneration (Fig. 1). Chromatin destructurement might be a general hallmark of NDs and other neurological disorders. Expression of repetitive elements, including TEs, increased LINE-1 DNA copy numbers, and the loss of repressive chromatin marks on such sequences have been documented in several neurological pathologies, from NDs to psychiatric disorders [96,123,124,127,129,131,133,142,147–160] as summarized in Table 1. The reawakening of TEs might thus well be a common feature in neurodegeneration as well as other neurological disorders [155,161].

TEs as potential pathogenic drivers

Although the molecular mechanisms through which TEs may contribute to the neurodegenerative process are not fully dissected, a scenario emerges whereby TEs might drive neurodegeneration through several

different pathways or a combination thereof. Which pathway predominates might additionally be dependent on cell type, brain region, and the TE-activating trigger.

TEs and genomic instability

As mentioned above, the accumulation of DNA strand breaks was reported in several models of NDs and diseased brain tissues. In addition to many other known sources (*e.g.*, oxidative stress) that cause DNA damage, the reawakening of TEs in NDs could be an additional source of DNA strand breaks compromising genome integrity (Fig. 2B) [162], and thereby contributing to neuronal death. Overexpression of LINE-1 ORF2p in human cells induces numerous DNA strand breaks [163]. Whether LINE-1 activation leads to DNA strand breaks in the context of NDs was explored in the *En1^{+/-}* mouse model of PD [129]. Acute oxidative stress, as expected, led to DNA damage in mouse dopaminergic neurons but also increased LINE-1 expression. Interestingly, the increase in

Table 1. Increased expression of TEs and other repetitive DNA-derived transcripts in neurodegenerative and neurological disorders.

Disease	TEs/ repetitive family	Observation ^{a,b}	References
Alzheimer's disease (AD)/tauopathies	LINE-1 HERVs SINEs Satellite DNA	Increased TEs transcript levels. Increased satellite DNA transcripts (mouse model). Loss of heterochromatin and presence of DNA damage response at satellite sequences	[123,124,127]
Parkinson disease (PD)	LINE-1	Increased LINE-1 transcript levels (mouse model)	[129]
Amyotrophic lateral sclerosis (ALS)–frontotemporal dementia (FTD)	LINE-1 HERV-K LTRs SINEs	Increased TE transcript levels. Chromatin decondensation around LINE-1 sequences. Increased LINE-1 copy number	[131,133,142,147,148]
Multiple sclerosis (MS)	HERVs	Increased transcript levels	[149]
Fragile X-associated tremor/ataxia syndrome (FXTAS)	LTRs	Increased transcript levels (fly model)	[150]
Ataxia telangiectasia (AT)	LINE-1	Increased LINE-1 copy number	[151,152]
Macular degeneration	Alu	Increased transcript levels	[153]
Rett syndrome (RTT)	LINE-1	Increased LINE-1 copy number	[96]
Sporadic Creutzfeldt–Jakob disease	HERVs	Increased transcript levels in CSF	[154]
Aicardi-Goutières syndrome (AGS)	LINE-1	Increased transcript levels. Increased LINE-1 copy number. Accumulation of cytosolic RNA/DNA (mouse model)	[155]
Autism spectrum disorder (ASD)	LINE-1 HERVs Alu	Loss of repressive marks on TEs. Increased TEs and Alu transcript levels (HERVs in PBMCs). Increased LINE-1 copy number	[152,156,157]
Bipolar Disorder (BD)	HERVs	Increased transcript levels	[158]
Schizophrenia (SCZ)	LINE-1 HERVs	Increased TE transcript levels. Increased LINE-1 Copy number (insertion in synapse and SCZ-related genes)	[158–160]

^aUnless stated otherwise, the observations were made in the post-mortem brain tissues of patients.; ^bThe analysis of LINE-1 DNA copy number by qPCR must be taken with caution as discussed in the text. CSF, cerebrospinal fluid; PBMCs, peripheral blood mononuclear cells.

LINE-1 transcripts preceded the occurrence of DNA strand breaks, suggesting that LINE-1 activity could contribute to oxidative stress-induced DNA damage. This was further supported by the fact that anti-LINE-1 strategies such as siRNA targeted against ORF2, Piwi1 overexpression, or a reverse transcriptase inhibitor (stavudine) all reduced DNA breaks induced by oxidative stress. Overexpression of LINE-1 in embryonic midbrain neuronal cultures (following transfection) increased DNA damage, which was mitigated by anti-LINE-1 strategies. Increased DNA damage following the unsilencing of TEs has also been reported in the *Bmi1* knockout mouse model of AD [127].

Although LINE-1 retrotransposition has been reported in certain neurological disorders such as schizophrenia [159,160], the question as to whether retrotransposition events can take place in postmitotic neurons in the adult is still a matter of debate. *De novo* LINE-1 insertions were initially thought to occur only in the germline. However, a growing body of evidence supports retrotransposition of LINE-1 in the healthy brain, at least in neuronal progenitor cells (NPCs) and during adult neurogenesis [151,164,165]. These somatic insertions seem to be rather specific to brain tissue. Compared to the germline, these insertions are mainly located in genes associated with neurogenesis and synaptic functions [164], a stochastic way to achieve neuronal mosaicism [165], although the frequency at which retrotransposition occurs is still debated and technical issues are not entirely resolved [140]. From a pathological point of view, abnormal expression of TEs and/or LINE-1 retrotransposition in neuronal progenitors during brain development might be at the origin of certain neurological disorders appearing in the adult age [12]. Interestingly, LINE-1 retrotransposition was recently demonstrated *in vitro* in nondividing mature neurons using a LINE-1 retrotransposition assay, suggesting that retrotransposition might also take place in postmitotic neurons *in vivo* [166]. Whether new insertions occur in mature neurons in the adult brain and contribute to the pathogenesis of NDs needs to be further investigated.

TEs and aberrant gene expression

Another way in which TEs could be pathogenic drivers is by contributing to the aberrant gene expression patterns observed in NDs [167,168]. It is now well documented that TEs can serve as regulatory elements during development [7,169,170]. The presence or absence of epigenetic marks on TE sequences can impact host gene transcription. TEs are thought to be

heavily repressed in adulthood. However, several genome-wide studies mapping transcriptional activities or binding of transcription factors suggest that TE repression might not be drastic but rather dynamic [171], allowing TEs to participate in gene regulation [172]. Indeed, whether full-length and actively transcribed or fossilized and inactive, these sequences contain promoters, binding sites for transcription factors, and cryptic splice sites [173–175]. Some TEs might have been co-opted by the cell and have become part of regulatory networks throughout evolution, while others may have remained tightly silenced by repressive epigenetic marks. For instance, using a CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and guide RNA (gRNA) multiplexing method, it has been established in human embryonic cells that transcriptional activation or silencing of LTR-5Hs elements (isolated promoters from a young human HERV-K family) was correlated to the up- or downregulation of hundreds of human genes, reinforcing the idea that HERVs can act as early embryonic enhancers [176]. Epigenetic modifier drugs (DNMT and HDAC inhibitors) induce transcription from LTRs and lead to a high number of chimeric RNAs [177]. It was recently shown that primate-specific KRAB zinc finger proteins and their target retrotransposons control gene expression in human neurons [178]. Activation of LINE-1 elements was also shown in human neuronal progenitors following global DNA demethylation [12]. The loss or alteration of repressive marks during aging or in NDs could allow TE sequences to alter the expression of hosting or neighboring genes [179]. For instance, intronic LINE-1 can modify the splicing of their host gene through a mechanism called exonization, leading to the presence of the LINE-1 as an additional exon in the gene transcript [174,180]. Alterations in gene splicing could disrupt gene expression by changing the reading frame, introducing premature stop codons, or decreasing transcript stability. Several RNA binding proteins which repress splicing were found to bind young LINE-1 sequences present in introns of pre-mRNAs to prevent alternative splicing and exonization of LINE-1-derived sequences by insulating numerous splice sites contained in active LINE-1 retrotransposons [174]. The polyadenylation signal in the 3'UTR of LINE-1 could alter the elongation of host gene transcription, resulting in fewer normal or shortened transcripts, leading to truncated proteins or even loss of proteins. Binding of transcription factors to promoters, such as LTRs or the 5'UTR of LINE-1, could modulate transcription of neighboring genes in an enhancer-like fashion. TE promoters could also serve as alternative promoters yielding

chimeric transcripts due to the sense and antisense promoters present in the 5'UTR of LINE-1 initiating bidirectional transcription [179]. It was recently shown that G-quadruplexes originating from evolutionarily conserved LINE-1 elements interfere with neuronal gene expression in AD [181]. Some of these mechanisms through which TEs can alter host gene expression are illustrated in Fig. 3.

Even though TE repression might not be as rigid as previously thought, repressive marks of heterochromatin present on these elements could spread over short distances, thus participating in local chromatin organization. Loss of these marks could derepress genes (in the vicinity), with potentially deleterious consequences, when expressed. As mentioned above, gene expression profiles from the brain of AD patients resemble that of fetal brains, which includes the re-expression of cell-cycle genes and might partly be due to TE dysregulation. The expression of cell-cycle genes indicates a loss of postmitotic neuronal identity and results in an attempt to re-enter into the cell cycle, a process which can lead to neurodegeneration [74,182,183]. Interestingly, mounting evidence suggests the direct effects of TE transcripts in the regulation of gene expression. LINE-1 transcripts, for instance, bind H2B histones and participate in chromatin decompaction [184], and m6A modification of LINE-1 transcripts might enhance their association with DNA to stabilize heterochromatin [185]. It was recently suggested that m6A RNA modification, which enhances LINE-1 mRNA translation and increases retrotransposition, might have been a driving force for the successful amplification of LINE-1 elements during evolution [186]. As mentioned above, it is conceivable that LINE-1 retrotransposition events could actively take place in the aging brain following neuronal de-

differentiation. To what extent epigenetic modifications and/or expression of TEs contribute to transcriptional dysregulation in NDs remains to be dissected.

Finally, recent studies support the idea that TEs could be involved in higher-order 3D chromatin organization [187–189], suggesting that alteration of their epigenetic state might perturb chromatin structuration and affect gene expression globally. The 3D organization of chromatin is essential for the formation of complex regulatory networks, allowing long-range interactions between enhancers and promoters [190]. TEs are suspected to have contributed to the emergence of species-specific loops in mammals and genome regulation by harboring binding sites for regulatory factors, like CCCTC-binding factor (CTCF). TEs constitute up to 15% of CTCF-binding sites in the genome [191], implicating TEs as topologically associating domain (TAD) organizers. The identification of CTCF as a factor binding to the 5' and 3'UTRs of LINE-1 further suggests their possible involvement in 3D chromatin structuration [124]. It was reported that LINE-1 transcription *per se* during early mouse development could increase global chromatin accessibility [192]. More recently, ERVs have also been shown to demarcate TAD boundaries in chromosomes [193]. Since the binding of CTCF to DNA is methylation-dependent, it is conceivable that DNA methylation changes during aging and in NDs might induce not only derepression of TEs but also a profound perturbation of the 3D organization of chromatin.

TEs and neuroinflammation

Neuroinflammation is a common feature of brain aging and NDs [194], but the origins have so far

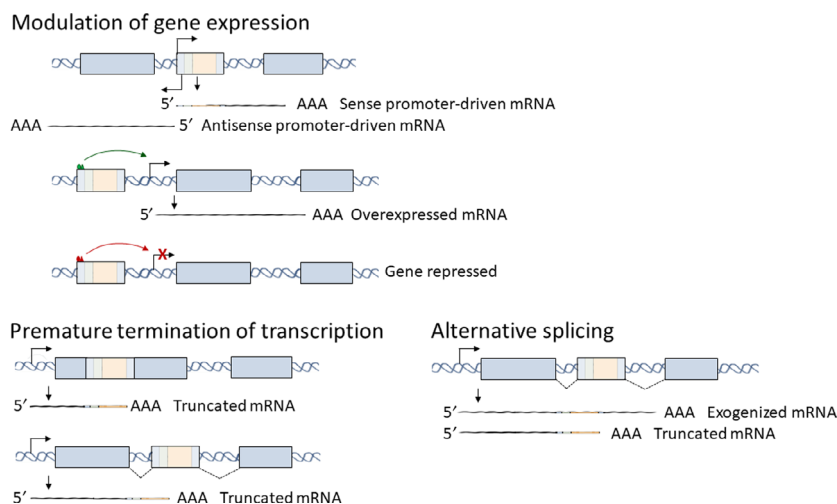


Fig. 3. TE contribution to altered host gene expression. Some striking mechanisms through which TEs could affect host gene expression are depicted. Modulation of host gene expression could occur through bidirectional transcription from intronic TEs and the extent of epigenetic modifications of TEs. Premature termination of transcription and alternative splicing could also affect host gene expression. See text for further details.

remained elusive. In recent years, mitochondria have emerged as an important player in activating innate immune response and neuroinflammation. The release of mitochondrial constituents (*i.e.*, mtDNA fragments or mitochondrial RNAs) in the cytoplasm, following mitochondrial stress, activates the innate immune system through the cytosolic DNA sensing cGAS (cyclic GMP-AMP synthase)-STING (stimulator of interferon response CGAMP interactor 1) or Toll-like receptors (TLRs) pathways [195,196]. Interestingly, the PD-related genes Parkin and PINK1 seem to mitigate STING-induced inflammation [196]. It should be recalled that the presence of cytoplasmic double-stranded RNA (dsRNA) is a hallmark of viral infections [197]. In mammalian cells, the detection of viral nucleic acids activates a signaling pathway that culminates in the expression of type I IFN (IFN1) and activation of proinflammatory cytokines. TE activity is a potential source of unusual, virus-resembling intracellular nucleic acid conformations (*i.e.*, RNA stem loops, dsRNA, ssDNA, or DNA:RNA hybrids) detected by the innate immune surveillance system and triggering an antiviral IFN1 response. Although this activation is a critical antiviral response, uncontrolled production of interferons (IFNs) could contribute to inflammatory or autoimmune diseases. As discussed above, repetitive element transcripts have been associated with toxicity and increased repetitive element expression has been observed in several NDs. For instance, transcripts from multiple classes and subclasses of repetitive elements (*i.e.*, LINE-1, ERVs, DNA transposons, simple repeats, *etc.*) were significantly increased in the frontal cortex of C9orf72 ALS patients [148]. Alu RNAs are known to be the most important source of dsRNA-mediated IFN response [198,199]. It was reported that cGAS detection of TE transcripts drives noncanonical-inflammasome

activation in age-related macular degeneration [200]. Interestingly, the nuclear RNA helicase DHX9 (DEXH-Box Helicase 9) neutralizes RNA processing defects caused by Alu invasion by resolving long dsRNAs, allowing proper RNA processing and nuclear export [201]. Moreover, constitutive activation of MDA5 (melanoma differentiation-associated protein 5, a cytosolic innate immune receptor that recognizes long dsRNA) in Aicardi Goutières syndrome (AGS) results from the loss of tolerance to cellular dsRNAs formed by Alu retroelements [202].

Nucleases such as TREX1 or RNase H2 also prevent the accumulation of cytoplasmic nucleic acids derived from TEs. Mutations resulting in loss of TREX1 activity lead to autoimmune or inflammatory diseases like AGS or some familial forms of lupus. A recent AGS study provided the proof of principle that LINE-1 cDNA accumulation could be a source of neuroinflammation [203]. TREX1 deficiency led to the accumulation of extranuclear single-stranded DNA (ssDNA) in the cytoplasm of both neurons and glial cells. This was prevented by short-hairpin RNA (shRNA) targeted against LINE-1 mRNA, indicating that LINE-1 activity contributes to the accumulation of cytoplasmic nucleic acids. The accumulation of LINE-1-derived cDNA in the cytosol leads to the neurotoxic secretion of IFNs. The phenotype resulting from TREX-1 deficiency was rescued by using reverse transcriptase inhibitors or blockers of neuronal IFN receptors. Thus, increased LINE-1 reverse transcriptase activity can mediate neuroinflammation and neurotoxicity through the IFN pathway (Fig. 4). Furthermore, two other studies recently supported the capacity of LINE-1 activation to trigger an inflammatory phenotype. LINE-1 derepression resulting from SIRT6 deficiency was identified as a source of inflammation in different tissues, including the brain. The

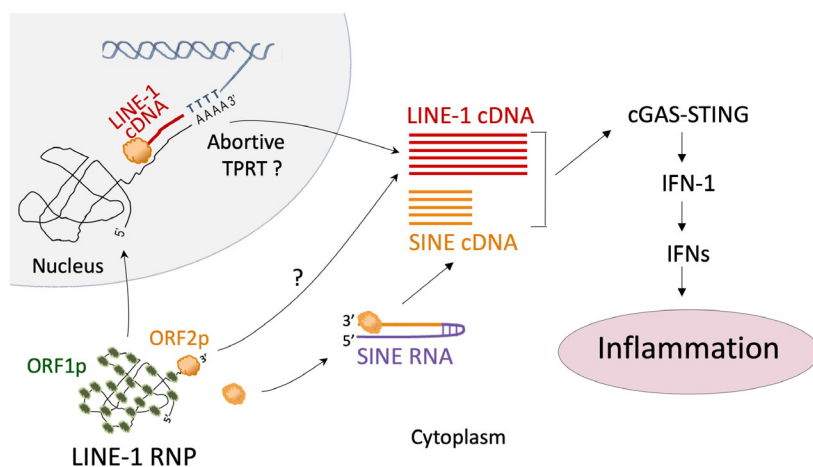


Fig. 4. TE activation as a potential source of neuroinflammation. Increased LINE-1 reverse transcriptase activity can lead to the accumulation of cytosolic cDNA, which could result in activation of IFN1 response, neuroinflammation, and neurotoxicity via the cGASSTING pathway. See text for details.

SIRT6 knockout mouse is a progeroid model of accelerated aging and displays growth retardation, elevated LINE-1 activity, and shortened lifespan. SIRT6 deficiency led to the accumulation of cytoplasmic LINE-1 cDNA in cells and tissues in this model, which triggered a strong inflammatory response by activating the IFN1 response through the cGAS-STING pathway [203,204]. Reverse transcriptase inhibitors improved the lifespan of these mice and mitigated the IFN response. LINE-1 knockdown using siRNAs reduced the IFN response as well as DNA damage in SIRT6-deficient cells. Likewise, LINE-1 transcripts, cytoplasmic cDNA, and IFNs were all elevated in aged wild-type mice, supporting the hypothesis that LINE-1 derepression is involved in sterile inflammation that occurs in aging (known as 'inflammaging'). The HUSH complex was also reported to be a gatekeeper of IFN1 through epigenetic regulation of LINE-1 [205]. As repressive mechanisms decline with age, LINE-1 derepression and increased reverse transcriptase activity of ORF2p in proliferating cells could activate the IFN1 response and lead to senescence-associated secretory phenotype (SASP) [206]. Neurons (as nondividing cells) can also present a senescent-like phenotype, and various senescent markers have been found in glial cells of AD and PD patients [207]. Neuroinflammation has also been observed in the *En1*^{+/-} mouse model of PD [37], which shows elevated levels of LINE-1 expression. However, an effect on cytosolic cDNA accumulation in dopaminergic neurons has not yet been tested in this model. A recent study showed that LINE-1 reverse transcriptase could also generate cDNA within the cytoplasm using SINE RNA as a template following self-priming [208], bringing closer to the possibility of LINE-1 RNA serving as a template to generate LINE-1 cDNA in the cytoplasm (Fig. 4). Finally, the production and aggregation of proteins encoded by ERVs activated during development were found to be another source of neuroinflammation appearing in the adult age. More importantly, this study showed for the first time that TEs expression alone in the absence of other alterations or pathology can be sufficient to induce microglial activation, a characteristic feature seen in most NDs [209]. Further studies are needed to examine whether and to what extent reawakening of TEs and LINE-1 activity contribute to neuroinflammation in NDs.

TEs and mitochondria

Emerging evidence suggests that mitochondrial integrity could also be impaired by TE activity. In the context of age-related macular degeneration, Alu elements

could be involved in mitochondrial dysfunction. Alu RNA can provoke mtDNA release into the cytosol by promoting the opening of mitochondrial permeability transition pore [200]. Moreover, in the absence of the endoribonuclease DICER1, the accumulation of Alu RNA leads to mitochondrial ROS production [210,211]. These two phenomena activate the NLRP3 (NLR Family Pyrin Domain Containing 3)-dependent inflammasome pathways. It is also noteworthy that Alu sequences appear to be preferentially located in introns of genes implicated in mitochondrial pathways, and epigenetic dysregulation of Alu elements could ultimately disrupt mitochondrial homeostasis within the central nervous system and contribute to the development of NDs [212]. LINE-1 ORF1p and ORF2p proteins interact with mitochondrial proteins [114]. ORF1p binds to ERAL1 (Era Like 12S mitochondrial rRNA chaperone 1), a mitochondrial GTPase, whereas ORF2p binds to TIMM13 (translocase of inner mitochondrial membrane 13) and TOMM40 (translocase of outer mitochondrial membrane 40), but the role of these interactions remains unknown [115,116]. All these observations point to important connections that might exist between the activity of TEs, mitochondrial dysfunction, and other pathological hallmarks of NDs (Fig. 1).

TEs as new therapeutic targets

It emerges from all the studies discussed above that inhibiting TE expression and/or blocking their activity could constitute a novel therapeutic approach in age-related pathologies and, more specifically, in NDs. In several models, targeted degradation of TE transcripts, delivery of transcriptional repressors, or use of reverse transcriptase inhibitors conferred neuroprotection and anti-inflammatory properties, extended healthy lifespan, and rescued pathological phenotypes in general. As mentioned above, anti-LINE-1 strategies prevent the loss of dopaminergic neurons in the *En1*^{+/-} mouse model of PD. It is noteworthy that the Engrailed protein itself is a therapeutic protein and protects dopaminergic neurons by directly repressing LINE-1 elements [129]. It would be interesting to test the therapeutic potential of strategies that block the expression or activity of TEs in NDs. Indeed, several ongoing clinical trials are currently testing the safety and tolerability of reverse transcriptase inhibitors in AD (<https://clinicaltrials.gov/ct2/show/NCT04500847>; <https://clinicaltrials.gov/ct2/show/results/NCT04552795>), ALS [213], and AGS (<https://clinicaltrials.gov/ct2/show/NCT02363452>). These approaches are based on the use of reverse transcriptase inhibitors either alone or in

combination with anti-HERV integrase inhibitors [143] to target different TEs. Another therapeutic target could be chromatin itself since chromatin relaxation occurs in aging and several NDs. Preventing the loss of repressive marks might avoid the expression of TEs and associated deleterious pathological effects. More importantly, epigenetic modifications of TEs might alter the entire spatial organization of chromatin. Maintaining a juvenile and healthy chromatin state could also prevent genome-wide alterations of the transcriptome observed with aging and neurodegeneration [214]. One way to prevent chromatin loss could be to overexpress proteins involved in heterochromatin maintenance. Indeed, overexpression of genes known to affect heterochromatin structure like Sirt2 (sirtuin 2), the orthologue of Sirt1 (sirtuin 1; a deacetylase important for gene silencing), Su(var)3-9 (an H3K9 methyltransferase), or DICER 2, which recruits Su(var)3-9 at TE sites, led to increased lifespan in drosophila, whereas shRNA against those genes accelerated aging and shortened lifespan [121]. Alternatively, heterochromatin-promoting drugs such as remodelin [215] or methotrexate [63] shown to restore a juvenile chromatin state in models of accelerating aging or

autoimmune diseases could also have a therapeutic potential in NDs.

Conclusions and perspectives

In conclusion, all of the studies discussed in this review support the concept that TEs represent a key pathogenic culprit linking brain aging and neurodegeneration. They also unveil a new unifying pathogenic axis for NDs in which age-induced chromatin deconstruction could lead to TE activation and its resulting deleterious effects, cumulating in neurodegeneration as illustrated in Fig. 5. Activation of TEs and a number of pathological features are common to various NDs, thus suggesting that they might be interconnected. As discussed above, this new axis also suggests important connections between mitochondrial activity and TEs. These new findings should revive interest in further exploring the role of ‘the dark side’ of DNA in neurodegeneration and other human diseases. It is tempting to speculate that TE activation might represent the tenth hallmark of aging and neurodegeneration. It is then not surprising that TEs are also being regarded as appealing targets for novel therapeutic interventions

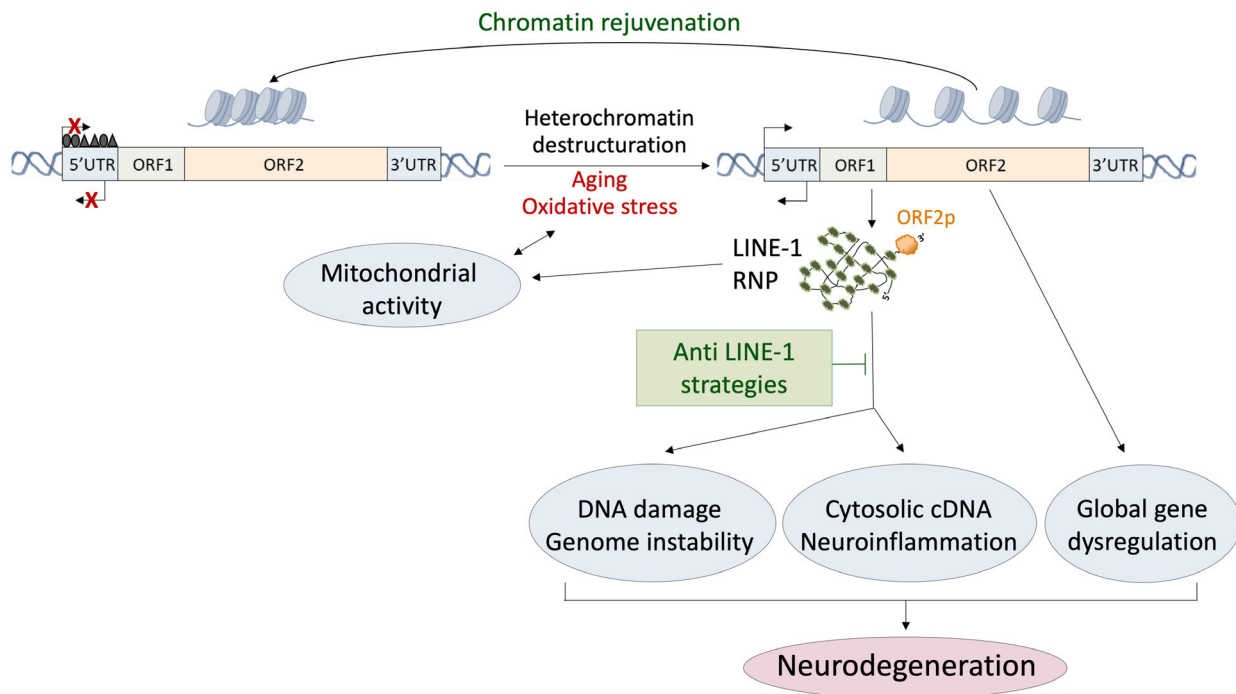


Fig. 5. A new emerging pathogenic axis for NDs. Chromatin relaxation with oxidative stress and aging can result in LINE-1 activation leading to several pathological consequences common to many NDs, namely DNA strand breaks and genomic instability, neuroinflammation, and gene dysregulation. A possible interplay between mitochondria and TEs is also depicted. Inhibition of TEs activity or chromatin rejuvenation represents potential targets for neuroprotection.

for aging and NDs. In this regard, it will be particularly interesting to evaluate the therapeutic efficacy of reverse transcriptase inhibitors for neuroprotection in NDs.

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