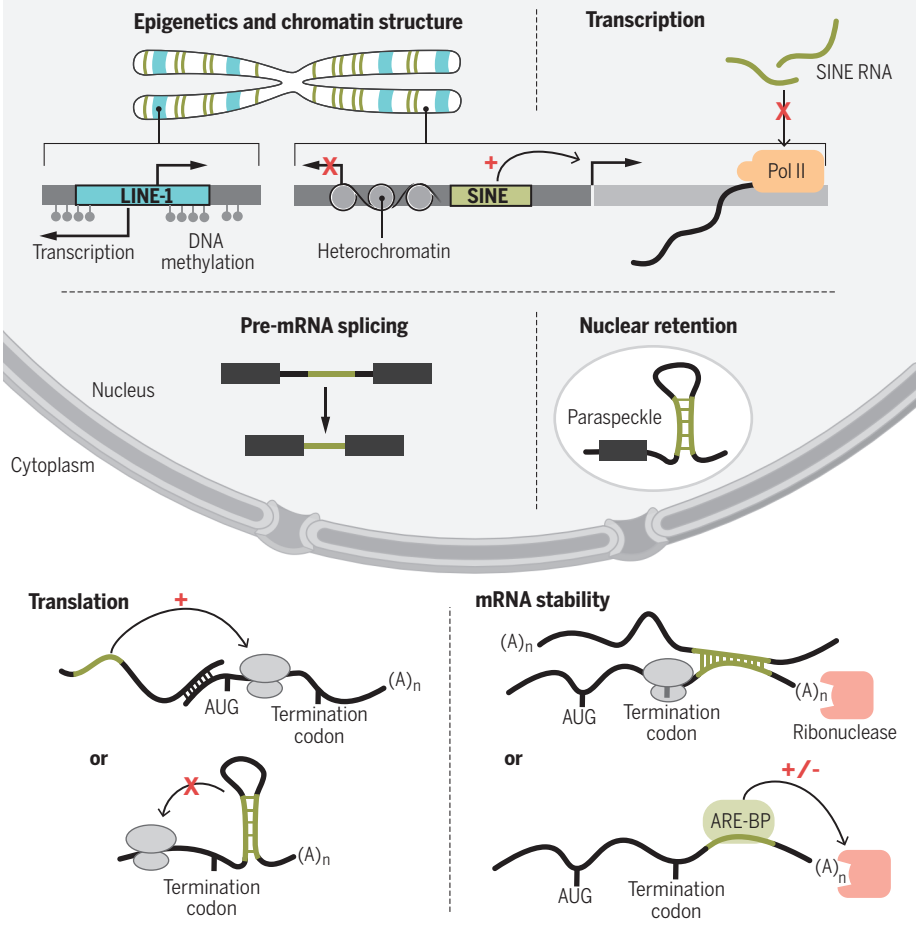
REVIEW SUMMARY

GENE REGULATION

Retrotransposons as regulators of gene expression

Reyad A. Elbarbary,* Bronwyn A. Lucas,* Lynne E. Maquat†

BACKGROUND: Genomes are subject to two types of changes: changes to the DNA sequence, and changes that are epigenetic in nature. Changes to the DNA sequence can result from errors made during DNA replication and/or repair, or from the insertion of mobile DNA. Mobile DNAs, also called transposable elements (TEs), have the potential to provide regulatory and/or protein-coding sequences at a new integration site. Depending on its nucleotide sequence and genomic insertion site, an individual TE can disrupt gene expression, directly or indirectly create an advantageous modification to gene expression, or be of no immediate consequence. Changes can be genetic, epigenetic, or both. In this way, TEs are molecular parasites and evolutionary drivers, each role originating from the ability to insert into, spread through, and restructure genomes. This review focuses on the types of TEs that transpose via RNA intermediates—retrotransposons—that are not bounded by long terminal repeats. The most abundant retrotransposons in animal genomes come in two forms: long interspersed elements (LINEs) and short interspersed elements (SINEs).



Some of the steps in the expression of mammalian genes that can be affected by cis- or trans-acting LINEs or SINEs. LINE and SINE genomic insertions can regulate gene expression by altering transcription and/or chromatin structure. When embedded in the transcripts of RNA polymerase II (Pol II)–transcribed genes, SINEs can influence nuclear pre-mRNA splicing, nuclear mRNA retention in paraspeckles, cytoplasmic mRNA stability, or cytoplasmic mRNA translation. ARE-BP, AU-rich element–binding protein.

ILLUSTRATION: K. SUTLIFF/*SCIENCE*

ADVANCES: The advent of deep genomic and transcriptomic sequencing, together with studies of individual LINE or SINE functions, has led to a greater appreciation of how the two TEs influence gene expression. Our review focuses principally on data that derive from human and mouse studies. These data demonstrate that LINEs and SINEs perform many diverse roles within cells. As DNA sequences, they can regulate gene transcription by altering chromatin structure and by functioning as enhancers or promoters. When transcribed as part of a larger transcript, they can create new transcript isoforms (by influencing alternative pre-mRNA splicing or 3′-end formation), alter mRNA localization, change mRNA stability, tune the level of mRNA translation, or encode amino acids that diversify the proteome. Further, the RNA transcripts of LINEs or SINEs may themselves function to regulate gene expression. Through their various roles, TEs influence many aspects of cellular metabolism, including the ability to divide, migrate, differentiate, and respond to stress.

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OUTLOOK: TEs continue to spread throughout our genomes in both gametes and somatic tissues, introducing new gene regulatory activities or causing disease. Although deep transcriptome sequencing has identified a myriad of SINE-containing noncoding RNAs, the functional importance of most of these transcripts remains unknown. Additionally, we need to understand the consequence of the very high degree of TE transposition in our brains. We also need to uncover the determinants that influence the effect of a specific SINE on gene expression, and, given that different organisms can contain SINEs of distinct origins, the extent to which these SINEs contribute to species-specific differences. Moreover, it will be important to determine the extent to which independently evolved SINEs have been co-opted for similar functions. ■

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REVIEW

GENE REGULATION

Retrotransposons as regulators of gene expression

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Transposable elements (TEs) are both a boon and a bane to eukaryotic organisms, depending on where they integrate into the genome and how their sequences function once integrated. We focus on two types of TEs: long interspersed elements (LINEs) and short interspersed elements (SINEs). LINEs and SINEs are retrotransposons; that is, they transpose via an RNA intermediate. We discuss how LINEs and SINEs have expanded in eukaryotic genomes and contribute to genome evolution. An emerging body of evidence indicates that LINEs and SINEs function to regulate gene expression by affecting chromatin structure, gene transcription, pre-mRNA processing, or aspects of mRNA metabolism. We also describe how adenosine-to-inosine editing influences SINE function and how ongoing retrotransposition is countered by the body's defense mechanisms.

Transposable elements (TEs) are DNA sequences that have the ability to be integrated elsewhere in a genome. With few exceptions, TEs have been identified in all eukaryotic genomes sequenced to date (*1*). There are two main classes of TEs: Retrotransposons (class I) transpose via an RNA intermediate, whereas DNA transposons (class II) transpose directly without an RNA intermediate (*2*). The three major retrotransposon orders are long terminal repeat (LTR) retrotransposons, long interspersed elements (LINEs), and short interspersed elements (SINEs). Retrotransposons propagate via a copy-and-paste amplification mechanism that has allowed them to accumulate in DNA, giving rise to the bulk of repeats in eukaryotic genomes.

Mobile LINEs are RNA polymerase II (Pol II)–transcribed autonomous retrotransposons of several thousand base pairs (bp) (*3*). In the copy step, their internal Pol II promoter generates an mRNA-like capped and polyadenylated transcript (*4*). The transcript of LINE-1 (L1), which is the only active class of autonomous retrotransposons in humans, contains two open reading frames (ORFs) that are crucial for retrotransposition: ORF1 encodes an RNA-binding protein, and ORF2 encodes a protein with reverse transcriptase (RT) and endonuclease activities (Fig. 1A) (*5*). In the subsequent paste step, these proteins recognize a specific sequence in the 3′ end of the LINE transcript that encodes them, create two staggered nicks at specific sequences in the genome and, by using the genomic sequence as a primer, reverse-transcribe the LINE RNA into cDNA that is simultaneously incorporated into the genome (Fig. 1B) (*5*, *6*). Acquisition of an additional L1 ORF 5′ to ORF1 (ORF0) was recently demonstrated in the primate lineage (*7*).

Mobile SINEs are RNA polymerase III (Pol III)–transcribed nonautonomous retrotransposons that do not encode any proteins (Fig. 1C) but retrotranspose by hijacking the RT and endonuclease activities of a partner LINE-encoded protein (Fig. 1B). In most cases, LINE-encoded proteins recognize SINE RNAs with 3′ sequences that are similar to the 3′ sequence of the LINE RNA from which these proteins were synthesized; subsequently, they generate and integrate a cDNA copy of the SINE RNA into the genome (Fig. 1, B and C) (*8*).

The lengths of SINE family members generally range from 85 to 500 bp (*9*). A SINE typically has three parts: a 5′ head, a body, and a 3′ tail. Head sequences, which harbor the internal Pol III promoter, have been used to categorize SINEs into three superfamilies according to their derivation from, and thus similarity to, cellular Pol III genes encoding tRNA (such as mouse B2 or ID elements), 7SL RNA (such as mouse B1 and human *Alu* elements), or 5*S* rRNA (SINE3) (*2*, *9*, *10*). Most LINEs and SINEs in mammalian genomes have lost their functional promoters and thus lack the ability to retrotranspose (*5*).

LINEs and SINEs constitute ~30% of the human genome sequence and show a nonrandom genomic distribution (*11*). SINEs are generally localized in gene-rich regions, whereas LINEs are enriched in intergenic regions (*12*). The relative sparsity of LINEs in genic regions likely reflects negative selection against insertion of their large sequence (several thousand bp) in or near genes. In contrast, the smaller SINEs are more apt to be tolerated, and some SINEs in genic regions have assumed regulatory roles that control gene expression. The expansion of LINEs and SINEs has drastically shaped the genomes of multicellular organisms by providing regions of similarity that act as hotspots for nonallelic homologous recombination (Fig. 1, D and E) and acting as reservoirs of potential coding, regulatory, or disruptive sequences (*13*, *14*). In addition to their own retrotransposition and that of SINEs, LINEs have supported the retrotransposition of mRNAs (*15*, *16*). The resulting "retrogenes," in the presence of their functional counterpart, are free from selective pressure and thus can accumulate mutations and acquire novel functions (*16*). Thus, retrotransposition contributes to genetic diversity within a species and among different species in many ways. Additionally, retrotransposition appears to be active in some somatic tissues, including early in development (*17*), in developing neurons (*18*, *19*), and in the adult brain (*20*), leading to mosaicism whereby different cells within an individual have different genetic sequences. Most insertion events are neutral or detrimental to the host; here, we describe instances whereby inserted LINEs and SINEs have been harnessed to regulate gene expression.

Regulation of chromatin structure and transcription

Primate LINEs and SINEs have a high GC content, making them hotspots for DNA methylation, which is used by cells to suppress transcription (*21*). The methylation of LINE- and SINE-embedded CpG islands has the potential to silence the expression of nearby genes (*22*). LINEs and SINEs can demarcate the boundary between heterochromatin and euchromatin. For example, one mouse B2 element functions as a boundary element to prevent cis-residing heterochromatin from silencing developmental expression of the five genes located in the mouse growth hormone locus (Fig. 2A) (*23*). LINEs also participate in X-chromosome inactivation (XCI) via one of two mechanisms: Transcriptionally silent L1 elements contribute to the formation of a silent nuclear compartment during XCI, whereas L1 RNAs that derive from young LINE elements (which are enriched in the X chromosome) participate in inactivating X-chromosome loci that would otherwise escape XCI (*24*).

SINEs, and Alu elements in particular (*25*), can function as transcriptional enhancers, as exemplified by two members of the ancient SINE family Amniota SINE1 (AmnSINE1), which act as enhancers for the genes encoding fibroblast growth factor 8 (Fgf8) and special AT-rich sequence–binding protein 2 (Satb2) in the developing brain (Fig. 2A) (*25*, *26*). Retrotransposons located immediately upstream of protein-coding genes may function as promoters because putative binding sites for many transcription factors have been identified in SINEs (Fig. 2A) (*27*). However, it is unclear whether the majority of SINE-embedded transcription factor binding sites act to modulate gene transcription or simply act as sinks that titrate transcription factors away from their active binding sites. LINEs and SINEs can also introduce a new transcription start site (TSS); 6 to 30% of human and mouse

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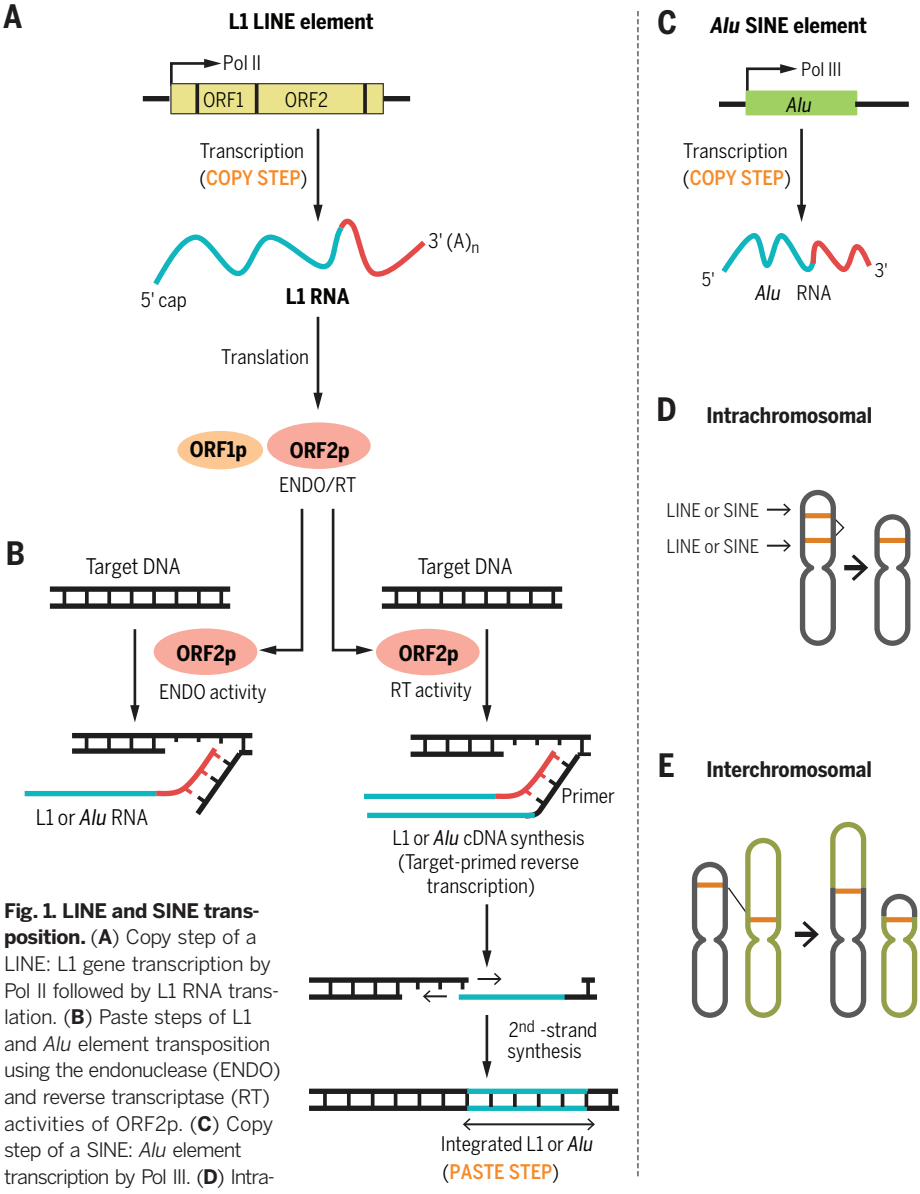

Fig. 1. LINE and SINE transposition. (**A**) Copy step of a LINE: L1 gene transcription by Pol II followed by L1 RNA translation. (**B**) Paste steps of L1 and *Alu* element transposition using the endonuclease (ENDO) and reverse transcriptase (RT) activities of ORF2p. (**C**) Copy step of a SINE: *Alu* element transcription by Pol III. (**D**) Intrachromosomal recombination between related LINEs or SINEs resulting in genomic deletion. (**E**) Interchromosomal recombination between related LINEs or SINEs resulting in genomic rearrangements.

5′-capped transcripts use repetitive sequence-associated TSSs (*27*).

The functional influences of LINEs and SINEs on transcription are mediated not only as DNA elements but also via the RNAs that they encode. SINEs normally are transcriptionally silenced in somatic tissues; however, in response to stressors such as heat shock, SINE Pol III promoters are activated and SINE RNAs are massively up-regulated. Stress-mediated up-regulation of human *Alu* and mouse B2 RNAs inhibits the transcription of most genes, excluding those up-regulated during heat shock, by binding to Pol II (Fig. 2B) (*28*, *29*).

Regulation of RNA processing

Some SINE insertions, in particular *Alu* elements, can influence gene expression by altering pre-mRNA splicing. In humans, 66% of *Alu* elements and 65% of mammalian-wide interspersed repeats (MIRs) are found in introns (*30*). In the antisense orientation, the consensus *Alu* sequence contains seven potential 5′ splice sites and 12 potential 3′ splice sites, whereas sense *Alu* elements contain three potential 5′ splice sites and one potential 3′ splice site (*31*, *32*). *Alu*-derived splice sites are usually cryptic, requiring few mutations to become functional and to promote exonization (i.e., inclusion of a intronic sequence within the resulting spliced mRNA) (Fig. 2C) (*31*). It is estimated that 5% of alternatively spliced exons in humans derive from *Alu* sequences and that most *Alu*-containing exons are alternatively spliced (*32*). Although the majority of exonized *Alu* elements form cassette exons that are included in one or more minor splice isoforms (*30*), in the human brain a substantial portion of *Alu*-containing exons reside in major splice isoforms (*33*). RNA-binding proteins are able to regulate the availability of splice signals within SINEs to associate with the splicing machinery (*34*).

When embedded within Pol II transcripts, the length of *Alu* elements (~300 bp) and their high (>70%) similarity (*14*) allow two elements that coexist in opposite orientation within the same transcript (inverted-repeat *Alu*s or IR*Alu*s) to form intramolecular imperfect duplexes of >100 bp (*35*, *36*). Recently, intronic IR*Alu*s have been shown to promote pre-mRNA "backsplicing" so as to facilitate the formation of circular noncoding RNAs (circRNAs) that may have biological functions (*37*–*39*).

The vast majority of protein-coding mRNAs, as well as many long noncoding RNAs (lncRNAs), are polyadenylated at their 3′ ends. Most polyadenylation occurs upon recognition of a polyadenylation signal (PAS) that consists of the conical AAUAAA sequence or the closely related AUUAAA sequence (*40*). Most human genes harbor more than one PAS that, when used, generate mRNA isoforms with alternative 3′ ends (Fig. 2D) (*41*). New PAS sequences are commonly created via spontaneous mutations within the A-rich tails of LINEs and SINEs (*42*–*44*). Retrotransposon-associated PASs are largely not conserved between different species, which suggests that retrotransposons have contributed to interspecies differences in transcript 3′ ends (*43*). *Alu*-derived PASs, 99% of which derive from sense *Alu* elements, are efficiently used (*43*, *44*). Some of these putative *Alu*-embedded PASs are intronic and result in shortened transcripts, presumably explaining the observed low abundance of sense *Alu* elements relative to antisense *Alu* elements in intronic regions (*44*).

When transcribed as part of mRNA 3′ untranslated regions (3′UTRs), SINEs have the potential to act in cis and/or in trans to influence mRNA turnover. The poly(T) sequence that exists in antisense *Alu* elements is the source of ~40% of identified 3′UTR AU-rich elements (AREs), which regulate mRNA half-life through the competitive binding of proteins that stabilize or destabilize the transcript (Fig. 3A) (*45*). Additionally, LINEs and SINEs can activate the function of microRNAs (miRNAs) by acting as promoters for miRNA synthesis or as miRNA-binding sites in target mRNAs (*46*, *47*) (Fig. 3B); miRNAs are ~22-nucleotide noncoding RNAs that mediate decay and/or translational repression of transcripts to which they bind.

As a consequence of their high similarity and presence in 5.7% of human mRNA 3′UTRs (*27*), *Alu* elements can also mediate intermolecular base pairing between two RNA molecules. For example, *Alu* elements in some human mRNA 3′UTRs can form base pairs with partially complementary, reverse-oriented *Alu* elements in lncRNAs (*48*) or in the 3′UTRs of other mRNAs (Fig. 3C) (*49*). The intermolecular double-stranded RNA (dsRNA) formed, if bound by the dsRNA-binding protein (dsRBP) Staufen 1 (STAU1) and/or its paralog STAU2, can result in mRNA decay in a mechanism that depends on translation (Fig. 3C) (*50*, *51*). This

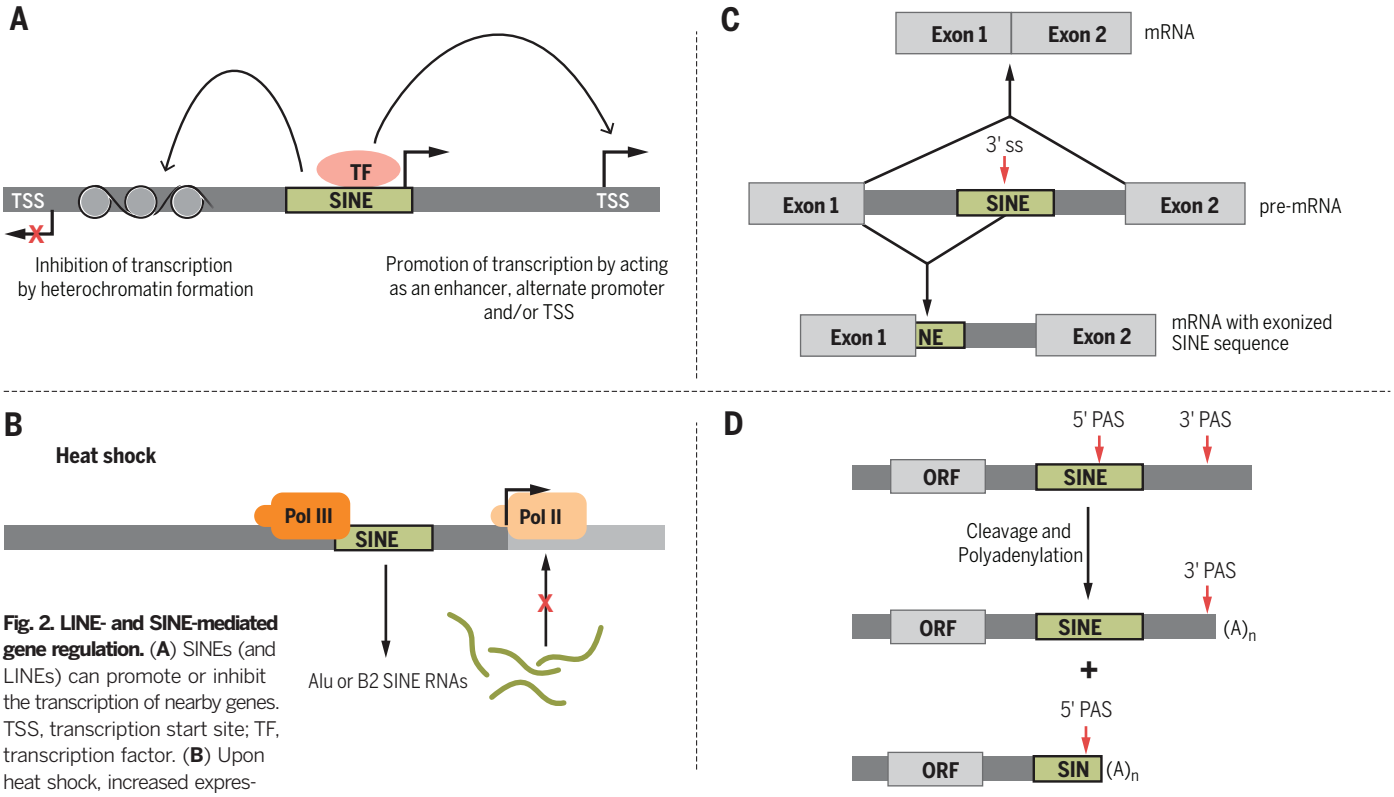

Fig. 2. LINE- and SINE-mediated gene regulation. (**A**) SINEs (and LINEs) can promote or inhibit the transcription of nearby genes. TSS, transcription start site; TF, transcription factor. (**B**) Upon heat shock, increased expression of *Alu* and B2 RNAs inhibits Pol II. (**C**) SINEs contain potential splice sites (ss) that, if used, can lead to mRNAs with intronic sequences. (**D**) SINEs (in particular, *Alu* elements) can contain a polyadenylation signal (PAS).

STAU-mediated mRNA decay (SMD) contributes to cell motility, cell invasion, and other processes (*48*, *49*, *52*). B SINEs and identifier (ID) SINEs in mouse mRNA 3′UTRs can also form duplexes with, respectively, partially complementary B and ID SINEs in lncRNAs (or, most likely, in the 3′UTRs of mRNAs) and likewise trigger SMD so as to regulate cellular processes (*53*). The presence of a 3′UTR *Alu* or B element is not always predictive of SMD (*54*). Both CUB domain–containing protein 1 (CDCP1) mRNA and BCL2-associated athanogene 5 (BAG5) mRNA have a 3′UTR *Alu* element that is predicted to bind the same lncRNA *Alu* element, but only CDCP1 mRNA is an SMD target in HeLa cells (*48*). The features that distinguish a SINE-directed SMD target remain to be determined until more is understood about transcript folding, what defines a STAU-binding site, and how other dsRNA-binding proteins compete with STAU for binding to duplexed SINEs (*48*).

Messenger RNA localization and translation

Not all mRNAs are efficiently exported from the nucleus to the cytoplasm for translation. Some nuclear-retained transcripts contain 3′UTR IR*Alus* (IR*Alus* mRNAs; Fig. 4A) (*55*–*60*) and are localized in paraspeckles (Fig. 4A), which are subnuclear bodies containing the lncRNA *NEAT1* and multiple RNA-binding proteins (*61*). Localization of IR*Alus* mRNAs can be determined by use of alternative PASs, which could exclude the 3′UTR IR*Alus* from product mRNA. STAU1 binding to the 3′UTR IR*Alus* of a subset of IR*Alus* mRNAs precludes the binding of $p54^{nrb}$ (a protein component of paraspeckles), thereby permitting their nuclear export (Fig. 4A) (*57*, *58*). Furthermore, the affinity of dsRBPs for IR*Alus* can be altered by posttranslational modifications. For example, the methylation of $p54^{nrb}$ by the coactivator-associated arginine methyltransferase 1 (CARM1) reduces the binding of $p54^{nrb}$ to the 3′UTR IR*Alus* of particular IR*Alus* mRNAs, promoting their nuclear export (Fig. 4A) (*59*, *60*). Because different mRNAs with apparently similar 3′UTR IR*Alus* manifest distinct subcellular localizations, the regulation of IR*Alus* mRNAs is substantially more complicated than depicted in current models.

In the cytoplasm, 3′UTR IR*Alus* can also repress the translation of their host mRNAs and accelerate their accumulation in stress granules (*57*, *58*, *62*–*64*). A subset of 3′UTR IR*Alus* mediate translational repression by binding and activating dsRNA-dependent protein kinase (PKR) (Fig. 4A), which is activated by autophosphorylation once dimerized on dsRNA. PKR activation results in phosphorylation of eukaryotic translation initiation factor 2α, which in turn inhibits the bulk of cellular translation (*57*, *58*, *64*). Thus, 3′UTR IR*Alus* can act as translational repressors not only in cis but also in trans. STAU1 binding to 3′UTR IR*Alus* in the cytoplasm precludes PKR binding, alleviating translational repression of STAU1-bound IR*Alus* mRNAs and, to a lesser extent, the bulk of cellular mRNAs (Fig. 4A) (*57*, *58*, *64*). During interphase, nuclear-retained IR*Alus* mRNAs are physically segregated away from cytoplasmic PKR, thereby preventing PKR activation (Fig. 4A) (*57*, *58*, *64*). However, after breakdown of the nuclear envelope during mitosis, the boundary between nuclear-retained IR*Alus* mRNAs and cytoplasmic PKR is removed, resulting in PKR activation (Fig. 4B) (*64*). Activated PKR is necessary for the regulation of mitosis because it acts as an upstream kinase for c-Jun N-terminal kinase (JNK), which controls the abundance of multiple mitotic factors (Fig. 4B) (*64*).

SINEs can also enhance mRNA translation in trans. The normally low cellular abundance of Pol III–synthesized *Alu* RNAs transiently increases under stressful conditions that include viral infection, heat shock, and the inhibition of protein synthesis (*65*). Other mammalian SINEs, such as mouse B1 and B2 elements and the rabbit C element, exhibit a similar response, suggesting a common mode of regulation during the stress response (*65*). During heat shock, *Alu* RNAs enhance translation, presumably by sequestering PKR to discrete loci so as to inhibit its activation (*66*). Additionally, transiently introduced *Alu* RNAs in human cells, and B1 and B2 RNAs in mouse cells, selectively enhance the translation of reporter mRNAs independently of PKR without affecting global cell translation (*67*). In mouse

cells, lncRNAs called SINEUPs stimulate the translation of mRNAs with which they form base pairs via 5′-end complementary sequences. Stimulation depends on a B2 element embedded within the SINEUP (*68*).

Influence of A-to-I editing on SINE function

Adenosine-to-inosine (A-to-I) RNA editing is a tissue-specific posttranscriptional process whereby adenosine residues located within dsRNAs are deaminated to inosines by the dsRNA-specific adenosine deaminase (ADAR) proteins (*69*). In primates, IR*Alu*s are the main binding site for ADARs and are subject to editing at multiple sites (Fig. 5) (*35*, *36*, *70*). More than 90% of A-to-I editing in humans occurs within *Alu* elements (*71*–*75*). Multisite A-to-I editing within exonized *Alu* elements are predicted to result in amino acid recoding, because inosines are recognized as guanosines by translating ribosomes (*55*, *76*, *77*). A-to-I editing within intronic IR*Alu*s can generate new splice sites that lead to the exonization of *Alu* elements (Fig. 5A) (*78*). For instance, exonization of the alternatively spliced exon 8 of human nuclear prelamin A recognition factor pre-mRNA results from the A-to-I editing–dependent generation of a functional 3′ splice site within an intronic *Alu* (*78*, *79*). The editing of IR*Alu*s embedded in UTRs is not site-specific and the biological significance is not known. One possible function of UTR-embedded IR*Alu*s is to act as "sponges" that titrate ADAR away from site-specific editing sites within ORFs to prevent amino acid recoding (*55*, *76*, *77*). Because inosine forms base pairs with cytosine, A-to-I editing influences the stability of the IR*Alu*s double-stranded structure by creating mismatches or, less likely, matches (Fig. 5B). Thus, A-to-I editing might change the repertoire of proteins that bind IR*Alu*s and thereby have an impact on the metabolism of transcripts within which IR*Alu*s reside.

A-to-I editing within *Alu* elements might also reprogram the interaction network between miRNAs and their *Alu*-embedded target sites via deactivating or, possibly creating miRNA-binding sites (*80*). Recent profiling of mRNAs that bind the miRNA machinery indicates that the majority of miRNA

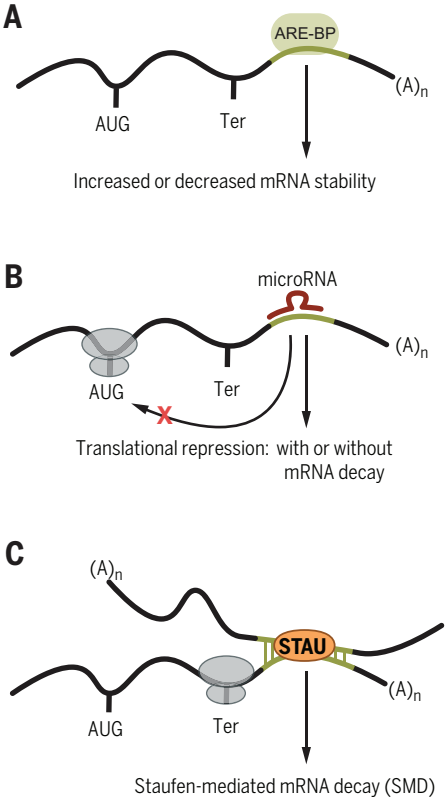

Fig. 3. Effects on mRNA stability by SINE insertions. (**A**) AU-rich element–binding proteins (ARE-BPs) may bind a 3′UTR *Alu* element–derived ARE and either stabilize or destabilize the mRNA. (**B**) *Alu* element–derived microRNA-binding sites within an mRNA can promote mRNA decay and/or inhibit mRNA translation. (**C**) Intermolecular base pairing via partially complementary SINEs can create Staufen-binding sites that trigger Staufen-mediated mRNA decay.

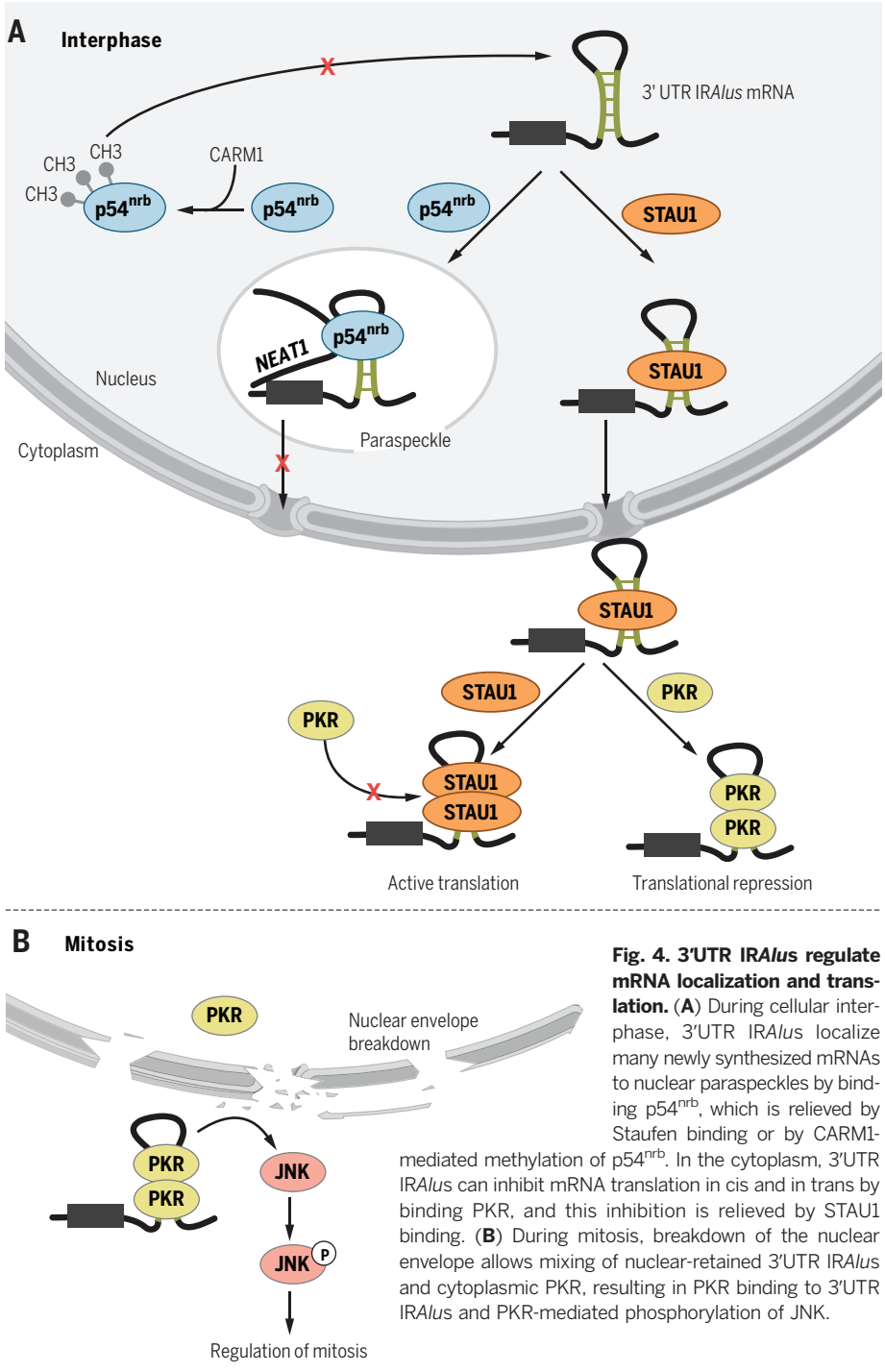

Fig. 4. 3′UTR IR*Alu*s regulate mRNA localization and translation. (**A**) During cellular interphase, 3′UTR IR*Alu*s localize many newly synthesized mRNAs to nuclear paraspeckles by binding p54^{nrb}, which is relieved by Staufen binding or by CARM1-mediated methylation of p54^{nrb}. In the cytoplasm, 3′UTR IR*Alu*s can inhibit mRNA translation in cis and in trans by binding PKR, and this inhibition is relieved by STAU1 binding. (**B**) During mitosis, breakdown of the nuclear envelope allows mixing of nuclear-retained 3′UTR IR*Alu*s and cytoplasmic PKR, resulting in PKR binding to 3′UTR IR*Alu*s and PKR-mediated phosphorylation of JNK.

targets within *Alu* elements are used less than those residing outside of *Alu* elements, presumably because *Alu*-element A-to-I editing and tight secondary structures prevent access to computationally predicted miRNA-binding sites within *Alu* elements (*81*).

Host defense against retrotransposition

Whereas some LINE and SINE insertions regulate gene expression, retrotransposition is necessarily mutagenic with the potential to cause disease. A small minority of L1, *Alu*, and SVA (SINE–variable number of tandem repeats–*Alu*) elements retain functional promoters that enable them to be transcribed and to retrotranspose. *Alu* elements are currently the most active retrotransposon in the human germ line, manifesting an estimated insertion rate of 1 in 20 live births (*82*). The estimated L1 insertion rate is 1 in 20 to 1 in 200 live births; the estimated SVA insertion rate is 1 in 900 live births (*3*). Germline insertions have been implicated in ~100 genetic diseases (Table 1) (*83*, *84*) and insertion events in somatic tissues, although not heritable, also have the potential to cause disease (*20*, *85*). Indeed, ongoing retrotransposition that results from the removal of inhibitory methylation marks on LINE and SINE promoters is a hallmark of many cancers (*86*) and also typifies neurological disorders, including schizophrenia (*87*) and Rhett syndrome (*88*).

Organisms have developed various mechanisms to protect their genomes from the deleterious effects of retrotransposon insertions [reviewed in (*89*, *90*)]. Transcriptional silencing of retrotransposons by DNA methylation has been described as a major host defense mechanism in mammals (*89*, *90*). However, recent evidence suggests that histone methylation, rather than DNA methylation, is the predominant suppressor of SINE transcription in human and mouse cells (*91*). Mammalian cells have also developed an arsenal of sequence-specific RNA degradation mechanisms to eliminate retrotransposon transcripts once produced. Endogenous small interfering RNAs (endo-siRNAs) or PIWI-interacting RNAs (piRNAs) can initiate degradation of LINE and SINE RNAs (*92*–*96*). Microprocessor, a nuclear complex of miRNA-processing enzymes, also recognizes and cleaves L1, *Alu*, and SVA transcripts, at least in vitro (*97*). The finding that L1 and *Alu* RNAs are enclosed within human cell autophagosomes has implicated autophagy (i.e., the delivery

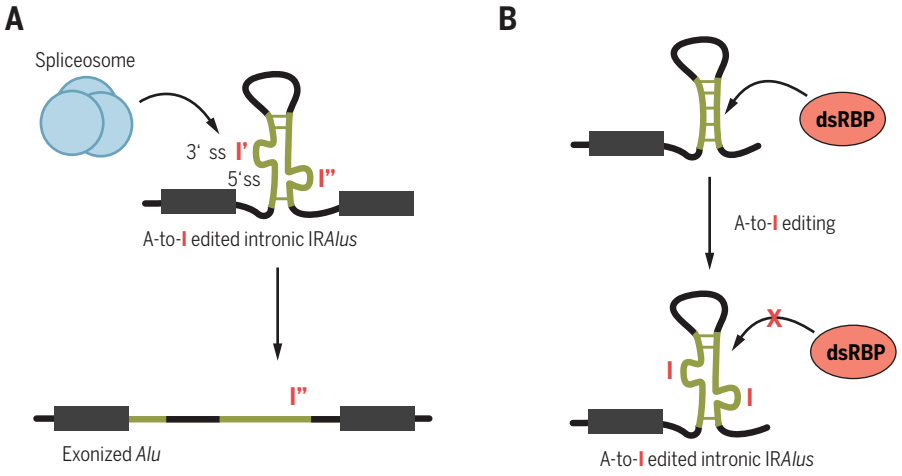

Fig. 5. The roles of A-to-I editing of IR*Alu*s. (**A**) Edited intronic IR*Alu*s can create a new splice site. (**B**) Editing in IR*Alu*s might destabilize their dsRNA structure and reduce dsRBP binding.

Table 1. Some human diseases linked to LINE and SINE insertions. The extensive role of LINEs and SINEs in the regulation of human gene expression suggests that they contribute to disease in as yet undiscovered ways.

Effect of LINE or SINE insertion	Possible mechanism(s) of pathogenesis	Examples of associated diseases	Reference
Genomic deletions and rearrangements	LINE/SINE-mediated homologous recombination: DNA sequence loss; genomic instability	Prostate cancer, pyruvate dehydrogenase complex deficiency, leukemia, Alport syndrome, breast cancer	(*83*)
		Hereditary nonpolyposis colorectal cancer, Von Hippel–Lindau disease	(*86*)
Disruption of protein-coding sequences	Aberrant protein production; nonsense-mediated mRNA decay (NMD)	Hemophilia B, breast cancer, colon cancer, neurofibromatosis type 1	(*83*)
Altered DNA methylation	Increased expression of LINE and SINE RNA	Early event in many cancers	(*86*)
Altered pre-mRNA splicing	Aberrant protein production; NMD	Fukuyama-type congenital muscular dystrophy, neurofibromatosis type 1, hemophilia A	(*83*)
		Neurofibromatosis type 1, hemophilia A, breast cancer, Coffin-Lowry syndrome	(*84*)
Altered 3′-end formation	Premature transcription termination; altered protein production; NMD; altered mRNA stability, localization, or translatability	X-linked retinitis pigmentosa	(*83*)
Altered mRNA stability	Reduced protein production; altered temporal and/or spatial gene expression	X-linked dilated cardiomyopathy	(*83*)
		Hemophilia A, hereditary nonpolyposis colorectal cancer, hyper–immunoglobulin M syndrome	(*84*)
Sites of A-to-I editing	Loss of ADAR editing of target sites, possibly at *Alu* elements	Amyotrophic lateral sclerosis (ALS), astrocytoma, metastatic melanoma, Aicardi-Goutières syndrome, hepatocellular carcinoma	(*100*)

of cytosolic constituents to the lysosome) as another host defense mechanism that degrades retrotransposon RNAs (*98*). Indeed, mice lacking the critical autophagy gene, Atg6/Beclin1, are characterized by higher levels of retrotransposon RNAs and increased rates of genomic insertions (*98*). Additionally, retrotransposition is restricted in both somatic and germ cells by members of the apolipoprotein B mRNA-editing enzyme 3 (APOBEC3) family (*89*, *99*).

Conclusions

Here we have focused on the functions of human and mouse LINEs and SINEs. However, the prevalence of LINEs and SINEs in other organisms, and known examples whereby evolutionarily unrelated human and mouse SINEs have been exapted for similar functions, leads us to propose that at least some of the LINEs and SINEs found in many organisms are likely to be used analogously as regulatory elements. In addition to their exaptation as functional sequences, the recent discovery that LINEs and SINEs are actively retrotransposing in somatic tissues (including brain) and the myriad of potential consequences of LINE and SINE insertions implicate LINEs and SINEs in the molecular pathogenesis of acquired diseases, including diseases of aging.

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Retrotransposons as regulators of gene expression
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Editor's Summary

Parasitic DNAs help and hinder evolution

Transposable elements are parasitic DNAs that can duplicate themselves and jump around their host genomes. They can both disrupt gene function and drive genome evolution. Elbarbary *et al.* review the roles of two classes of transposable elements in gene regulation and disease: long interspersed elements (LINEs) and short interspersed elements (SINEs). Roughly a third of the human genome consists of LINEs and SINEs. They contribute to a broad range of important genome and gene regulatory features, while at the same time being responsible for number of human diseases.

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